1. Diagnosis

DO SYMPTOM DIMENSIONS OR CATEGORICAL DIAGNOSES BEST DISCRIMINATE BETWEEN KNOWN RISK FACTORS FOR PSYCHOSIS?

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BACKGROUND: Considerable overlap exists between the different categories of psychotic diagnoses. In order to develop potentially more valid representations of psychoses, recent research has focused upon identification of symptom dimensions via exploratory factor analyses (EFA). AIM: To describe symptom dimensions using detailed psychopathological information from epidemiologically defined incident cases, which include the full spectrum of functional psychosis, across all age ranges, then to assess the relationship of these dimensions to known demographic and risk factors. METHOD: 464 incident cases of psychosis assessed using the Operational Checklist for Psychotic Symptoms (OPCRIT) were included in an EFA. The association between dimensions and premorbid risk factors were assessed using linear or logistic regression and the likelihood ratio test. RESULTS: Iterated principal factor analysis on the tetrachoric correlation matrix of psychopathological items obtained five dimensions of manic, disorganisation, depressive, delusional and auditory hallucinatory symptoms, explaining 58% of the total variance. Different dimensions were differentially associated with the pre-morbid risk factors. Neither the dimensional nor the categorical representation of psychosis was sufficient to explain associations with pre-morbid demographic variables and risk factors. CONCLUSION: Strategies combining dimensional and categorical representations of psychosis are likely to be most informative in finding the causes and correlates of psychosis.

CONTRIBUTION OF DIMENSIONAL AND CATEGORICAL MODELS IN THE ASSOCIATIONS WITH PREMORBID RISK FACTORS

Dependent variable in logistic /linear model Pre-morbid risk factor	Comparison of full model with model constrained by dropping the categorical diagnoses		Comparison of full model with model constrained by dropping the dimensions	
	Likelihood ratio statistic	p value	Likelihood ratio statistic	p value
Gender	10.68	0.06	4.44	0.49
Age at presentation	22.78	<0.001	86.14	<0.001
Single at presentation	8.20	0.15	15.38	<0.01
Unemployed at presentation	13.63	0.02	10.25	0.07
Poor work adjustment	15.61	<0.01	15.35	<0.001
Poor social adjustment	19.25	<0.001	2.59	0.76
Alcohol /drugs misuse	6.06	0.19	18.92	0.002
Psychosocial stressor	12.90	0.02	18.07	0.002
Family History schizophrenia	6.25	0.28	6.37	0.27
Family psychiatric history	1.84	1.84	8.67	0.12

DISEASE BIOMARKERS IN FIRST-ONSET SCHIZOPHRENIA

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At present, little is known about the basic mechanisms that underlie the schizophrenia disease process. This lack of knowledge is most likely due to the fact that until recently large-scale expression profiling studies were technologically impossible. Thus, most researchers employed a "candidate gene/protein" approach. With recent technological advances in genomics, proteomics and metabolomics techniques, it is now possible to globally investigate the molecular underpinnings of psychiatric conditions which should result in improved knowledge and hopefully new (pre-symptomatic) diagnostic, therapeutic and preventative regimes. My laboratory combines advanced computing and bioscience technologies with functional genomics studies. Using this powerful approach we explore the molecular "fingerprints" of psychotic disorders from early onset through their progressive stages, exploring alterations at the gene, protein, lipid and metabolite level. This in turn should reflect and reveal dynamic changes of interlinked pathways in the normal and disease brain. I will present results from our biomarker discovery studies. To date we have identified a number of highly significant peptides and metabolites that distinguish first-onset paranoid schizophrenia patients from healthy controls. Our findings suggest brain-specific alterations in glucoregulatory processes in the CSF of drug-naïve patients with first-onset schizophrenia, implying that these abnormalities are intrinsic to the disease, rather than a side effect of antipsychotic medication. Short-term treatment with atypical antipsychotic medication resulted in a normalization of the CSF disease signature in half the patients well before a clinical improvement would be expected. Furthermore, our results suggest that the initiation of antipsychotic treatment during a first psychotic episode may influence treatment response and/or outcome. Thank you to the Stanley Medical Research Institute and the Henry Smith Trust for Centre support.

SCHIZOPHRENIA: DIAGNOSTIC CLASS OR DOMAINS OF PATHOLOGY

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Schizophrenia has the status of a clinical syndrome. It comprises a number of pathologic attributes, each of which is observed in other diagnostic classes. At the level of psychopathology, two approaches have reduced heterogeneity of the syndrome. The first involves deconstructing schizophrenia into discreet domains of pathology. The second involves determining is specific domains define a valid disease entity. A body of work with primary negative symptoms will be used to illustrate the validity of examining domains [rather than schizophrenia as a class] for etiologic, pathophysiologic and therapeutic factors. In addition, the case for one domain [primary negative symptoms] identifying a disease entity within the syndrome will be presented with validation at the etiologic, neuropathologic, and therapeutic levels.

CHARACTERISTICS OF HOSPITALIZED ANTIPSYCHOTIC-POLYTHERAPY PATIENTS

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Background: Despite lack of research support, antipsychotic polytherapy is prevalent. This study considered clinical characteristics and outcomes of hospitalized psychotic disorder patients given single vs. multiple antipsychotic drugs. Method: We reviewed medical records of an 8-month sample of McLean Hospital inpatients diagnosed with DSM-IV schizophrenia, treated with antipsychotics in March–May of 2002 and 2004, for all current psychotropic drug treatments, chlorpromazine-equivalent (CPZ-eq mg/day) doses of antipsychotics, clinical status at admission and discharge, and days hospitalized. We retrospectively rated the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI), and Global Assessment Functioning (GAF). We compared antipsychotic poly- vs. monotherapy subjects on CGI, GAF and PANSS-derived positive and negative symptom scores. Results: Among 650 inpatients treated with antipsychotics, 171 randomly selected with DSM-IV psychotic-disorder diagnoses (26%) constituted the study sample (54% women; age: 42±14 years). Discharge diagnoses ranked: schizoaffective disorder (54%) > schizophrenia (24%) > psychosis-NOS (21%) > delusional disorder (1%). At discharge, subjects averaged 2.65 psychotropics/patient. Schizoaffective disorder patients received more antipsychotics and more total psychotropics than those with other psychoses. Antipsychotic polytherapy cases had higher admission CGI and higher PANSS-positive than -negative scores, were hospitalized longer, and received higher CPZ-eq total mg/day doses than those given monotherapy, but improved as well as other subjects by discharge. Conclusion: Psychotic disorder subjects given two or more antipsychotic drugs had higher admission illness ratings, more positive than negative symptoms, received greater total daily antipsychotic drug doses, and were hospitalized longer.

COMPUTERIZED MEASUREMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Accurate measurement of negative symptoms is crucial for understanding and treating schizophrenia. However, current measurement strategies are reliant on subjective symptom rating scales which have considerable psychometric and practical limitations. Computerized analysis of patients' speech offers a sophisticated and objective means of evaluating negative symptoms. The present study examined the feasibility and validity of using widely-available acoustic and lexical-analytic software to measure flat affect, alogia and anhedonia. These measures were examined in their relationships to clinically-rated negative symptoms and social functioning. Natural speech samples were collected and analyzed for patients with clinically-rated flat affect, patients without flat affect and healthy controls. Each of the computer-based negative symptom measures discriminated patients with clinically-rated flat affect from controls at a large effect size level, and the computer-based measure of alogia discriminated the clinically-rated flat and non-flat patients at a large effect size level. Of all the measures of negative symptoms examined in this study, only the computer and clinical measures of anhedonia corresponded to social functioning impairments. Computerized assessment of negative symptoms offers a number of advantages over traditional symptom scale-based approaches.

DURATION OF PRODROMAL SYMPTOMS AND CONVERSION TO PSYCHOSIS IN THE NORTH AMERICAN PRODROMAL LONGITUDINAL STUDY (NAPLS)

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The onset of psychosis is typically preceded by a prodromal period characterized by attenuated positive symptoms. While criteria defining symptom severity are relatively well established, the developmental course of these symptoms is not as well understood. The Structured Interview for Prodromal Syndromes (SIPS) focuses on the onset or worsening of attenuated (pre-psychotic) positive symptoms in the past 12 months. However, the outcome associated with earlier appearing prodromal symptoms has not yet been systematically studied. In this study, we assess those subjects in the NAPLS data base who, at baseline, displayed moderate to severe attenuated positive symptoms for 12 months or less (APS only, excluding subjects with brief intermittent psychosis or at genetic high risk not meeting APS criteria; n=357) compared to those subjects also meeting SIPS attenuated positive symptom severity criteria, but with longer durations (n=107; long duration prodromals; LDP). At the end of follow-up (2 1/2 years), the conversion rate for the APS-only group was 37.9 % compared to 16.1% for LDP subjects. However, LDP subjects were significantly younger (16.8 vs. 18.2 years), and were more functionally impaired, especially in terms of premorbid adjustment, overall functioning and social skills, suggesting that conversion rate may increase with continued follow-up. Clinically the LDP subgroup was comparable to APS-only subjects in severity of negative, disorganized and general symptoms as measured by the SIPS, but were not as severe on total positive symptoms, consistent with the lower conversion rate. For a subsample of 241 subjects (including 39 who converted), symptom duration could be calculated as days from symptom onset to study entry. For this sample, overall, there was no association between symptom duration and conversion for either the single longest appearing symptom, or for four of the five positive symptoms analyzed separately. The only exception was unusual thought content which was of significantly longer duration for those subjects who did not convert. Thus, while strongly supporting the predictive validity of the SIPS-defined APS syndrome, these results suggest that a somewhat longer risk window may also contribute to our understanding of the course of illness. Additional prospective research involving a larger number of long-duration subjects is necessary to establish optimal time limits for the prodromal phase of illness.

VALIDITY OF THE EPPENDORF SCHIZOPHRENIA INVENTORY (ESI) AS A SCREENER IN HIGH RISK ASSESSMENT FOR PSYCHOSIS

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Implementing a self rated screen could give mental health workers a first indication as to the presence of high risk symptoms of psychosis, thereby increasing the yield of 'valid'referrals for further specialised diagnostics. ESI-questionnaires were filled in by patients referred to the AMC for psychosis evaluation. Patients were diagnosed as being prodromal, psychotic or sub-threshold on the basis of structured interviews (SIPS/BSAPS) and evaluated by interviewers blind to ESI-score. Scaling technique was used to assess internal validity of the ESI-questionnaire, and sub-scale scores were compared across diagnostic groups. After minor adjustments were made the ESI-scales proved to be of satisfactory internal validity. Furthermore, ESI scores can predict group membership (prodromal, psychotic or sub-threshold. This preliminary result suggests the ESI can be used as a 'high risk screen'.

THE NEUROSCIENCE INSTITUTE OF SCHIZOPHRENIA AND ALLIED DISORDERS (NISAD): 10 YEARS OF AUSTRALIA'S FIRST 'VIRTUAL' RESEARCH INSTITUTE

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The development of NISAD has been unique in the Australian research landscape, being the first medical research institute in Australia to adopt a 'virtual' or 'institute without walls' structure. This has meant that NISAD's research program has been network-focused rather than edifice-based. NISAD's evolution is described, including the formation of the institute, as well as an overview of the first ten years of the institute's schizophrenia research program and outcomes. This includes the initial program aimed at developing research infrastructure to provide a foundation, with a subsequent focus on developing a multi-disciplinary program of schizophrenia research, across the basic to applied research spectrum. NISAD has succeeded in building a framework to apply the latest developments in neuroscience to the study of schizophrenia, using a non-traditional 'virtual institute' model, and has formed a multidisciplinary network of Australian clinicians and neuroscientists who are actively collaborating on a wide range of research initiatives. The 'virtual institute' structure of NISAD has proven cost efficient and consistent with innovative thinking about research resource management.

CATECHOLAMINE REGULATED PROTEIN (CRP40), AS A POSSIBLE CLINICAL BLOOD BIOMARKER IN SCHIZOPHRENIA

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The overall objective of this research proposal is to further investigate the role of catecholamine regulated proteins (CRP's) in schizophrenia. The proposed studies will be carried out to investigate: (i) whether human subjects with a clinical diagnosis of schizophrenia reveal reduced expression of CRP40 in platelets by a simple blood test; (ii) whether increased antipsychotic drug (APD) treatment normalizes CRP40 expression in the platelets at the RNA level of these subjects; (iii) whether increased APD treatment results in increased platelet aggregation, which may be implicated in cardiovascular disease in subjects with psychosis. Our laboratory has discovered and cloned a human chaperone-like protein, (CRP40), which may play a key role in schizophrenia (SZ). Specifically, human CRP40 is a novel catecholamine regulated protein that has high homology with the 70kDa mitochondrial heat shock protein, mortalin-2 generated by alternative splicing; and functionally has been shown to bind to dopamine along with being localized in the mesocorticolimbic and nigrostriatal regions of the human brain. Recent reports have shown that CRP40 protein expression is significantly reduced in both: 1) postmortem brain specimens of SZ relative to normal controls; 2) CRP40 mRNA and protein expression has been shown to exist in human platelets, evidenced by real-time PCR. Platelet preparation involved 20 ml of fresh blood that was collected in 2 BD vacutainer tubes (ACD solution) and the RNA was isolated by TRIzol method. Preliminary results have shown that a significant reduction of CRP40 expression was seen in 2 first-episode schizophrenic subjects relative to age/sex matched controls. Second, quantification of human platelet aggregation was performed with flow cytometry as described in Joseph Gabriele Ph.D., thesis, using CRP40 fusion protein which resulted in significant aggregation of platelets. The expected results should conclude that CRP40 expression will be significantly reduced in first episode patients and normalized with APD treatment, along with increased platelet aggregation with increased APD treatment. Our working hypothesis states that "decreasing endogenous chaperone levels/activity of CRP40 accelerates the course and severity of neuronal loss in SZ due to oxidative stress" and/or mitochondrial dysfunction. Project funded by Canadian Institute of Health Research (CIHR)

CLEARING THE CONFUSION IN THE IDENTIFICATION, CLASSIFICATION, AND MANAGEMENT OF DRUG-INDUCED MOVEMENT DISORDERS: AN INTERACTIVE TOOL

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The expanded use of psychotherapeutic drugs has increased the number and type of clinicians using these medications. It is essential that clinician education include the etiology, diagnosis, and management of drug-induced movement disorders (DIMDs) associated with psychotherapeutic agents. While research has focused primarily on DIMDs associated with antipsychotics, DIMDs can also emerge with the use of mood stabilizers, antiepileptics, central anticholinergics, dopamine agonists, antihistaminics, and antidepressants. A comprehensive understanding of DIMDs that can be readily applied in daily clinical practice is vital. A three-module, interactive CD-ROM was developed to address identified educational needs. Clinician feedback about the utility of the CD-ROM tool in the clinical setting is being gathered and analyzed. The Overview module provides background information and a presentation of the most common DIMDs. The second module outlines the diagnosis and management

of DIMDs, and includes animation and videos of patients experiencing movement disorders. The Library module provides a glossary and a description of common movement disorder scales. Preliminary clinician feedback from geriatric psychiatrists and other physicians regarding the usefulness of the tool validates its utility. An interactive CD-ROM program has been developed to educate clinicians regarding the identification, classification, and management of DIMDs. Clinician feedback regarding this tool demonstrates its usefulness in a clinical setting. Supported by funding from Janssen, L.P.

SCHIZOPHRENIA IS NOT A NOSOLOGICAL MONOLITH

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Notwithstanding decades of research, schizophrenia remains a broad clinical syndrome characterised by extreme variability of its symptoms, behavioural signs and patterns of course. The existence of a specific brain disease or genetic diathesis underlying schizophrenia is still a working hypothesis, for which no conclusive proof or refutation has yet been produced. All this raises doubts in its coherence as a valid entity, sometimes leading to proposals to discard the diagnostic category. However, simply dismantling the concept is unlikely to beget an alternative model that would account for a host of clinical phenomena and research data that indirectly favour a disease hypothesis of schizophrenia. Genetic findings in schizophrenia are highly suggestive of biological complexity and etiological heterogeneity that cannot be tackled using the potentially fallible phenotype of clinical symptoms alone. There is growing evidence that intermediate (endo-) phenotypes in the domains of cognition, brain physiology and brain morphology provide research tools capable of dissecting the complex disorder into more homogeneous units of analysis. Our research group developed a novel endophenotyping approach, allowing the aggregation of multiple cognitive and neurobehavioural measures into composite quantitative traits. This resulted in the delineation of a heritable, homogeneous subtype of schizophrenia characterized by pervasive cognitive deficit, bearing a close resemblance to P. Meehl's notion of schizotaxia. The whole-genome scan of 388 members of Western Australian families with schizophrenia demonstrated a distinct genetic basis for this subtype and taxometric analysis confirmed its taxonic nature. Thus, schizophrenia, as defined by the DSM-IV and ICD-10 criteria, is very likely a conflation of several distinct disorders whose systematic phenotypic delineation will foster greater coherence in etiological research.

PANSS RATER TRAINING USING INTERNET AND VIDEOCONFERENCE

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The purpose of this pilot study was to evaluate a new approach to training novice raters on the administration of the Positive and Negative Symptom Scale (PANSS) using new technologies. Twelve trainees with prior experience with schizophrenic patients but no prior PANSS experience participated. The training involved two components: didactic training via CD-ROM and applied clinical training conducted in real time via videoconference. Prior to any intervention, trainees administered a PANSS interview to a standardized patient, which was videotaped for later evaluation. Trainees then completed an interactive CD-ROM tutorial on the PANSS, including a pre-test, review of general guidelines for administering the scale, key concepts and scoring conventions for 8 of the 30 PANSS items (chosen for the pilot for their recognized difficulty), and a 20-item post-test. After passing the didactic post-test (>80% correct), trainees participated in two applied training sessions where they remotely interviewed a standardized patient in another location by videoconference. An expert trainer observed the interview and provided feedback after the session via videoconference on the trainees' scoring accuracy and clinical interview skills (adherence, followup, neutrality, clarification) using the Rater Applied Performance Scale (RAPS)(Lipsitz, 2003). As a post test, trainees interviewed a standardized patient, which was also videotaped. A panel of experts blindly scored the pre- and post-training videotaped interviews on the RAPS, blind to which tapes were pre-and which were post-training. Results: A significant improvement was found in didactic knowledge, with mean number of correct answers improving from 12.42 to 17.33, $t(11)=7.488$, $p<.001$. On applied clinical skills, the mean RAPS score improved from 10.92 to 12.25, $p=.194$. The agreement in scoring between the trainee and blinded expert (ICC) improved from $r=.19$ prior to training ($p=.248$) to $r=.52$ after training ($p=.034$). While this was a small sample, results provide support for the efficacy of this training approach for improving novice raters' understanding of and skill in conducting PANSS interviews. The use of remote training technologies helps facilitate access to scarce training resources, and may improve the quality of the training by providing an opportunity to evaluate and improve applied clinical skills, an area of training that is often overlooked. Funded by NIMH Grant R43MH074173.

AN EVALUATION OF PSYCHIATRIC DIAGNOSES PRECEDING BIPOLAR DIAGNOSIS

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Patients with bipolar disorder are often misdiagnosed, resulting in potentially inappropriate treatments and worsening outcomes. The objective of this study was to analyze the psychiatric diagnoses preceding the first bipolar diagnosis for the different age groups of bipolar patients. Data from administrative claims (1995-2005) were used for this study. Bipolar patients were identified based on at least 2 outpatient diagnoses of bipolar disorder (ICD-9-CM diagnosis codes: 296.4x, 296.5x, 296.6x, 296.7x, 296.89), or at least 1 inpatient bipolar diagnosis. Bipolar patients who had a psychiatric diagnosis (ICD-9-CM diagnosis codes: 290.xx -319.xx) preceding the first bipolar diagnosis and a continuous eligibility from that diagnosis to the first bipolar diagnosis were included in this study. Sensitivity analyses using bipolar patients without prior eligibility requirement or with continuous eligibility in the 1 year prior were conducted. Among the 11,897 bipolar patients identified, the most common disorder preceding the first bipolar diagnosis was depression (48%), followed by anxiety (10%), adjustment to chronic stress disorder (8%), substance abuse syndromes (8%), ADHD (6%), conduct and oppositional defiant disorder (4%), and schizophrenia (3%). Younger patients (age less than 14) with bipolar diagnosis represented 10% of the total bipolar patients and had a unique pattern of previous diagnoses. They were most likely to have a previous diagnosis of ADHD (33%), followed by depression (20%), conduct and oppositional defiant disorder (16%), adjustment to chronic stress disorder (13%), and anxiety

disorder (4%). In contrast, adult bipolar patients (age 18 – 65) were most likely to have a depression (52%), anxiety (12%), substance abuse syndromes (9%), adjustment to chronic stress disorder (8%), and schizophrenia diagnosis (4%). A high percentage of bipolar patients had a depression diagnosis preceding the first bipolar diagnosis, followed by anxiety disorder, adjustment to chronic stress disorder, substance abuse syndromes, ADHD, schizophrenia and conduct disorder. The pattern of diagnoses preceding bipolar diagnosis in children was different from that in adults. A better understanding of the complexity of the diagnosis of bipolar disorder will assist clinicians in the proper diagnosis and effective treatment of patients with bipolar disorder. Funded by Eli Lilly and Company.

POTENTIAL VULNERABILITY MARKERS WITHIN THE AFFECTIVE DOMAIN IN SUBJECTS AT GENETIC AND CLINICAL HIGH RISK FOR SCHIZOPHRENIA

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Relative to high-risk studies on neurocognitive function, only a few high-risk studies have examined affective functioning components as possible vulnerability markers. In this study, we comprehensively assessed baseline affective functioning in subjects at clinical high risk (CHR) and genetic high risk (GHR) for schizophrenia, and normal controls, and compared the results to elucidate possible vulnerability markers in the affective domain. We studied three groups of subjects: those with clinical high risk for schizophrenia (CHR, N = 15), genetic high risk (GHR, N = 24), and a healthy control group (N = 24). Affective process- and affective content-related functioning were assessed using eight emotion-related scales. CHR subjects showed impairments in emotional awareness, mood repair, and emotional inhibition relative to healthy subjects and GHR subjects, whereas GHR subjects were only impaired in mood repair. In respect to affective content, CHR subjects had less positive and more negative affect scores, as well as higher depression, anxiety, and hostility than either the GHR or the healthy control groups. However, there were no significant differences in any components of affective content between the GHR and healthy control groups. The CHR and GHR results revealed disturbances in several components of affective processing and content, which correspond to previous findings of prodrome studies of schizophrenia and chronic schizophrenia. These results suggest that emotional awareness, emotional inhibition, mood repair in affective process, as well as less positive and more negative affect in affective content, may be potential candidates of vulnerability markers.

THE FIVE-FACTOR STRUCTURE OF THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS): A CRITICAL REVIEW OF ITS CONSISTENCY ACROSS STUDIES

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Sixteen principal component analyses of the PANSS (Positive and Negative Syndrome Scale) revealed that a five-factor solution representing positive, negative, disorganisation, depression/anxiety and excitability/hostility symptoms better explained the scale structure than the original three-subscale solution. Our goal was to identify to which of these five factors each of the PANSS items could be attributed based on the consistency of published factor analyses. For each study reporting a five-factor solution, the items were assigned to any of the five factors according to the factor on which it had the strongest factor loading. Items were then rated as reaching or not our between-study stability criteria of 75% of agreement. Seven items did not meet our stability criteria: Stereotyped thinking, Somatic concern, Tension, Mannerism/posturing, Lack of judgment/insight, Disturbance of volition and Preoccupation. Consistent results with regards to factor assignment were found for 23 out of 30 of the PANSS items, highlighting a relatively stable 5-factor structure across studies from independent samples. A few items were nevertheless inconsistently attributed to one factor or to the other. Given those inconsistencies, further studies using the PANSS 5 factor would benefit focusing on items consistently attributed to any of these five factors.

AFFECTIVE INCONGRUITY OF PSYCHOTIC SYMPTOMS IS ASSOCIATED WITH COGNITIVE DEFICITS AND POOR GLOBAL FUNCTIONING IN FIRST EPISODE PSYCHOSIS

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The distinction of psychotic disorders into categorical diagnoses has been increasingly challenged with studies suggesting an overlap in genetic etiology. There is the suggestion that within bipolar disorder, for instance, those with affect incongruent psychotic symptoms are more genetically related to schizophrenia than those without. The purpose of this study was to use neurocognitive assessments in individuals with a first-episode psychosis, including all diagnostic groups, to assess whether the affective congruity of psychotic symptoms was associated with particular deficits. Method: Comprehensive cognitive assessment (CANTAB) and psychotic symptom ratings (PANSS) were recorded for 131 consecutive referrals to CAMEO, an early intervention for psychosis service in Cambridge, UK. Subjects were diagnosed as having either mania with psychotic symptoms (n=35), schizophreniform psychosis (n=61), schizoaffective disorder (n=16)or major depressive disorder with psychosis (n=19). Affect incongruent psychotic symptoms were defined as items on PANSS P1(delusions), P3(hallucinations), P6(suspiciousness), or P7 (hostility).79 patients had mood incongruent symptoms, 45 had no affect incongruent symptoms. Results: Patients' cognitive functions were heterogeneous. Those with mood incongruent psychotic symptoms performed significantly worse on tests of spatial working memory, rapid visual processing and set shifting compared with those with no mood incongruent symptoms. When compared by diagnosis the patients with schizophrenia also performed worse on spatial working memory and rapid visual processing tasks, but with no difference shown in set shifting tasks. The presence of affect incongruent symptoms was also strongly associated with poor global functioning (GAF) $p<0.001$, which was not shown when groups were compared by diagnosis ($p=0.054$). These data support the hypothesis that affect incongruent psychotic symptoms are a meaningful way of discriminating the psychotic disorders. They provide evidence for an associated underlying neurocognitive deficit in set shifting. Further follow up of this group is required to establish diagnostic stability and prognostic value of these measures.

RELEVANT DIMENSIONS OF DELUSIONS: CONTINUING THE CONTINUUM VERSUS CATEGORY DEBATE

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Background: Delusional ideation has been shown to be common among healthy individuals. However, the beliefs held by healthy individuals might differ in their phenomenology and their origin from delusions experienced by persons with schizophrenia. Hypothesis: Specific dimensions of delusions, such as the distress associated with them, the preoccupation with them, the level of conviction or their content might be more relevant in distinguishing persons with from persons without schizophrenia than the mere presence of delusional beliefs alone. It is also expected that delusional beliefs in the general population will be less closely linked to hallucinatory experiences than in persons with schizophrenia. Method: The Peters et al. Delusions Inventory (Peters et al., 1999) and the Launay Slade Hallucination Scale – Revised (Bentall & Slade, 1985) were used to assess delusional ideation and hallucinatory experiences in a population sample that reflects the general population in age, education and gender (n=359) and in persons diagnosed with life-time schizophrenia who were recruited from in- and outpatient settings (n=53). Results: Judged by the number of delusional beliefs alone, 24 percent of the population sample would have been classified as having schizophrenia, whereas 37 percent of the patients would have been classified as healthy. Stepwise discriminant function revealed the distress associated with delusions as well as beliefs involving persecution and loss of control to be more relevant in distinguishing persons with from persons without schizophrenia than the number of delusional beliefs. Contrary to the expectation, there was a strong association of delusional ideation and hallucinatory experiences in both groups. Conclusions: The results underline the importance of a multi-dimensional assessment of delusions. Also, particular emphasis should be laid on distress and content of beliefs in order to estimate the clinical relevance of a delusional belief.

PARENTAL REPORT ON THE PRODROMAL QUESTIONNAIRE: SCREENING FOR ULTRA HIGH RISK FOR PSYCHOSIS

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Parents are frequently the first observers to notice signs of emerging psychosis in their adolescent children, and prodromal/ultra-high-risk screening interviews often informally utilize reports from family members. However, the usefulness of parental report in screening and diagnosis of at-risk syndromes has not yet been systematically examined. In this study, adolescents and young adults who were referred for a suspected psychosis prodrome to the Staglin Music Festival Center for Assessment and Prevention of Prodromal States (CAPPS) at UCLA completed the Prodromal Questionnaire (PQ) and Structured Interview for Prodromal Syndromes (SIPS). A parent or other close family member completed parallel versions of both instruments; the majority of the informants were mothers. Analysis of data from 108 proband-parent pairs showed poor to moderate agreement between probands and parents for individual PQ items (Cohen's kappa) and for PQ scales and subscales (Pearson r correlations). Probands endorsed more positive and disorganized items than their parents, while parents endorsed more affective/role functioning items than their children. When PQ symptom scales from both reporters were used to predict clinician-assigned SIPS diagnosis by logistic regression, self-report of positive symptoms and parent-report of disorganized symptoms emerged as significant factors. Overall, these results are consistent with the typical discrepancies between child and parent reports found across most forms of psychopathology. They also suggest that parents may be uniquely positioned to recognize signs of behavioral disorganization in their children that suggest ultra-high-risk status, which the patients themselves may not be able to accurately report. Additional research is needed to determine whether parental report of symptoms is also predictive of conversion to full psychosis.

COMPARISON OF NEUROCOGNITIVE AND STRUCTURAL BRAIN ENDOPHENOTYPES ACROSS THE PSYCHOSIS SPECTRUM

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Introduction: In psychiatry, categories of illness have been developed based on clinical phenomenology. However, recent data are accumulating to suggest that a dimension of illness, like psychosis, may generate a more biologically meaningful classification system. Therefore, we have begun exploring this across different psychosis diagnoses. The primary goal of this research is to characterize objective markers of psychosis across the schizophrenia (SZ) and bipolar I disorder (BD) spectrum by comparing and contrasting neuropsychology and brain morphometric endophenotypes. We divided SZ and BD patients as follows: schizophrenia alone (SZ), schizoaffective disorder, mainly schizophrenic type (SAD-S), schizoaffective disorder, mainly affective type (SAD-A), bipolar I disorder with psychotic features (BD-P), bipolar I disorder without psychotic features (BD-NP). Methods: Thus far 53 patients have been enrolled with diagnoses spanning the diagnostic categories as follows: 24 SZ, 9 SADS, 3 SADA, 12 BDP and 5 BDNP; groups will be increased to at least N=10/group. A broad battery of neuropsychological testing was performed. Structural imaging data are being collected for VBM and ROI volumetric analysis using the ADNI protocol. Results: Socio-demographic characteristics (age, race, gender distribution, educational level) are comparable between patient groups. So far, BD-P and SZ patients do not differ significantly in neuropsychological performance. However, BD-P and BD-NP differ moderately in IQ and declarative memory with better performance in BD-NP (effect sizes = 0.63 and 0.81, respectively). Interestingly, performance in SAD patients looked different than either BD-P or SZ. In particular, SAD-S performed worse than BD-P in measures of working memory, declarative memory and attention (effect sizes = 0.66, 0.77, and 0.57 respectively). Volumetric data from structural image analyses will be reported. Conclusions: Although the sample size is small, these preliminary results suggest there is a continuum in neuropsychological performance across SZ and BD. Future analyses aim to identify specific structural endophenotypes which may mark a liability for psychosis.

THE MMPI-2 IN DIFFERENTIAL DIAGNOSIS OF SCHIZOPHRENIA AND SUBSTANCE INDUCED PSYCHOSIS

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The similarity of the clinical presentation of first episode schizophrenia and substance-induced psychosis may result in mis-diagnosis, undermining appropriate early intervention. The phenotype may be similar, but a different etiology should be reflected in discrete endophenotypic markers. Several markers have been suggested, including deficits in sustained attention, working memory, eye movements, and self-reported schizotypal features, all with good sensitivity but questionable specificity. The objective of the study was to examine the sensitivity and specificity of a common psychological assessment, the Minnesota Multiphasic Personality Inventory (MMPI-2), to the differential diagnosis of first episode schizophrenia, from first episode substance-induced psychosis. The primary hypothesis was that the MMPI-2 scales presumed most sensitive to Paranoia (Scale 6), Schizophrenia (Scale 8), and Schizophrenia Proneness (SzP) would be elevated in the schizophrenia sample, despite similarities between the two groups on other scales sensitive to non-specific personality features (e.g. Scale 2 for Depression). A secondary hypothesis was that MMPI-2 scales presumed sensitive to substance abuse including the MacAndrew Alcoholism Scale Revised, Addiction Potential Scale and Alcohol Acknowledgement Scale would show greater elevations in the substance-induced psychosis sample. The method entailed administration of the Structured Clinical Interview for DSM-IV TR (SCID-IV-TR) and the MMPI-2 to 53 patients entering the Edmonton Early Psychosis Intervention Clinic of the Regional Mental Health Program of Capital Health. The results based on 23 patients meeting SCID-IV TR criteria for substance-induced psychosis (43%) and 30 patients meeting criteria for schizophrenia (n=30, 57%) showed a significant difference between the two groups on Scale 6 (paranoia, $p<.02$), and SzP (schizophrenia proneness, $p<.03$). Both groups showed elevation on scale 8. In addition, the schizophrenia group showed elevation on BIZ (bizarre mentation). Also, both groups tended to deny alcohol use and did not show elevation on the MacAndrew Alcoholism Revised Scale, Addiction Potential Scale and Alcohol Acknowledgement Scale. In summary the MMPI-2 appears sensitive to common clinical phenotype associated with schizophrenia and substance-induced psychosis, but only Scale 6 (paranoia) and SzP (schizophrenia proneness) showed any potential value to differential diagnosis.

FUNCTIONAL IMPAIRMENTS ASSOCIATED WITH "AT-RISK" STATES

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Significant impairments in social and vocational function are present at the first episode of schizophrenia, however it as yet poorly understood when in the course of illness the functional impairments develop. The prodromal stage may represent a critical period characterized not only by the emergence of symptoms but also by the development or worsening of functional deficits. We have investigated functional status associated with "at-risk" prodromal symptoms in The North American Prodromal Longitudinal Study (NAPLS) data base, that includes commonly collected variables from 8 separate National Institute of Mental Health (NIMH) funded longitudinal studies of the schizophrenia prodrome. We compared functional status of 368 subjects that met either the Attenuated Positive Symptom (APS) criteria (n=357), Brief Intermittent Psychosis (BIP) criteria (n=11) of the Criteria of Prodromal States (COPS) to that of 196 healthy comparison subjects at study entry. In order to combine data related to functional outcomes from the individual study sites two 10-point scales were developed by NAPLS investigators (TDC, BC) rating vocational function (Instrumental Role Functional Scale—IRFS)and social function (Global Social Functioning Scale-GSFS) with higher scores indicating better function. As rated by these scales, controlling on age, race, and sex, at study entry the "at-risk" subjects had significantly lower social (mean score 6.2, sd 1.5) and vocational (mean 6.1, sd 1.7) function compared to the healthy subjects (mean 8.6, sd 1.0, and mean 8.7, sd 1.0, respectively) ($p< 0.0001$ for both comparisons). Baseline Global Assessment of Function (GAF) score was similarly lower for at-risk (mean 46.4, sd 12.2) than healthy subjects (mean 87.0, sd 7.6) ($p < 0.0001$). In addition at-risk subjects had a significant ($p < 0.0001$ for all analyses) decline in function compared to healthy subjects in the year prior to study entry, as measured by change from GAF, IRFS and GSFC scores. The results of this analysis support the hypothesis that the "at-risk" state as defined by APS and BIPS criteria is associated with significant impairments in social and vocational function, and that these impairments represent a decline from a higher level of function. It may be important for early identification and intervention strategies to target the initial declines in social and vocational function associated with "at-risk" states.

SUBSTANCE INDUCED PSYCHOSIS AND SCHIZOPHRENIA: HORMONES FOR DIFFERENTIAL DIAGNOSIS

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The differential diagnosis of schizophrenia and substance-induced psychosis is particularly difficult in first episode patients. The Edmonton Early Psychosis Intervention Clinic (EEPIC) is attempting to delineate biological and psychological markers useful to the differential diagnosis of a psychotic episode caused by drug abuse from a psychotic episode caused by schizophrenia. Epidemiological and preclinical studies have implicated estrogen and progesterone in psychosis, and the current investigation assessed the sensitivity and specificity of the hormones to differential diagnosis. Twenty-two young unmedicated men referred to EEPIC were stratified with the Structured Clinical Interview for DSM-IV into a schizophrenia (n=13) or a substance induced psychosis (n=8) group. The schizophrenia sample exhibited more severe symptoms of psychosis (PANSS Positive, Negative, General), but was similar to the substance induced psychosis group in psychosis vulnerability (MIS, SAS), depression (BDI, CDI), anxiety (HAM-A, STAI), mania (BRMS), and obsessions and compulsions (Y-BOCS). Although very similar in overt presentation, the schizophrenia sample exhibited higher serum progesterone and lower serum estradiol than the substance induced psychosis sample. Most notable was the greater proportion of the schizophrenia sample with high progesterone (85% with values > 3 nm/L) or low estradiol (77% < 150 pm/L) compared to the substance induced psychosis sample (25% with high progesterone, and 25% with low estradiol). Estradiol and progesterone appear to show good sensitivity and reasonable specificity in the differential diagnosis of schizophrenia from substance induced psychosis.

POTOMANIA IS ASSOCIATED TO ALCOHOL ABUSE IN CHRONIC SCHIZOPHRENIC SUBJECTS

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Background: Potomania is known to be relatively frequent among schizophrenic (SZ) subjects (particularly in institutional residential settings) and may lead to severe medical and behavioural complications associated to water intoxication. However, little is known on its association with other characteristics of psychotic illness. Hence, we took advantage of a cohort of 114 subjects extensively assessed on natural history and clinical variables to examine the correlates of potomania in chronic SZ. Methods: We randomly sampled DSM-IV SZ subjects from 2 strata defined according to level of functioning. The lower functioning stratum included patients living on long-term psychiatric wards or in highly structured group housing facilities. The higher functioning stratum included patients living in the community without supervision. Subjects were assessed for lifetime severity of positive, disorganized, negative and depressive symptoms, both during acute psychotic episodes and during the stabilized stage, for premorbid adjustment, age of onset and level of functioning and also for a history of potomania. Results: 12 subjects (10.5%) met our operational criteria for potomania. All but one of these subjects lived in institutional setting, for a prevalence of 27.5% in this subgroup. We observed more severe symptoms on all dimensions, earlier onset, poorer premorbid and current adjustment as well as more frequent alcohol abuse in potomanic subjects. When limiting comparisons to patients living in institutional setting, differences on clinical and natural history variables vanished but the association between potomania and substance abuse persisted (72.7% in potomanic vs. 20.7% in non-potomanic subjects; Odds ratio = 10.2; $p < .01$). Discussion: Potomanic schizophrenic subjects are characterized by a greater severity on a broad array of clinical and natural history variables and by a specific association with alcohol abuse. Thus, research on the pathophysiology of this serious problem may benefit from taking into account data gathered from research on alcohol abuse.

DECONSTRUCTING SCHIZOPHRENIA INTO COMPONENT PHENOTYPES

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The search for schizophrenia susceptibility genes, as well as clear identification of its pathophysiology and comprehensive treatment, have been difficult because of the complex and multifactorial nature of the disorder. The disorder is likely caused by varied combinations of genes and environmental factors, each with small effects. Previous research has identified several physiological deficits in schizophrenia that are stable and trait like in probands, and occur in a proportion of their non-ill relatives. These deficits, ranging from impairments in cognitive functions, eye tracking and sensory or sensory motor gating, are thought to mark schizophrenia liability. It's unclear whether these varied deficits mark the same or independent aspects of schizophrenia risk. To address this question, in an ongoing schizophrenia family study we examined a battery of biomarkers that included 11 measures: smooth pursuit eye movements, antisaccades, memory saccades, pre-pulse inhibition, P50 sensory gating, and 5 composite neurocognitive measures (attention, memory, executive function, problem solving and processing speed) in schizophrenia probands and their first degree relatives. These measures were selected because they are thought to mark schizophrenia liability and are associated with moderate to high heritability estimates ranging from 0.33 to 0.90. Data are available from 94 subjects. Results of Principal Component Analysis with varimax rotation showed 4 factors (eigenvalue > 1.0) that cumulatively explained 70% of the variance. The first factor included neurocognitive measures, antisaccade and memory saccade (factor loading ranging from 0.66 to 0.80 and explained 34% of the variance). The second factor consisted of entirely smooth pursuit eye movement measures with factor loading of 0.82 and explaining additional 17% of the variance. The third factor explained additional 10% of the variance and included PPI with a factor loading of 0.97, and the fourth was made up of P50 (factor loading 0.98 explaining additional 9% of the variance. These data suggest that many of the schizophrenia liability markers mark independent aspects of schizophrenia risk. This conclusion was further supported by the results from genetic association studies in larger samples that showed that different candidate genes were associated with different liability markers. Functional polymorphisms in COMT and DAT1 affected eye-tracking measure and Neuregulin-1 gene was associated with PPI.

THE CONSTRUCTION OF A MODIFIED FIVE-FACTOR MODEL OF THE POSITIVE AND NEGATIVE SYNDROME SCALE BY USING A TEN-FOLD CROSS-VALIDATION

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Objective: 25 previously published five-factor models for the PANSS items, could not be confirmed. This can be due to the statistics used. The purpose of this study was to use a 'new' statistical method to develop and confirm an improved five-factor model. The improved model is both complex and stable. Complex means that symptoms can have multiple factor loadings, because they have multiple causes, not because they are ill defined. Stable means that the complex structure is found repeatedly in validations. Methods: A ten-fold cross-validation (10CV) was applied on a large data set (N=5769) to achieve an improved factor model for the PANSS items. The advantages of 10CV are minimal effect of sample characteristics and the ability to investigate the stability of items loading on multiple factors. Results: The results show that twenty-five items contributed to the same factor all ten validations with one item showing a consistent loading on two factors. Three items were contributing to the same factor nine out of ten validations, and two items were contributing to the same factor six to eight times. The resulting five-factor model covers all thirty items of the PANSS, subdivided in the factors: positive symptoms, negative symptoms, disorganization, excitement, and emotional distress. The five-factor model has a satisfactory goodness-of-fit (Comparative Fit Index = .905; Root Mean Square Error of Approximation = .052). Conclusions: The five-factor model developed in this study is an improvement above previously published models as it represents a complex factor model and is more stable. Reference: Van der Gaag, M. et al. (2006). The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophrenia Research, 85(1-3), 280p-287.

EPIDEMIOLOGICAL AND PSYCHOPATHOLOGICAL APPROACHES OF A DIAGNOSIS OF SCHIZOPHRENIA: ARE WE GETTING SOMEWHERE?

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The diagnostic constructs that go under the name of schizophrenia and bipolar disorder have clinical utility and reasonable reliability but remain of uncertain validity. Basic epidemiological and psychopathological approaches towards enhancing the validity of these diagnoses have been: I) Showing mean differences between i) controls and diagnostic groups and ii) different diagnostic groups in course, outcome, treatment and cognitive, developmental and biological correlates; II) Subtyping within diagnostic groups (isolating individuals with extreme features within a diagnostic group and showing mean differences, for example deficit syndrome); III) Single-symptom research (analyzing cognitive and biological correlates of, for example, hallucinations or hypomanic mood); IV) Identifying dimensions of related symptoms within specific diagnostic categories or (better) within broadly defined groups with any psychotic disorder; V) Direct comparisons between different diagnostic representations of psychotic disorders, eg direct comparisons between dimensional and categorical representations. VI) Identifying population distributions of subthreshold expressions of psychosis and their correlates in the general population, and linking these to clinical phenotypes. The above approaches have shown that: I) Diagnostic categories and their subtypes, however defined, show mean differences on some variables and similarities on other. However, diagnostic likelihood ratios approaching clinical utility have not consistently been established for any cognitive, psychopathological, developmental or biological variable. II) There is no evidence that alternative categorical classifications of psychosis, or that any of the existing or alternative subtypes of psychosis add substantially to the diagnostic function. III) The combined diagnostic use of dimensional and categorical representations of psychosis does appear to add to the diagnostic function. IV) Single symptom approaches including cognition as a separate symptom domain may improve the diagnostic function. V) In terms of the validity question: what is schizophrenia and what is bipolar disorder, the likely answer may be that they are broadly distributed population phenotypes, only part of which is associated with need for mental health care. There is an emerging diagnostic science of the transition from subthreshold to clinical states.

2. Phenomenology

DESIGN FEATURES AND SAMPLE CHARACTERISTICS OF THE NORTH AMERICAN PRODROME LONGITUDINAL STUDY

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Since 2000 the National Institute of Mental Health has funded eight research projects in the U.S and Canada that focus on the schizophrenia prodrome. In 2004 Principal Investigators for these projects agreed to combine data on psychosis risk factors and clinical outcomes for 888 subjects enrolled in prodromal schizophrenia research programs. The collaborative project is known as the North American Prodrome Longitudinal Study. The Structured Interview for Prodromal Syndromes (SIPS) was utilized across sites to diagnose psychosis risk status at baseline evaluation, to monitor changes in prodromal status over time, and to determine conversion to acute psychosis. Excellent diagnostic reliability was achieved on the SIPS both within (kappas >0.80) and across participating research sites (kappa =0.90). Six subject groups define the longitudinal database: individuals believed to be at heightened risk for psychosis (HRP; n=370); those at genetic high risk but without prodromal symptoms (n=65); those who meet criteria for schizotypal personality disorder but do not display prodromal symptoms (n=56), those who have already developed psychotic symptoms (n=28) and two comparisons groups, namely help-seekers who failed to meet criteria for being at elevated risk (n=173) and non-psychiatric controls (n=196). Within the HRP group 9n=370), 96% met criteria for attenuated psychotic symptoms (APS); only 2 subjects met criteria for genetic risk plus deterioration (GRD), 11 had brief intermittent psychotic symptoms (BIPS), 2 had APS & BIPS and 6 had APS & GRD. Generally, HRP subjects were relatively similar across sites in terms of the severity of prodromal symptoms, comorbid diagnoses, premorbid and current functioning (most p>0 .05). The samples differed in age and education due to variation in site criteria for ascertainment (p<0.0001). This presentation will (1) describe how eight independently-conceived projects were integrated including the mechanics of building collaboration and creating a consortium, (2) outline how diagnostic reliability was established, (3) review the process of selecting and aggregating descriptive, clinical, and functional outcome variables into a federated, longitudinal database, and (4) present selected demographic and clinical variables for 888 at-risk and comparison subjects. Finally, we will describe how the NAPLS dataset will be utilized to address a series of fundamental scientific questions about the nature of the prodromal syndrome.

IS IT POSSIBLE TO DIFFERENTIATE BETWEEN PERSONALITY AND PSYCHOTIC SYMPTOMS IN DEFINING SCHIZOTYPY?

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The prodrome for schizophrenia has been recognised as a period of change marked by emerging symptoms and decreasing function. Measures developed to quantify the prodrome are intended for use in clinical settings and do not have the ability to identify psychosis prone individuals at a population level. Many measures are lengthy interviews which although thorough are time consuming and difficult to use as screening tools in a research setting. It is beginning to be recognised that prodrome measures may only identify a subset of individuals, excluding those who 1. do not present to services, 2. do not have a rapid deterioration in functioning, and 3. present with more insidious negative symptoms initially. The use of schizotypy measures to identify psychosis prone individuals has been criticised because of the emphasis placed on the trait approach in these measures. The results presented here aim to demonstrate that 1. prodrome measures and schizotypy measures are highly correlated; and, 2. a measure which allows participants to identify for themselves which are long terms versus short term problems may elucidate more information both concerning the dimensions of schizotypy and their relationship to prodromal symptoms. We present data from 157 participants, mean age 22 (sd=3) years, 29% male. All participants completed a new scale called the State-Trait Schizotypy Scale where an attempt was made to represent all aspects of the prodrome and not just the positive symptoms. Additionally, unlike the Prodrome Questionnaire participants gave more information about their experiences including degree of distress, duration, frequency and preoccupation for items endorsed. Trait schizotypy was measured using the O-LIFE (n=47) and the Schizotypal Personality Questionnaires (n=110) as measures of trait schizotypy. Additionally, more state-like variables were collected using two measures which examined experiences over the last month: the Prodrome Questionnaire (n=154) and the General Health Questionnaire (n=110). A principal components analysis of the STSS items identified 3 components which were highly correlated and had internal consistency values of 0.9. Correlations between the questionnaires were examined. There appears to be an overlap between many of the tools used to identify schizotypy and the Prodrome Questionnaire. The STSS demonstrates good internal consistency and was highly correlated with the Prodrome Questionnaire.

PARENT- AND CHILD-BASED SEMI-STRUCTURED INTERVIEW RESULTS IN A PRESCHOOL GROUP REFERRED FOR MANIA SYMPTOMS

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The idea of preschool mania is highly controversial. Because typically-developing children are frequently excited, how is one to differentiate normal excitement from mania? In beginning a line of research to answer this question, both diagnostic methodology and diagnostic criteria are highly important. This pilot study focuses on the issue of diagnostic methodology—examining the feasibility of utilizing semi-structured instruments for parent and child. We identified 34 preschool children aged 3.5 to 6 years: 22 with manic-like symptoms and 12 typically-developing children. We excluded children with autism, mental retardation, physical /sexual abuse, major medical/neurological disorders, and severe language disorder. We investigated the issue of a mania diagnosis with semi-structured DSM-IV diagnostic interviews with parents. Child-based information can be vital to the identification of certain psychiatric conditions; we used a semi-structured interaction with children, the MacArthur Story Stem Battery (MSSB). The results showed that manic and manic-like symptoms occur significantly more frequently in mood-disordered than typically-developing children. Based on

MSSB data, the mood-disordered group, compared to the typically-developing group, manifested more violent and bizarre responses to certain emotional challenges in the story stems. Based on the above findings, it is suggested that careful DSM-IV diagnostic interviewing of parents and administration of the MSSB to children may be sensitive methods for characterization of mood disorders in very young children. The MSSB may be useful in assessing for early signs of thought disorder. Specificity of the findings to a true mania diagnosis has yet to be investigated, and will require both the addition of other clinical groups and long term follow-up.

CARDIOVASCULAR RISK FACTORS IN SEVERE MENTAL DISORDER: COMPARING THE PREVALENCE IN BIPOLAR DISORDER AND SCHIZOPHRENIA

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Objective: Patients with severe mental disorders have increased rates of somatic disease and mortality, particularly from cardiovascular disease. In schizophrenia, this is shown to correspond with an increased prevalence of cardiovascular risk factors, such as smoking and the metabolic syndrome. Less attention has been paid to the somatic burden of bipolar disorder. In this study we compare the prevalence of smoking and metabolic disturbances in bipolar disorder and schizophrenia from a representative sample of patients under naturalistic conditions. We also compare the prevalence of risk factors in each diagnostic group with the general population. *Method*: Baseline data from the Oslo TOP Study (110 bipolar disorder patients and 163 schizophrenia patients), were compared with data from the 2000-2001 Oslo Health Study (15 186 individuals from the same geographical and sociocultural area). Prevalence of cardiovascular risk factors was compared between diagnostic groups, and age adjusted risk factors in both groups were compared with the general population. *Results*: Patients with bipolar disorder had higher levels of education, better social functioning, less psychiatric symptoms and less medication than patients with schizophrenia. High density lipoprotein was significantly lower in schizophrenia, and systolic blood pressure was higher in bipolar disorder . There was no significant inter-group difference in the prevalence of smoking, obesity, high triglycerides or diabetes, and both diagnostic groups had a prevalence of cardiovascular risk factors about twice that of the general population. *Conclusion*: The prevalence of cardiovascular risk factors was alarmingly high, and approximately the same, in bipolar disorder and schizophrenia.

RELATIONSHIP BETWEEN EXECUTIVE FUNCTIONING, POSITIVE AND DEPRESSIVE SYMPTOMS WITH INSIGHT INTO SCHIZOPHRENIA

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Lack of insight into illness and its clinical manifestations of the disease is a core symptom of schizophrenia. In order to explain the lack of insight associated to schizophrenia, three major explanatory hypothesis have been proposed: (i) lack of insight as an inherent consequence of the psychotic condition, (ii) lack of insight as an adaptive psychological coping style, which would include denial; and (iii) lack of insight as the result of some neurological or neuropsychological dysfunction, similar to the concept of anosognosia. The goals of this study were to assess the associations of insight with clusters of psychopathological symptoms, and with neurological or neuropsychological impairment as well as to estimate the prediction power of these variables combined and separately assessed. Sixty-seven patients diagnosed of schizophrenia or schizophreniform disorder, according to DSM-IV diagnosis criteria, including a group of 20 first episode patients, were included in the study. Insight was assessed with the Scale for Assessment of Unawareness of Mental Disorder; psychopathological status was assessed by the PANSS; and soft neurological signs by means of the NES. A comprehensive neuropsychological battery that included measures of attention, working memory, learning and memory, parietal-related functions, and executive functioning was administered. Poorer insight was associated with more positive ($r = 0.419$) and depressive symptoms ($r = 0.382$), but not with negative, hostility-excitation or disorganization symptoms. Among cognitive variables, only working memory ($r = -0.342$) and executive functioning ($r = -0.340$) significantly correlated with insight. Soft neurological signs did not show any association with insight. The total variance of insight explained by the combination of symptoms and cognitive functioning ranged from 13% to 19% among the different insight dimensions. In summary, our results provide supporting evidence for two of the three explanatory models assessed. According to our results, lack of insight might be partially explained by a conjunction of more prominent positive symptoms, and cognitive impairment of selected higher functions, such as abstraction and cognitive flexibility. Unexpectedly, poorer awareness of the need for treatment was associated to more severe depression symptoms. Interestingly, different dimensions of insight are selectively explained by different predictive variables.

CORRELATES OF INSIDER AND OUTSIDER CONCEPTUALIZATIONS OF RECOVERY

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Background: Two different conceptualizations of recovery exist, one with an objective orientation and an emphasis on symptoms and the other subjective based on the lived experience of people with mental illness. We propose a framework for examining recovery describing these models as insider and outsider perspectives. The purpose of the study was to examine the pattern of recovery correlates between the insider and outsider concepts. Methods: 66 individuals with schizophrenia, bipolar disorder, or major depression participated in the study. Measures from the insider perspective included The Empowerment and The Hope Scale and measures from the outsider perspective included the BPRS and a battery of cognitive measures. Results: For symptoms, depression and anxiety had the strongest relations with hope and empowerment. Positive and negative symptoms had few correlations with the insider measures and those that existed were weak. Cognition was associated with a subset of the empowerment scale focused on activism, power and anger. There were strong relations among hope and empowerment but few relations among symptoms and cognition. Conclusion: There are relationships between the insider and outsider conceptualizations of recovery. In this study, dysphoria had a stronger association with hope and empowerment than did other symptoms suggesting that more attention should be paid to depression and anxiety in people with serious mental illness. This study also indicates that the insider variables of hope and empowerment may be further divided into

an internal and an activist dimension. The cognitive variables were most associated with this activist dimension. Overall these data suggest the division of the two conceptualizations of insider and outsider views is unfounded and both sets of variable should be considered in intervention and research

	Hope Agency	Hope Pathways	Hope Total	Self Esteem	Power	Activism	Optimism	Anger	Empower Total
BPRS Dep/anx	-.27**	-.25*	-.30*	-.36*	NS	NS	-.35**	NS	-.25*
BPRS Neg SX	NS	NS	NS	NS	NS	-.28	NS	NS	NS
BPRS Pos Sx	-.29*	NS	NS	NS	NS	NS	-.26*	NS	-.27*
BPRS Total	=.26*	NS	-.26*	-.33**	NS	NS	-.25*	NS	-.25*
D2	NS	NS	NS	NS	.48**	NS	NS	.43**	.28*
RVLT	NS	NS	NS	NS	.32*	.27*	NS	.38**	NS
Trails B	NS	NS	NS	NS	-.31*	-.31*	NS	-.28	-.27*
Digits Forward	NS	NS	NS	NS	.40**	NS	NS	.48**	NS
COWA	NS	NS	NS	NS	.38**	NS	NS	.35**	.34**

*Significant at .05 level
**Significant at .01 level

EMOTIONAL EXPRESSIVITY AND SOCIAL FUNCTIONING IN SOCIAL ANHEDONICS

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Social anhedonia has been shown to be a promising indicator of schizotypy. Studies have also shown individuals with high levels of Social Anhedonia to exhibit poorer social functioning on broad indicators of social success when compared to controls. Of additional relevance is preliminary evidence which indicates that social anhedonia is associated with the diminished expression of emotion. Given the role of emotional expressivity in social interactions, it would be informative to examine the relationship between social dysfunction and emotional expression in social anhedonics. Specifically, it was hypothesized that the diminished emotional expression exhibited by anhedonics would negatively affect peers' willingness to interact with them, and that peers would find their interactions with anhedonics less pleasurable. In order to examine this hypothesis the current study utilized both self- and peer-ratings of emotional expressivity and social success, to investigate the relationship of emotional expression in the interpersonal relationships of social anhedonics. We adopted this novel approach to better understand how social anhedonics are viewed by individuals in their social environment. The sample consisted of 21 social anhedonics and 42 controls drawn from a large sample of female undergraduate students residing in university dorms. Group status was determined based on scores on the Revised Social Anhedonia Scale (RSAS). Individuals were asked to complete measures of emotional expressivity and social adjustment. The roommates of participants were also contacted and asked to complete ratings of the emotional expressivity of their roommate, their willingness to interact with the roommate, and a social pleasure scale indicating the pleasure derived from interacting with the roommate. Compared to controls, anhedonics reported lower emotional expressivity ($p < .05$) as well as poorer social adjustment ($p < .05$). Contrary to expectations, there were no group differences on peer ratings of expressivity, willingness to associate, or social pleasure. These findings indicate that social dysfunction and diminished expression of emotion are replicable features of social anhedonia. The use of peer informants may provide an important source of information for future studies of social anhedonia and other schizotypy-related constructs.

COGNITIVE CORRELATES OF SEMANTIC LANGUAGE DISORDER IN FIRST-EPISODE SCHIZOPHRENIA

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Introduction Language disorder in schizophrenia is commonly measured using instruments such as the Thought, Language and Communicative disorder rating scale (TLC). However, the TLC score represent an aggregate measure of abnormalities at different linguistic levels. The Clinical Language Disorder Rating Scale (CLANG) was developed (Chen et al., 1996) based on psycholinguistic levels. Factor analysis yielded three distinct levels of abnormalities: semantic, poverty and general. The diagnostic significance for CLANG has been suggested (Ceccherini-Nelli and Crow, 2003). The present study aimed to explore the relationship between language disorder and cognition in a sample of first episode schizophrenic patients. Methods 45 first-episode schizophrenic patients (DSM-IV) in Hong Kong, were recruited at the time of their illness presentation (drug naïve). The mean age was 25 sd 8.9), mean education was 11.4 years (sd 2.57). Cognitive measures included IQ, verbal fluency, letter number span, visual production, stroop, logical memory, trail making, six element test and Wisconsin Card Sorting Test (WCST). Results Stepwise linear regression analyses were computed for each of the CLANG dimensions. "Semantic" dysfunctions are associated with trail making B ($p<0.001$), WCST perseverative response ($p=0.009$) and Hayling completion test error ($p=0.019$), with an r-square of 0.514. "poverty" was significantly associated with Hayling completion test error ($p<0.001$), WCST perseverative response ($p=0.01$) and Stroop word error ($p=0.013$) with an r-square of 0.478. The CLANG "general" was associated only with the trail making version B ($p=0.01$) with an r-square of 0.12. Conclusion Using the CLANG we captured different dimensions of language disorganization. We demonstrated each of these dimensions have distinctive cognitive correlates. Reference Ceccherini-Nelli, Alfonso. Crow, Timothy J. (2003) Disintegration of the components of language as the path to a revision of Bleuler's and Schneider's concepts of schizophrenia. Linguistic disturbances compared with first-rank symptoms in acute psychosis. British Journal of Psychiatry. 182:233-40 Chen EYH, Lam, LCW, Kan CS, Chan CKY, Kwok CL, Nguyen DGH, Chen RYL (1996) Language disorganization in schizophrenia: validation and assessment with a new clinical rating instrument. The Hong Kong Journal of Psychiatry, 6(1), 4-13.

NEUROLOGICAL SOFT SIGNS AND MINOR PHYSICAL ANOMALIES IN PATIENTS WITH SCHIZOPHRENIA, THEIR FIRST-DEGREE BIOLOGICAL RELATIVES, AND NON-PSYCHIATRIC CONTROLS

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Objective: This study hypothesized that: (1) the mean neurological soft sign (NSS) score would be greater in patients with schizophre-

nia than in controls, and that first-degree relatives of patients would have an intermediate mean NSS score; (2) the mean minor physical anomaly (MPA) score would be greater in patients than controls, but that relatives would have a mean score similar to controls; and (3) NSS scores and MPA scores would be independent. The study also sought to confirm that NSS would be associated with negative and disorganized symptoms of schizophrenia, whereas MPAs would not be associated with symptom domains. Method: Forty-one patients with schizophrenia and related psychotic disorders, 27 first-degree relatives, and 38 non-psychiatric controls were assessed. Measurements included the Neurological Evaluation Scale, a structured examination for MPAs, and the Positive and Negative Syndrome Scale in patients. Analyses accounted for clustering within families. Results: NSS were greater in patients than in controls, and first-degree relatives had an intermediate NSS score. MPAs were greater in patients than controls, but first-degree relatives had a mean MPA score similar to controls. NSS and MPAs were not associated. In patients, NSS were associated with negative and disorganized symptoms, whereas MPAs were not. Conclusions: These findings suggest that NSS and MPAs represent two quite distinct markers of risk for schizophrenia. Future research on multivariable risk prediction models may benefit from the use of somewhat independent risk markers or endophenotypes that stem from genetic factors (such as NSS), as well as markers related to environmental/developmental influences.

BELIEFS ABOUT HEARING VOICES IN PSYCHOTIC AND MENTALLY HEALTHY RELIGIOUS GROUPS

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The study investigates factors influencing the subjective experience of hearing voices in terms of phenomenology, meanings attributed to the experience arising from religious beliefs and the support/acceptance of others. A comparison study collected data from i) mentally healthy Christians hearing voices, ii) UK mental health patients hearing voices with no religious beliefs, and iii) as for ii) but with Christian beliefs. Subjective experiences of hearing voices were assessed using self-report questionnaires replicating research by Davies et al (2001). Beliefs about hearing voices and their emotional and behavioural consequences were explored using a semi-structured interview based on the Assessment of Voices Schedule (Chadwick and Birchwood 1994) and adapted to explore support/acceptance of others. Voices heard by the three groups were not distinguishable by phenomenological characteristics alone, although voices were heard less frequently by mentally healthy Christians. The experiences of mentally healthy Christians were significantly more positive than those of patient groups, although the experiences of Christian patients were more positive than those of non-religious patients. The meanings attributed to hearing voices differed between the three groups. In both Christian groups, voices were interpreted in line with Christian beliefs, but the interpretations of mentally healthy Christians were invariably positive, whereas Christian patients made both positive and negative interpretations. Although religious interpretations did not increase control over the voices per se, mentally healthy Christians perceived the voices' power as benevolent and authoritative and reported greater acceptance of their experiences. Mentally healthy Christians also experienced greater levels of social support than patient groups. Cognitive models regard the negative cognitive interpretation of voice hearing to be central to a negative experience. Religious belief however, provides a pervasive cognitive belief system that was hypothesised to mitigate against negative interpretations. Religious beliefs did not mitigate against all negative interpretations, but did offer more protection than having no religious beliefs at all.

PSYCHOPATHOLOGICAL DIMENSIONS IN THE AESOP FIRST ONSET PSYCHOSIS STUDY

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There is growing evidence that psychotic symptoms segregate into psychopathological dimensions. Previous studies on symptom dimensions have often used relatively small samples of patients with chronic psychosis. We investigated underlying psychopathological dimensions in a large epidemiological sample of patients with first onset psychosis and examined the association of these dimensions with demographic and clinical variables. We recruited 536 patients as part of a multicentre, population based, incidence study of psychosis. A Principal Axis Factor analysis was performed on symptom scores, using Varimax rotation. The relationship between dimension scores and specific variables was then examined. Factor analysis gave rise to a pentagonal solution of manic, reality distortion, negative, depressive, and disorganisation symptoms, accounting for 47% of total variance. Manic dimension scores were associated with a shorter duration of untreated psychosis ($r=-.23$, $p<0.01$), scores for the reality distortion with longer duration of untreated psychosis ($r = .14$, $p=0.002$) whereas negative dimension scores were significantly associated with being male ($Z=-2.55$, $p<0.01$) and an insidious onset of psychosis ($Z=-2.03$, $p<0.04$). Conversely, manic dimension scores were associated with an acute onset ($Z=-3.39$, $p<0.01$). Associations between dimensions and various social variables fell short of statistical significance, but trends were observed for a relationship between neurological soft signs and negative dimension scores ($p=0.06$), and higher reality distortion scores ($p=0.07$). The pattern of item segregation indicates that a dimensional structure previously reported in patients with chronic psychosis emerges even at the time of first onset of psychosis. Furthermore, these dimensions show significant associations with socio-demographic and clinical parameters, suggesting that a dimensional approach may play an important role in deconstructing psychoses.

LIFE EVENTS AND HIGH TRAIT REACTIVITY TOGETHER PREDICT SYMPTOM INCREASES IN SCHIZOPHRENIA

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Purpose: Schizophrenia patients as a group become more symptomatic in response to stressful life events. Some patients appear to be more vulnerable than others in this regard. The present study was part of a series of studies investigating predictors of differences among patients in symptom exacerbation in response to stressful life events. Methods: Longitudinal data was collected from twenty-five outpatients with schizophrenia or schizoaffective disorder. At the initial assessment, symptom severities were rated using the PANSS, and patients completed a self-report measure of trait sensory and emotional reactivity. At a follow-up session nine months later, stressful life events were assessed for the month immediately preceding the

follow-up session, and patients' symptoms were rated again. Two-way ANOVAs were conducted to assess interactions between high vs. low trait reactivity and presence vs. absence of objectively-rated independent stressful life events in the prediction of symptom changes over time. Results: In the prediction of increases of the core psychotic symptoms of delusions and hallucinations, there was a marginally significant main effect of presence of an independent stressful life event (p = .07), a significant main effect of high trait reactivity (p = .007), and most importantly, a significant interaction effect between life events and reactivity (p = .04). Changes in negative symptoms were not significantly related to life events or trait reactivity, nor were changes in emotional symptoms. Conclusions: These findings support the idea that individual differences in trait reactivity in patients influence the degree to which their psychotic symptoms will be exacerbated by stressful life events. This work was supported by an Independent Investigator grant from NARSAD and by NIMH.

SELF RATING OF APATHY IN FIRST EPISODE PSYCHOSIS

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Negative symptoms are assessed mostly through observation. In order to more fully understand the nature of the different negative symptoms, comparison between patient's rating and staff rating of symptoms can be of importance. The 55 first episode psychosis patients (mean age 27 SD+/-6.8, 53% male, 34 weeks (median) duration of untreated psychosis (DUP), DSM-IV schizophrenia spectrum disorder n = 32, major depression with psychosis n = 8, psychosis nos n = 15) in the ongoing multi-cite Norwegian TOP Study, were given the self fill out version of the Apathy Evaluation Scale (AES-S). The self fill out version has identical questions as the clinical/ research version (AES-C) where these symptoms are evaluated by an external rater. Both forms showed good psychometric properties with Cronbach`s alfa AES-S = .883, and AES-S =.904. A score of 34 or more is considered as being apathetic. Results: The mean AES-S score was 39.8 (SD +/- 9.5) for the whole group, which was not significant different from the clinician mean score of 40.7 (SD+/-9.9). Correlation between the AES-S and AES-C were high (r=.67, p<0.01). Patients diagnosed with schizophrenia spectrum disorder scored the level of apathy (M=40.2 SD+/-8.9) significantly lower than the researcher (M=43.4 SD+/-9.0; t(31)-2.2, p<0.03) with a moderate to large effect size (eta squared 0.1). For the two other diagnostic groups, major depression with psychosis: (AES-S:M=46.0, SD+/-9.1,AES-C:M=42.8, SD+/-8.1,) and psychosis nos:(AES-S:M=35.3,SD+/-9.3, AES-C: M=33.7, SD+/-9.9). There were no statistical differences between the patient score and staff score There was a significant difference (F(2.52)=3.75, p<.03) in mean score of AES-S between the diagnostic groups of moderate to large effect size (eta squared 0.12), the difference being of significance between the psychosis nos (M=35.3 SD +/-9.5) and major depression with psychosis (M=46.3,SD+/-8.9). These results show that patients with schizophrenia spectrum disorder asses their level of apathy significantly different, and lower, than other patients with a first episode psychosis. The difference is not due to a particularly high mean level of apathy, since the major depression group has similar levels of apathy as the schizophrenia spectrum group, but rate their level of apthy similar to the staff. This supports results that have linked apathy to lack of insight as a specific feature for the schizophrenia spectrum disorders.

CHILDHOOD BEHAVIOR, DEVELOPMENTAL MILESTONES, AND SCHIZOPHRENIA-SPECTRUM SYMPTOMATOLOGY: AN INVESTIGATION OF PSYCHOMETRICALLY IDENTIFIED PUTATIVE SCHIZOTYPES

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Premorbid factors associated with the development of schizophrenia have been examined utilizing genetic high risk, retrospective, or cohort methodologies. The present study sought to investigate the relationship between childhood abnormalities of development and behavior in individuals identified using the psychometric high-risk paradigm. This approach involves the use of self-report measures of personality characteristics believed to be related to increased risk of schizophrenia. Social anhedonia, considered a defining feature of schizophrenia, has been previously shown to be a promising predictor that may identify at-risk individuals. It was hypothesized that social anhedonics would have significantly more childhood behavior problems and developmental milestone delays than controls, and that those anhedonics with greater childhood problems and developmental delays would display elevated levels of schizophrenia-spectrum symptoms. The study utilized a representative community sample selected from 2,226 18-year olds who completed a screening packet containing the Revised Social Anhedonia Scale (RSAS; Eckblad et al., 1982). Recruited individuals were identified by elevated scores on the RSAS (N =86) and matched with non-anhedonic controls (N=88). Both probands and mothers of the probands were contacted by mail to participate. Mothers were asked to complete a modified retrospective Child Behavior Checklist (CBCL; Achenbach et al, 1991) for each of three age ranges (0-5, 6-12, 13-8), and questions concerning the age of attainment for six developmental milestones. Probands were asked to complete a modified retrospective version of the Youth Self Report form (YSR; Achenbach et al, 1991) for two age ranges (6-12, 13-18). Examining proband reports (N=70), social anhedonics endorsed greater internalizing, thought, and attention problems than controls. No significant group differences emerged from mother ratings (N=50), however there was a trend for increased internalizing problems (d=.59) and delayed walking (d=.51) in the anhedonic group. For social anhedonics, proband and mother rated childhood behavior problems correlated significantly with independent clinician-rated schizophrenia-spectrum symptoms, assessed when probands were 18 years old. These findings indicate the presence of childhood behavior problems in social anhedonics and demonstrate an association between these early behavior problems and current clinical symptoms within the putative high-risk group.

PHENOMENOLOGY OF BIPOLAR DISORDER: A VIEW FROM THE 21ST CENTURY

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With the discovery of lithium carbonate treatment of bipolar disorder in the middle of the 20th Century, our field entered a period of

complacency in which we essentially stopped thinking about either its phenomenology or its treatment. With the 1990's came the recognition that bipolar disorder was anything but a problem solved. Rather, even with apparently adequate treatment, the most common scenario was one of repeated episodes and chronic dysfunction. This change of view led to an explosion of research on both pharmacologic and psychotherapeutic interventions for bipolar disorder and a reconsideration of its phenomenology. First, there is now general agreement that rather than being neatly divided into the clear manic and depressive phases described by Kraepelin, bipolar disorder is typically characterized by long periods of subsyndromal depression punctuated by episodes that are almost always mixed to a greater or lesser degree. Second, we now recognize that individuals with this illness cannot be grouped neatly into psychotic and non-psychotic subgroups. Rather, psychosis in bipolar disorder appears on a continuum from, for example, mildly unrealistic thinking about one's abilities and objectives or mild forms of religious preoccupation to clear delusions of grandeur or extreme paranoia. Third, in contrast to the romanticized notion that most individuals with manic-depressive illness are highly functioning geniuses when not acutely ill, we now know that many patients with bipolar disorder suffer from pronounced cognitive impairment, much of which probably went unrecognized in the past because of the relatively high level of social skills that seems to characterize sufferers from this illness. This presentation will focus on the evidence for these assertions and on new clinical approaches to addressing these recently recognized complications of bipolar illness.

EMOTIONAL REACTIVITY TO DAILY LIFE STRESS IN BORDERLINE PERSONALITY DISORDER AND PSYCHOTIC DISORDER

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Psychotic experiences are common in borderline personality disorder. It is, thus, attractive to hypothesize common etiological mechanisms underlying psychotic disorders and borderline personality disorder. Sensitivity to daily stress has been reported to be an underlying mechanism for psychosis. The current study compared emotional reactivity to daily life stress in patients diagnosed with psychotic disorders, borderline personality disorder and healthy control subjects. Patients with borderline personality disorder (n=55), patients with a psychotic disorder (n=42), and healthy controls (n=49) were studied with the Experience Sampling Method (a structured diary technique assessing current context and mood in daily life) to assess: 1) appraised subjective stress related to daily events and activities; and 2) emotional reactivity conceptualised as changes in positive (PA) and negative affect (NA). Multilevel regression analysis revealed that subjects with borderline personality disorder reported the strongest emotional reactivity to daily life stress, reflected in an increase in NA and a decrease in PA (for NA: B= 0.13 (SE=0.01), for PA: B= -0.18 (SE=0.01)); and patients with psychotic disorder reported intermediate levels of emotional reactivity (for NA; B= 0.09 (SE=0.01), for PA: B=-0.14 (SE=0.01), both significantly larger compared to healthy controls (for NA: B= 0.02 (SE=0.01), for PA: B=-0.08 (0.01)). The results suggest that emotional reactivity to small disturbances in daily life may be a common underlying mechanism related to both psychotic and borderline personality disorder, but is most pronounced in borderline personality disorder.

EARLY MOTOR AND SOCIAL DEVELOPMENT IN CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA: RELATIONSHIP WITH COGNITIVE FUNCTION AND NEGATIVE SYMPTOMS

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The presence of early developmental abnormalities has long been associated with the later development of schizophrenia. These include mild delays in gross and fine motor function and subtle differences in social cognition. Since there is considerable heterogeneity in the presence of these developmental abnormalities, it is our hypothesis that individuals with greater delays in gross and fine motor function and social development within the first 4 years will show an earlier decline in cognitive function, an earlier age of onset of psychotic symptoms, and greater negative symptoms. Forty-three children and adolescents with a non-affective psychotic illness (mean age of 14.9 years, SD 2.99) were recruited for the study. Diagnoses were performed using the Kiddie-SADS-PL and 19 subjects had a diagnosis of schizophrenia, 7 had schizoaffective disorder, 3 had schizophreniform disorder, and 14 had psychosis NOS. A retrospective timeline was constructed during the interview that assessed the development of psychotic symptoms, cognitive decline, and negative symptoms. In addition, parents completed a modified version of the Yale Children's Inventory that assessed developmental milestones. The clinical information was obtained separately from both the parent and the child and, when possible, was confirmed by school records or other collateral sources. Data on 40 subjects demonstrated that 24 subjects had significant cognitive decline, 10 had moderate decline, 3 had mild decline, and 3 had no cognitive decline. In addition, 14 subjects had abnormal/delayed development in fine and/or gross motor function or social deficits relating to their relationship with their parents during in the first 4 years of life. The remaining 26 met milestones on time and had no impairment in social interaction. Both cognitive decline and abnormal development are common in children and adolescents with schizophrenia spectrum disorders. We will present the relationship between cognitive decline and negative symptoms against motor and social development. In light of the considerable heterogeneity in the clinical phenomenology of schizophrenia, these results will assist in the better identification of higher risk youth.

DECONSTRUCTING SCHIZOPHRENIA INTO COMPARTMENTS OF COGNITIVE PATHOLOGY

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Cognitive impairment appears to be present in the great majority of patients with schizophrenia and is clearly more common on a cross sectional basis than any of the current A criterion symptoms of the illness. Similar to many other symptoms of schizophrenia, however, cognitive impairment appears, at least on the surface, diverse and multidimensional. In contrast to other symptoms, however, cognitive impairment may require specialized assessments that are not within the realm of most everyday clinicians' competencies. Thus, inclusion of cognitive impairment into the diagnostic criteria would require an additional assessment step not required by any current

criteria and requires then that inclusion of this as a diagnostic criterion have substantial validity. In this presentation, I will review several large sets of data regarding some of the major issues in cognition in schizophrenia. These include the dimensional structure of schizophrenia (is it a global impairment or is there are specific factor structure?), the prevalence of cognitive impairment in schizophrenia (what is the evidence that it is present in so many patients that it is a meaningful diagnostic indicator?), and whether there are certain core deficits that provide differential diagnostic utility. Further, I will link these findings intro current models of the causality of schizophrenia, arguing that cognitive deficits in schizophrenia are a core feature of the illness and that severity of impairment may reflect an element of specificity to schizophrenia as compared to other psychotic disorders.

NIACIN SKIN FLUSH AND ERYTHROCYTE FATTY ACID COMPOSITION IN PATIENTS WITH SCHIZOPHRENIA RELATED PSYCHOSES

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Introduction: Previous studies have investigated niacin skin flush, erythrocyte (RBC) fatty acids (FA) and psychopathology (PANSS) in schizophrenia. However, no study has concomitantly investigated the relation between RBC-FA, niacin skin flush and PANSS. Impaired niacin skin flush in general and lower RBC-arachidonic acid (AA; 20:4ω6) contents have been reported. Skin macrophage AA is a substrate for niacin induced prostaglandin-mediated skin flush. We hypothesized that RBC-AA content is related to niacin skin flush intensity. The relation between psychopathology, RBC-FA and niacin skin flush was also investigated. Subjects and Methods: Blood samples were collected from 36 patients [75% men, median (range) age 33 (18-57) years, median duration of disorder 7 (0-26) years]. The skin test was performed by applying 50 μL of 0.1 M α-methyl nicotinate for 5 min onto the inner forearm skin. Redness was assessed on a categorical scale of 0 to 3. PANSS-scores were obtained. RBC-FA composition was analyzed by gas-chromatography. Results: Compared with controls, patients exhibited impaired flushing [mean (±SD) redness: 1.30 [±0.72] vs. 1.81 [±0.45]; p=0,013], lower (for all p<0.01) RBC-AA, -docosahexaenoic acid (DHA; 22:6ω3), -docosapentaenoic acid (DPA; 22:5ω6), -polyunsaturated FA (PUFA), and higher -monounsaturated and -saturated FA (for both p<0.001). Patients had a median (range) positive PANSS score of 10 (7-24), a negative PANSS score of 10 (7-24), a global psychopathology score of 24 (16-44) and a total PANSS score of 44 (33-79). RBC-AA was unrelated to skin flush (r= -0.131; p=0.445), whereas RBC-PUFA related inversely to flush (r= -0.46; p<0.01). PANSS total- and subscale- scores were unrelated to RBC-PUFA or skin flush. The PANSS-item 'depression' related inversely to RBC-DHA (r= -0.390; p=0.019). Discussion: We did not observe the hypothesized relation between RBC-AA and niacin skin flush. The assumption that FA in skin macrophages are reflected by RBC-FA may be precarious. However, the inverse relation between RBC-PUFA and flush suggests an effect of (some) RBC-FA on skin flush. We could not confirm previously reported relations between PANSS total and subscale scores, RBC-FA and flush. However, the item depression was related to RBC-DHA, which was also found in previous studies. The present study may be limited by the small number of patients and the small variance of symptomatology.

ANHEDONIA IN SCHIZOPHRENIA: WHAT IS THE NATURE OF THIS HEDONIC DEFICIT?

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Anhedonia, the diminished capacity to experience pleasure, is a common, treatment-resistant feature of schizophrenia that is associated with poor community functioning. Recent research findings have raised fundamental questions about the nature of this emotional disturbance. On the one hand, individuals with schizophrenia typically report lower levels of pleasure in their daily lives than non-patients, yet on the other hand, they report experiencing levels of pleasant emotions that are similar to non-patients in laboratory studies that involve direct exposure to emotionally evocative stimuli. This presentation will describe a series of studies aimed at reconciling this discrepant set of findings. Guided by neurobehavioral models that include separable components of hedonic experience, we have examined the hypothesis that schizophrenia is characterized by impaired appetitive pleasure (derived from anticipating enjoyable experiences) but intact consummatory pleasure (experienced while directly engaged in enjoyable activities). Data will be presented from studies using a recently developed self-report trait measure and the experience sampling method that supports this hypothesis. On-going efforts to further evaluate the integrity of consummatory and appetitive aspects of pleasure using electrophysiological paradigms and a new interview-based negative symptom rating scale will also be discussed. Clarification of the nature of anhedonia in schizophrenia may help to identify novel, functionally relevant treatment targets.

ENDOCRINOLOGICAL PROFILE OF PATIENTS WITH FIRST EPISODE TREATMENT NAIVE SCHIZOPHRENIA

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Patients with schizophrenia are at a greater risk of diabetes mellitus than the general population. The exact reasons for this are not clear. Some of the known risk factors for the development have not been examined systematically in patients with schizophrenia. In order to control for the effects of medication, we examined fasting insulin, leptin, ghrelin and adiponectin in patients with first episode neuroleptic naïve schizophrenia. Thirty patients with first episode neuroleptic naïve schizophrenia were matched with fourteen healthy controls on age and sex. Blood samples were drawn on all participants after an overnight fast. Patients with first episode neuroleptic-naïve schizophrenia had significantly greater fasting insulin (p= 0.04) and lesser adiponectin levels than matched controls (p=0.04). Ghrelin and leptin levels were comparable between the two groups. Regardless of their use of antipsychotic medications, patients with schizophrenia seem to be at increased risk for type 2 diabetes mellitus. Converging data suggests a broad pattern in which hormones under sympathetic control are increased and hormones under parasympathetic control are decreased. A better understanding of this phenomenon requires further studies. This work was supported by funds received from NIMH grants MH45156,

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	Patients	Controls	p vaue
Age	22 (5.5)	21 (3.6)	.40
Race	W 18 AA 10 A1 PI 1	W11 AA 1 A2 PI 0	.15
Insulin	19.8 (14.4)	12.8 (5.2)	0.04
Adiponectin	8.9 (3.5)	11.9 (4.5)	0.04
Ghrelin	806.9 (281.2)	869.5 (306.2)	.55
Leptin	11.0(8.9)	8.9 (6.4)	0.49

SCHIZOPHRENIA-LIKE BEHAVIORAL AND MOLECULAR SIGNATURES IN RATS FOLLOWING DEVELOPMENTAL STRESS EXPOSURE

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Environmental factors play a well-documented role in the etiology of schizophrenia. Epidemiological studies defined the late first and second trimesters of pregnancy, as a period of increased vulnerability for schizophrenia in the offspring should there be exposure of the mother to a stressful occurrence. Using this knowledge, we exposed pregnant female rats to an unpredictable stress regimen during the final week of gestation. This period of rat development overlaps with human brain development during the late first and second trimesters of pregnancy. The offspring were evaluated prior to and after puberty for behaviors related to aspects of the schizophrenia phenotype including prepulse inhibition, N40 gating, psychostimulant-induced locomotion, object and social recognition, and social withdrawal. These tests revealed that rats exposed to stress during a vulnerable period of pregnancy have enduring deficits in gating sensory information, hyperdopaminergia, cognitive impairments and social deficits that parallel aspects of schizophrenia-related behavioral changes. In addition, molecular phenotyping of these rats identified underlying changes in glutamatergic function in the frontal cortex, as well as changes in presynaptic and postsynaptic transmitter release mechanisms similar to expression differences reported in the schizophrenic brain. This animal preparation is being used to evaluate novel antischizophrenic mechanisms to establish not only the face and construct validity of the model but its predictive validity, as well.

CHILDHOOD TRAUMA AND INCREASED STRESS-SENSITIVITY IN PSYCHOSIS: AN EXPERIENCE SAMPLING STUDY

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Increasing epidemiologic evidence suggests that traumatic experiences in childhood are associated with the development of clinical and subclinical psychosis in adulthood. However, the mechanism through which trauma leads to an increased risk for psychosis remains unclear. Previous studies of our group (Myin-Germeys, van Os et al. 2001) have demonstrated that increased sensitivity to daily life stress is part of the underlying vulnerability for psychosis. The current study hypothesises that early trauma increases the risk for psychosis through sensitizing people for the small stresses of daily life. The sample consisted of three groups: patients with a diagnosis of psychotic disorder (n = 54), their first degree relatives (n = 50) and healthy control subjects (n = 41). The Experience Sampling Method (ESM; a structured diary technique) was used to assess stress-reactivity in daily life defined as (1) emotional reactivity (increase in negative affect) and (2) psychotic reactivity (increase in psychosis intensity) in reaction to stress. Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ). Multilevel analyses revealed significant three-way interaction effects between group, stress and childhood trauma on both NA ($\chi 2(2)=13.50$, $p=0.0012$) and psychosis intensity ($\chi 2(2)=27.69$, $p=0.0001$), indicating that the effect of trauma on stress-sensitivity, both in terms of emotional and psychotic reactivity, was significantly larger in the patients compared to the relatives and controls. Similar effects were found for all trauma dimensions (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect). The results suggest that a history of childhood trauma sensitizes people to the stresses of normal life resulting in stronger emotional and psychotic reactions to stress. However, this sensitization process is most pronounced in subjects with an increased vulnerability for psychosis. Dr. Myin-Germeys was supported by a 2003 Narsad Young Investigator Award and a Veni Grant from the Dutch Medical Council. References Myin-Germeys, I., J. van Os, et al. (2001). "Emotional reactivity to daily life stress in psychosis." Archives of General Psychiatry 58(12): 1137-44.

IS REACTIVITY TO STRESS AN ENDOPHENOTYPE FOR PSYCHOSIS? FINDINGS FROM A GENERAL POPULATION TWIN STUDY

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Several studies suggest that emotional reactivity to daily life stress constitutes an endophenotype for psychosis. These studies, however, did not resolve the issue of contamination by current (sub)-clinical psychotic experiences. The current study, therefore, used a general population twin sample to examine whether emotional experiences in reaction to stress can truly be considered an uncontaminated and unconfounded indicator of the risk for psychosis. The sample consisted of 289 female, general population twin pairs (age 18-46). The Experience Sampling Method (ESM – a structured diary technique) was used to assess mood (negative affectivity or NA) in reaction to stress in daily life. Sub-clinical psychotic experiences were obtained with the Community Assessment of Psychotic Experiences (CAPE). Cross-trait, within twin multilevel linear regression analyses were conducted to investigate, within subjects, the association between the positive and negative dimension of the subclinical psychosis phenotype on the one hand and stress sensitivity on the other. Cross-twin, cross-trait associations were established between stress reactivity measured in the proband and the risk for psychosis, as indicated by a history of sub-clinical

psychotic experiences in the co-twin. Cross-trait, within twin analyses displayed significant interaction effects between the positive and negative dimension of the subclinical psychosis phenotype on the one hand and stress on the other on NA (β=0.016 (SE=0.002), p<0.001 and β=0.013 (SE=0.002), p<0.001, respectively). In addition, cross-trait, between twin analyses showed a significant interaction effect of the co-twin positive and negative psychosis phenotype and stress sensitivity in the proband (β=0.005 (SE=0.002), p<0.02 and β=0.011 (SE=0.002), p<0.001, respectively). These results, thus, confirm that increased vulnerability for psychosis is associated with increased emotional reactivity to stress in daily life. More importantly, the results suggest that stress sensitivity may be an unconfounded and uncontaminated endophenotypical marker for psychosis.

EXPERIENCE AND EXPRESSION OF EMOTION IN SOCIAL ANHEDONIA: AN EXAMINATION OF SOCIAL AFFILIATIVE STATE IN SCHIZOTYPY

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Social anhedonia is an important feature of schizophrenia and it is a promising indicator of schizotypy. Although social anhedonia is defined as deficit in the capacity to experience pleasure, little is actually known about the affective correlates of social anhedonia. Prior laboratory research is limited in that no prior study has used affiliative social stimuli in examining affective reactions associated with anhedonia. This study sought to extend prior research through an examination of the expression and experience of emotion in social anhedonics by using a novel social affiliative film stimulus. We hypothesized that social anhedonics would demonstrate reduced emotional expressivity as well as reduced positive affect in response to the affective stimuli, especially in response to the social stimulus. After screening a large sample of female undergraduate students (N = 1,085), a cohort of psychometrically identified social anhedonics (n = 34) and normally hedonic controls (n = 45) participated in laboratory assessments involving trait affectivity, self-reported dispositional emotional expressiveness, and the expression and experience of emotion in response to neutral, non-affiliative (i.e., comedy) and affiliative film clips. Results showed that social anhedonics had lower trait positive affect compared to controls, but there were no group differences in trait negative affect. At baseline, social anhedonics reported lower state positive affect and less warmth and affection compared to controls, but there were no group differences in state negative affect. Social anhedonics also reported the disposition to be less emotionally expressive compared to controls. Consistent with their reports of attenuated emotional experience and expression outside of the laboratory, social anhedonics reported less positive affect and displayed less positive facial expressions in response to the affective stimuli in the laboratory. There were no group differences in warmth and affection across the films. Contrary to expectations, social anhedonics demonstrated diminished positive emotional responding across both affiliation and comedy films. Whereas a disjunction of experience and expression of emotion had been reported for individuals with schizophrenia, this study found synchronicity in the diminished experience and diminished expression of positive emotions among non-clinical participants with social anhedonia. Implications will be discussed.

AN ANALYSIS OF COMMON ENDOPHENOTYPIC AND GENETIC CHARACTERISTICS OF NEGATIVE SYMPTOMS SPECTRUM DISORDER: AUTISM, ASPERGER'S DISORDER, AND SCHIZOPHRENIA: A PROPOSED MODEL FOR GENETIC INVESTIGATION FOR LINKING CANDIDATE GENE POLYMORPHISMS TO COMMON ENDOPHENOTYPES ACROSS DIFFERENT DISORDERS

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Although the psychiatric literature to date has referred to "negative symptoms" almost exclusively within the context of schizophrenia, there seem to be a number of similar social deficits and cognitive/behavioral stereotypies in autism, Asperger's disorder, schizoid personality disorder, and schizotypal personality disorder as well. With the working hypothesis that these disorders may have overlapping genetic diatheses that could contribute to overlapping endophenotypes, we first systematically compared the DSM-IV diagnostic criteria for the different diagnoses to identify common endophenotypes. The results indicated that all of the disorders present with receptive and expressive deficits of emotion in social context as well as cognitive and behavioral stereotypies. Furthermore, they present in familial patterns, strongly suggesting a genetic cause or predisposition. A review of the literature indicated substantial information was available for genetic markers in schizophrenia, autism and Asperger's syndrome, but not for schizoid and schizotypal personality disorders. We mapped all of the gene markers that had been reported to have significant linkage disequilibrium across the three disorders and found multiple regions that suggested overlap (Xp22.33, Xq13,1q21-22, 3p14-21, 4p15, 4q31, 6q16, 7q31, and 13q14-21). The results for the X chromosome are particularly intriguing in light of the male predominance of Asperger's and autism as compared to schizophrenia. Moe in depth information is needed since all of the studies classified linkage disequilibrium with the disorders as a whole and not by their endophenotypes. The results in sum suggest that cross-disorder endophenotyping of specific symptoms should receive more emphasis in whole genome mapping work to identify particular regions of the genome that may be associated across different disorders with common endophenotypic symptomatology. The goal of this work was to propose a new technique for identifying potential susceptibility and protective genetic loci for disorders with similar endophenotypes to use as diagnostic and therapeutic targets.

EMOTIONAL RESPONSE TO THREATENING STIMULI IN PSYCHOSIS AND PHOBIA

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Our aim is to study threat experience in each group,depending on the kind of stimuli and comparing the disorders in order to elucidate the possibility of different underlying mechanisms.24 psychotic,24 phobic patients and 24 controls completed a task consisting on 80 images:40 emotionally neutral(20 human and 20 non human) and 40

threatening (20 human and 20 non human).Each subject answers 2 questions about threat (arousal) and pleasantness(valence) for each image.We found that the absolute valence of negative emotion in the Schizophrenia group was significantly less negative than in the control and anxiety group. There is a correlation between psichoticism and threat perception as well as between psichoticism and pleasantness, only for the psychotic group. The phobic group shows significantly a lower punctuation for pleasantness specially with human images.These results suggest that schizophrenic patients might suffer a decreased capacity to experience threat while phobic patients might suffer an enhanced experience of threatening emotions. However it is possible that the results were influenced by other reasons such as the fact that it was a too heterogeneous group of schizophrenics or the difficulty they found in understanding the task because of their cognitive deficits. Moreover, they are receiving an antipsycotic treatment, and that diminishes their salience. Our results support previous findings of Green and Phillips,2004 * about attentional bias and those of the importance of arousal for threat response in paranoid subjects(Lee,2006,*).The result shows a different emotional response which leads to a possible different underlying mechanism that should be studied, and it could be nuclear for their insecurity and vulnerability.This paradigm and their results may have important implications to neurobiological and evolutive aspects of these disorders and their psychological therapy. * Green,M:J.,Philips,M.L.,2004 Social threat perception and the evolution of paranoia *Lee,Kim.,2006 Aberrantly flattened responsavityto emotional pictures in paranoid schizophrenia

NEUROLOGICAL SIGNS AND SCHIZOPHRENIA: RELATION TO COGNITION

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Defining the significance of neurological abnormalities in schizophrenia has advanced considerably over the last two decades. Neurological signs are common, associated with a poor response to treatment, more severe negative symptoms, greater cognitive impairment, more pronounced functional compromise, and poor outcome. But, knowledge of the specificity and nature of these relationships remains limited. This presentation will focus on what neurological signs tell us about cognitive changes associated with schizophrenia. Issues of measurement, connection of neurological signs to psychopathology, and the broadening array of detection techniques will be discussed. Lack of a clear theoretical model for neurological signs is one obstacle to the creation of an adequate theory of schizophrenia. Candela S, Manschreck T (2003). Neurological soft signs in schizophrenia: Research findings and clinical significance. Psychiatric Annals. 33: 157-166.

RECOVERY FROM SCHIZOPHRENIA – A SYSTEMATIC REVIEW AND META-ANALYSIS

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Recovery in schizophrenia is still a poorly understood and controversial issue, the aim of this systematic review was to collate studies related to this topic and to synthesize these data with meta-analytic techniques. We identified potentially relevant studies from seven electronic databases and from manual literature searching. As a title search we used keywords "schizo* or psychotic or psychos*s" and "recovery or remission or outcome* or course or prognosis or follow-up or longitudinal". The second search in abstracts included keywords "schizophrenia" and "recovery or remission". We included studies that were in English, presented primary data, not therapy/drug trials/interventions, had at least 15 subjects and had follow-up data for at least two years. Recovery needed to be measured on both clinical and social dimensions. All abstracts and articles were critically analysed by two of the authors. Currently, we have examined all studies published between 1995-2004 and a random sample of studies outside this range. The search identified 4234 unique potentially relevant articles. After further screening, we identified 670 articles for inclusion. So far all the studies published 1995-2004 (N=210) and a random sample (N=100/460, 28%) of other articles have been evaluated. Only twelve articles have met all our criteria. Based on these studies, between 2% to 25% of the subjects 'recovered' (mean 14.7%). In the five older studies (published 1943-1980) on average 20.6% of the subjects recovered, while in the seven more recent studies (published 1995-2005), only 10.6% of the subjects recovered (meta-regression, z test 2.73, p=0.006). Based on these findings, the recovery from schizophrenia seems to be uncommon. The proportion of patients meeting recovery criteria appears lower in recently published studies. There is relatively little primary data on recovery in schizophrenia. Various conceptual and methodological pitfalls cause challenges when studying the course and recovery in schizophrenia. Thus, more accurate reporting of multidimensional recovery is needed.

RESOLUTION OF DELUSIONS IN FIRST EPISODE OF SCHIZOPHRENIA: A GRADUAL PROCESS

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Background and Methods: Understanding the process of change of delusional states in first episode of schizophrenia is instrumental in setting appropriate expectations and targeting treatment. We looked at patients enrolled in a first episode of schizophrenia study in which they were randomly assigned to olanzapine or risperidone. All subjects received psychosocial treatment including psychoeducation, supportive and cognitive therapy. Ratings were made by a highly trained clinical assessor using the Schedule for Affective Disorders and Schizophrenia Change Version with psychosis and disorganization items (SADS-C+PD) (Spitzer & Endicott, 1978) during the first 12 months of treatment. We categorized delusions as (1) full delusions; (2) residual delusions; and (3) partial delusions. Full delusions were defined as clear false fixed beliefs; residual delusions were defined as delusional material believed to have occurred in the past but no longer happening; and partial delusions were defined as continuing to think of delusional material but subject questions the veracity of the delusion. Results: Fifty-six subjects met criteria for full delusions at study entry and had assessments over a one-year period. Subjects were an ethnically diverse group of patients, 73% male, ages 16-40, mean age 23. At the end of the first 16 weeks of treatment 20 (36%) subjects had no delusions, 11 (19%) had full delusions, and 25 (45%) had residual delusions. At 24 weeks 28 (50%) had no delusions, 9 (16%) had full delusions, and 19 (34%) had residual delusions At 52 weeks 32 (57%) had no delusions, 9 (16%) had full delusions, and 15 (27%) had

residual delusions. Conclusion: Many patients with first episode of schizophrenia experience a gradual resolution of delusions. Recognition of this slow process advises of the necessity of psychosocial—along with medication therapy—to support patients over a lengthy period of recovery. For first episode patients discovering they have a serious mental illness causing their mind to "play tricks" on them may destabilize their sense of self and cause feelings of shame and hopelessness leading to depression and anxiety. During this period, psychoeducation, supportive therapy and cognitive therapy can help patients challenge delusional thinking, improve coping skills, and decrease feelings of hopelessness and shame. Additional targeted interventions may also be required to improve medication adherence and decrease substance use. (MH60004)

EMOTIONAL REACTIVITY TO STRESS: THE MECHANISM UNDERLYING POSITIVE SYMPTOMS OF PSYCHOSIS

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Background: It is attractive to speculate that different etiological mechanisms may underlie the extensive clinical heterogeneity in schizophrenia that can be reduced to two main types: a good outcome type with higher levels of positive symptoms and a more chronic type with high levels of negative symptoms. Previous studies have demonstrated that altered stress-sensitivity is a putative endophenotype of psychosis that is independent from cognitive impairments, an endophenotype that is often associated with negative symptoms. The current study, therefore, will investigate whether altered stress-sensitivity is associated with positive symptoms, both at the clinical and subclinical level. Methods: The sample consisted of 55 patients with a diagnosis of psychotic disorder, 53 of their healthy first-degree relatives, and 42 healthy control participants. Positive and negative psychotic symptoms in the patients were measured with the Comprehensive Assessment of Symptoms and History (CASH). Subclinical psychotic experiences in relatives and controls were assessed with the Community Assessment of Psychotic Experiences (CAPE). The Experience Sampling Method (a structured diary technique) was used to assess stress reactivity defined as increases in negative affect (NA) in reaction to stress in daily life. Results: Multilevel linear regression analyses revealed that the positive symptoms significantly interacted with stress in their effect on NA, both at the clinical (β=0.06 (SE=0.02), $p<0.01$) and subclinical level (β=0.01 (SE=0.00), $p=0.02$). For the negative symptoms, an inverse effect was found with stress on NA in the patients (β= -0.05 (SE=0.02), $p<0.01$). In contrast, at the sub-clinical level a positive interaction effect was found with the negative symptom dimension (β=0.01 (SE=0.00), $p<0.01$). Conclusions: The results provide support for the hypothesis that increased stress-sensitivity is specifically associated with positive symptoms. The positive association between subclinical negative symptoms and stress-sensitivity might be due to the fact that subclinical symptom dimensions of psychosis are highly correlated. Overall, the current results support the notion that the different subtypes reflect partly independent syndromes caused by partly separable underlying aetiologies reflected in distinguishable endophenotypic pathways. Dr. Myin-Germeys was supported by a 2003 Narsad Young Investigator grant and a VENI-grant from the Dutch Medical Council.

VALIDATING THE CRITERIA FOR REMISSION IN SCHIZOPHRENIA: PRELIMINARY FINDINGS

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Published methods for assessing remission status in schizophrenia are variable and none have been definitively validated or standardized. Andreasen et al (2005) suggest systematic operational criteria using eight PANSS items for which patients must score ≤ 3 (mild) for at least six months. Data from a previously conducted study was analyzed in order to test the validity of this construct. Methods: Using data from a one year, multi-site clinical trial (n=675, Mahmoud et al, 2004) remission criteria were compared to total PANSS scores and other endpoints. Patients in the trial were in "relapse" at baseline using a study definition that included inpatient admission to a psychiatric unit or acute psychiatric care prior to enrollment in the study. Subjects were categorized according to the eight-item remission criteria and analyses were conducted at each time point (cross-sectional) and across time points, applying the temporal component of the remission criteria (longitudinally). Overall psychopathology was assessed using total PANSS scores. Based on findings by Leucht et al., cutoffs of 60 and 75 were compared to remission status. Results: When cross-sectional data was analyzed, remission status was strongly associated with overall psychopathology. At baseline, when all patients were in study-defined relapse, the remission criteria were highly sensitive (sensitivity=0.97), with a positive predictive value of 100%. Compared to total PANSS score of 60 points and other criteria, at time points > 6 months (8 and 12 months) the specificity of the remission criteria was 85%, i.e. of the patients who had a total score >60, 85% were classified as "not in remission." Sensitivity was also very high; 75% of patients with scores of <60 were classified as "in remission." Patients who dropped out of the trial were more likely not to be in remission in their final study visit. Using a longitudinal approach, the likelihood of being in remission at the conclusion of the study for those patients who achieved and maintained remission status over the prior 8 months was approximately nine times greater than for those who did not. Conclusions: These findings indicate that the remission criteria are both sensitive and specific indicators of clinical status. Additional analyses are required to determine if remission status predicts other outcomes, such as employment, independent living, and prognosis.

PSYCHOPATHOLOGY FACTORS IN FIRST-EPISODE AFFECTIVE AND NON-AFFECTIVE PSYCHOTIC DISORDERS

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Since the onset, prevalence, and course of specific psychopathological features rarely have been analyzed simultaneously from the start of dissimilar psychotic illnesses, we compared symptom-clusters in 377 first-episode DSM-IV affective and non-affective psychotic disorder patients hospitalized for first-lifetime primary psychotic illnesses and followed prospectively for ≥2 years. We ascertained initial symptoms from baseline SCID and clinical assessments, applying AMDP and Bonn psychopathology schemes systematically to describe a broad range of features. Final consensus diagnoses were based on intake and follow-up SCID assessments, family inter-

views, and medical records. Factor-analytic methods defined first-episode symptom-clusters (Factors), and multiple-regression modeling related identified Factors to DSM-IV diagnoses and categories (affective, non-affective, or schizoaffective disorders). Psychopathological features were best accommodated by four Factors: I represented mania with psychosis; II a mixed depressive-agitated state; III an excited-hallucinatory-delusional state; IV a disorganized-catatonic-autistic state. Each Factor was associated with characteristic prodromal symptoms. Factors I and III associated with DSM-IV mania, II with major depression or bipolar mixed-state, III negatively with delusional disorder, IV with major depression and negatively with mania. Factors I and II predicted later affective diagnoses; absence of Factor I features predicted non-affective diagnoses, and no Factor predicted later schizoaffective diagnoses. The findings contribute to descriptive categorizations of psychopathology from onset of dissimilar psychotic illnesses. This approach was effective in identifying and subtyping affective psychotic disorders early in their clinical evolution, but nonaffective-schizoaffective conditions appear to be more complex and less stable.

SMOKING AND NEUROPHYSIOLOGICAL MARKERS OF INFORMATION PROCESSING IN SCHIZOPHRENIA

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The primary aim of this study is to characterize and compare smoking habits and patterns of nicotine consumption among patients with schizophrenia and a matched community control sample using a multi-pronged measurement approach, including self-report and biological indexes of nicotine use as well as behavioral measures of smoking topography. Secondarily, this study will test the hypothesis that aspects of nicotine consumption are more closely associated with abnormalities in sensory gating and eye tracking performance among smokers with schizophrenia than smokers in the general population. Participants are currently being recruited from inpatient and outpatient facilities at the Maryland Psychiatric Research Center and from the Baltimore/Washington D.C. community. Preliminary analyses of data collected from 50 smokers with schizophrenia and 10 healthy control smokers provide some evidence to support the primary hypothesis; patients exhibit greater levels of self-reported nicotine dependence on the Fagerstrom Test for Nicotine Dependence and the Nicotine Dependence Symptoms Scale with effect sizes in the small (d = 0.35) and medium (d = 0.52) range respectively. In both groups, self-reported nicotine dependence is significantly correlated with number of cigarettes per day, with patients smoking at a greater rate than comparison controls. Despite the fact that groups do not differ on smoking years, patients exhibit significantly greater blood plasma levels of cotinine, a nicotine metabolite (d = 0.85), and baseline blood plasma levels of nicotine (d = 0.81). Data collected during an ad-libitum smoking session currently suggest that patients smoke at a faster rate with greater puffs per cigarette and greater puff velocity than controls, with effect sizes in the medium range (d = 0.58 to 0.67). Among the patient group, evidence is mounting to support the link between smoking and neurophysiological function, with greater smoking induced increases in plasma nicotine levels significantly correlated with poorer performance on eye tracking and pre-pulse inhibition tasks. Data are currently being collected to investigate whether similar associations occur among smokers in the general population. Preliminary findings thus support the hypothesis that smoking behaviors and nicotine dependence are clinically meaningful to schizophrenia and further investigation may better elucidate the pathophysiological link.

CORRELATES OF CANNABIS USE DISORDERS IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA

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Background: First-episode patients frequently have co-occurring cannabis use disorders, and cannabis use is associated with poor outcomes in first-episode patients. Studies in recent onset schizophrenia have shown differences in sex, premorbid functioning, duration of untreated psychosis, and symptoms between schizophrenia patients with and without cannabis use disorders. Methods: Forty-nine subjects with first-episode schizophrenia and DSM-IV criteria for cannabis abuse or dependence were compared to 53 subjects with first-episode schizophrenia and no cannabis use disorders for: age at the time of study entry, sex, race, education, general premorbid adjustment, age at onset of psychosis, duration of untreated psychosis, baseline severity of illness, positive, negative, depressive symptoms. Statistical significance was defined as a p-value of 0.01 or less. Results: Compared to first-episode patients without cannabis use disorders, first-episode patients with cannabis use disorders had developed psychotic symptoms at a younger age (mean age 20 ± 4 (SD) years vs. 21.8 ± 5 years, t=8.0; p<.01), and were younger at the time of study entry (mean age 22 ± 4 vs. 25 ± 6; t=9.6; p<.01). Patients with cannabis use disorders also were more likely to be male (82% vs. 58%; chi-square = 6.4, p<0.02), had poorer general premorbid social adjustment (t=5.08; p<.03) and more severe delusions (t=0.04; p<.05) at study entry, but these differences did not reach the 0.01 threshold of statistical significance. Conclusion: We found that first episode patients with co-occurring cannabis use disorders develop psychotic symptoms at an earlier age than first episode patients without cannabis use disorders. This early onset of psychosis happens at a critical time for psychosocial and brain development, and may have consequences on the prognosis of the illness. Our results are also consistent with the hypothesis that cannabis precipitates the onset of psychosis in vulnerable individuals.

THEORY OF MIND PERFORMANCE IN INDIVIDUALS PRODROMAL FOR SCHIZOPHRENIA

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Social dysfunction is prevalent in schizophrenia, including its prodrome, and accounts for much of the morbidity of the illness. It is unclear if this social dysfunction is related to social anxiety, social anhedonia or deficits in social cognition. Social cognition can be assessed through measures of Theory of Mind (ToM), or

"mentalizing," for which there are deficits in schizophrenia. However, little is known about the timing of onset of ToM deficits or whether they exist in the prodromal phase. ToM deficits were characterized in a sample of 28 patients, defined as prodromal using the Structured Interview and Scale of Prodromal Symptoms. Patients were characterized as to demographics, prodromal symptom severity and social function (Social Adjustment Scale). Five ToM measures were used to assess varying levels of difficulty: one first order ("What is in the kettle?"; achievable by age 4), two second order ("What does A know about B?"; achievable by age 6), and two "high order" tasks ("Strange Stories Task" (SST) and the "Reading the Mind in the Eyes" ("Eyes") task, which is normally distributed with no ceiling effect). There were 28 prodromal patients (6 female), mean age 19.1 (s.d. 3.8) with mean education of 12.1 (2.9) years, such that all subjects were old enough to perform first and second order ToM tasks without error. Subjects had mean scores of: 5.6 (0.7) of 6 on the first order task; 5.4 (1.3) of 6 and 13.6 (1.1) of 14 on the second order tasks; 31.8 (5.6) of 38 on the SST; and 25.6 (4.5) of 37 on mental state recognition and 35.8 (1.4) of 37 on gender recognition on the "Eyes" task. 25% of subjects made errors on the first order task and respectively 43% and 18% on the two second order ToM tasks. On the SST, errors were most common for double bluff (25% of subjects), contrary emotion (18%), and appearance/reality (14%). On the "Eyes" task, subjects performed at chance level on 6 of the 37 items and on 2 items, only 17% and 39% obtained the correct response. These data provide the first evidence that ToM deficits exist in prodromal patients. The presence of ToM deficits in individuals at risk for schizophrenia with poor social function suggests that ToM may be a trait factor that accounts for social deficits. Data will be presented relating these findings to symptom and function measures.

THE ROLE OF TRAUMA-RELATED INTRUSION IN PSYCHOSIS

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There is growing evidence of phenomenological similarities within the intrusive mental experiences associated with both Posttraumatic Stress Disorder (PTSD) and psychosis. However, although there have been theoretical developments in our understanding of the psychological mechanisms which may be involved in the maintenance of such intrusions, there is currently little understanding of how such mental experiences may be formed within psychosis. Two studies are reported. First, an analogue study which explored vulnerability factors, including measures of schizotypy and dissociation, which may predict the frequency of posttraumatic intrusive cognitions. Participants watched a short video containing traumatic scenes and subsequently recorded any intrusions of the video content, which occurred within the following week. The only independent predictor of intrusive experiences was high positive symptom schizotypy. A second study exploring the relationship between schizotypy and the frequency intrusive experiences, within a group of individuals waiting for psychological intervention following a traumatic event, also indicated schizotypy is associated with frequency of traumatic memories. Results are considered in relation to other psychological mechanisms which may contribute to the role of trauma-related intrusions occurring within psychotic symptoms.

TEST RETEST RELIABILITY OF THE COMPUTERIZED BINARY SCALE OF AUDITORY SPEECH HALLUCINATIONS (CBSASH)

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Background: The computerized binary Scale of Auditory Speech Hallucinations (cbSASH) allows sub-grouping Auditory Verbal Hallucinations (AVH) according to their phenomenological characteristics, and includes two subscales (malingering and inconsistency) to assess the reliability of the patient report. As the pathophysiology of AVH likely varies according to their characteristics, the cbSASH could be a useful tool in hallucinations research. In this study we examine the test retest reliability of the cbSASH. Method: 29 stable psychotic patients who suffer from AVH took the cbSASH at two time points 3-8 weeks apart. The cbSASH allows the identification of non-malingering and consistent (NM-C), and malingering and inconsistent (M-IC) subgroups. To avoid the problem of multiple comparisons, we compared the NM-C and M-IC subgroups with respect to overall test-retest reliability. First, for each question, the fraction of stable responses was computed within each group. Then the difference in response stability between the two groups was evaluated across all questions using the Wilcoxon non-parametric matched-pairs singed-ranks test. Results: The NM-C subgroup had significantly higher test retest-reliability than the M-IC subgroup ($p<0.0001$). The NM-C were more reliable than the M-IC patients in their responses for 111 questions. The two groups were tied on 13 questions and the NM-C group was less stable on 44 questions. The latter questions belonged to the categories of frequency, associated abnormal perceptions, triggering emotions, and space location of the perceptions. Conclusion: The cbSASH exhibits significant overall test-retest reliability on the vast majority of the questions in the NM-C subgroup. Reliable patients may have difficulty describing some aspects of their hallucinations such as triggering emotions. Other variables such as frequency could change over time.

SHORT-TERM INSTABILITY OF SELF-ESTEEM ACROSS THE PARANOIA CONTINUUM

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It has long been argued that self-esteem is implicated in the formation of paranoid beliefs. Studies investigating the relationship between paranoia and self-esteem have mainly focused on level of self-esteem and have yielded inconsistent results. Paranoia has been found to be associated with both low and relatively normal or high levels of self-esteem. A possible explanation for these inconsistencies concerns the failure to neglect the dynamic aspects of self-esteem. The purpose of current study was to investigate whether paranoia was associated with both a lower level of self-esteem and higher self-esteem instability. The following individuals differing in symptoms and degree of vulnerability to psychosis were included: patients with positive psychotic symptoms (n=79), individuals with an at-risk mental state for paranoid psychosis (n=38), and control subjects (n=38). The Experience Sampling Method, a structured self-assessment diary technique, was used to assess short-term instability of self-esteem in daily life. In order to assess underlying paranoia across the continuum, subjects were asked to complete the Paranoia Scale.

Unilevel and multilevel regression analyses showed that underlying paranoia was associated with both a lower level and higher instability of self-esteem. Self-esteem instability was consistently found using three approaches: fluctuations from moment-to-moment (B[SE]=.11 [.03]; p<.001), fluctuations within the day (B[SE]=.21 [.06]; p=.001) and overall fluctuation as a subject characteristic (B[SE]=.13 [.03]; p<.001). These results remained significant after controlling for sex, depression and self-esteem level. Paranoid individuals are therefore not only characterised by a lower level of self-esteem, but also by a higher instability in their self-esteem. This is consistent with the hypothesis that paranoia is associated with dysfunctional strategies of self-esteem regulation.

IMPAIRED HUMOUR RECOGNITION ASSOCIATES WITH FRONTAL EXECUTIVE DYSFUNCTION AND POOR SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Humour plays an important role in human interactions and it is essential to optimal quality of life. Patients with schizophrenia have difficulties in social cognition and their experience in enjoying humour is likely to be compromised. In this study, we hypothesed that individuals with schizophrenia would have diminished ability to detect and to appreciate humorous events compared with healthy controls. The relationship between humour experience and clinical symptoms, cognitive as well as social functions was also examined. Thirty English-speaking individuals with DSM-IV diagnosis of schizophrenia (21 males; mean age = 42.1 ± 9.3, mean National Adult Reading Test [NART] IQ = 106 ± 11) were compared with thirty age, sex and IQ matched healthy controls (21 males; mean age = 38.1 ± 12.4, mean NART IQ = 110 ± 11). Humour recognition was measured by identification of humorous moments in four short silent slapstick comedy film clips. Humour appreciation was measured by comparing self-report mood state before and after each clip. Executive and social functions were assessed by the Wisconsin Card Sorting Test (WCST) and the Life Skills Profiles (LSP) respectively. Sensitivity for humour recognition was calculated as d-prime according to signal detection theory. Results showed that patients with schizophrenia had a lower sensitivity in recognising humour compared to the controls, $t(58) = 2.60$, $p = 0.01$. The difference in humour recognition between patients and controls remained significant after controlling for the performance of a baseline recognition task with a non-humorous video clip, $F(1,57) = 8.01$, $p = 0.006$. In patients, the sensitivity for humour recognition was negatively correlated with the perseverative error score of the WCST, $r = -0.38$, $p = 0.04$, and the total scores of the LSP, $r = -0.38$, $p = 0.04$. There was no statistically significant difference between patients and controls in humour appreciation. Our results indicate that patients with schizophrenia demonstrated reduced ability in humour recognition. Though preliminary, these findings suggest that frontal executive dysfunction may contribute to the difficulties individuals with schizophrenia have in recognising humour, and hence result in psychosocial impairment. This study is supported by a grant from the Sheffield Health and Social Research Consortium.

3. Epidemiology

MORTALITY AND SUICIDE IN SCHIZOPHRENIA

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Our aim was to analyze the mortality and especially rate and predictors of suicide in psychotic disorders (mainly schizophrenia) in the Northern Finland 1966 Birth Cohort. The Northern Finland 1966 Birth Cohort Study is an unselected, general population birth cohort ascertained during mid-pregnancy. 10,934 members of the Cohort who were alive at the age of 16 were followed up to the age of 39 years. We used validated hospital diagnoses until 1997 and information on mortality until 2005. Risk ratios (RR) were calculated having healthy subjects as comparison group. Crude and adjusted hazard ratios (HR) and their 95% confidence interval (95% CI) for suicide by school performance were computed using Cox regression. RR of death for all cohort members suffering from psychosis (n=155) was 6.19 (95% CI 3.96-9.49). For schizophrenia patients (n=100) RR was 7.07 (4.24-11.42). Predictors of mortality due to any cause were violent criminality and male gender. Due the young age of cohort members the leading cause of death was suicide. At the end of year 2005 (age 39) 7 of 100 schizophrenia patients had commit a suicide. Suicide rate for females was 2.9% (1/35) and for males 9.2% (6/65). Suicide risk was high especially in early phase of disease; two thirds of suicides in schizophrenia occurred within three years after the onset of illness. Suicide rate of schizophrenia patients was nearly 2-fold higher six years after first discharge from psychiatric care (Log Rank = 7.74, df =1, p=0.0054) compared to hospital treated patients with non-psychotic disorder. Good school performance was a predictor of suicide (1). For psychotic persons having good school performance (highest 20%), the adjusted hazard ratio (HR) for suicide was 3.56 (0.97–13.05) compared with the remaining 80%. In the non-psychotic population (97% without psychiatric hospitalization), accordingly, adjusted HR was 0.28 (0.07–1.16). Interaction (school performance x psychiatric diagnosis) was significant (P=0.01) even when adjusted with gender and social class. We conclude that suicide risk is high especially for males and in early phase of disease. Good school performance at age 16 years is associated with increased risk of suicide (before age 35 years) in persons who develop psychosis. 1. Alaräisänen A, Miettunen J, Lauronen E, Räsänen P, Isohanni M. Good school performance is a risk factor of suicide in psychoses. Acta Psychiatrica Scandinavica, in press.

SHORT-TERM MORTALITY AMONG PATIENTS WITH SCHIZOPHRENIA IN BUTAJIRA, A RURAL COMMUNITY IN ETHIOPIA

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Background: A better prognosis for schizophrenia is reported in developing countries but there are few studies that have investigated the mortality associated with schizophrenia in low-income settings. Aims: To examine mortality and associated factors in patients with schizophrenia in a predominantly rural community in Ethiopia. Method: A population-based cohort of 318 persons with schizophrenia was followed up monthly for a mean period of 2.5 years Result: Ten percent (n=33) of cases died during the follow-up period. The most frequent cause of death was infectious disease. The sex-standardized mortality ratio (SMR) was 4.91 (95% CI: 3.39 to 6.90), 5.40 for men and 2.56 for women. The age-standardized SMR was 4.35 (95% CI: 2.99 to 6.10). Mortality was elevated in patients with higher SANS scores, low SAPS scores and those who were not on neuroleptic treatment at baseline. The survival analysis showed that cases in the higher 50% distribution of SANS score had a shorter time to death compared to those in the lower half (P<0.02). Adjusting for sociodemographic variables and use of neuroleptic medication, the relative risk for mortality was significantly higher among long-standing cases with SANS scores in the upper 50% compared to those who were within the lower half (RR=4.67; 95% CI, 1.13 to 19.3). Conclusions: Our study found mortality to be increased over four-fold in people with schizophrenia. This level of excess mortality is higher than has previously been reported, and the commonest cause of death also differed from other settings. Negative symptoms of schizophrenia, which are indicators of poorer outcome, were strongly associated with increased mortality in keeping with previous reports.

NEUROTRANSMITTER PATHWAY GENES AND NORMAL COGNITION: EFFECTS AND INTERACTIONS OF CATECHOL-O-METHYLTRANSFERASE AND MONOAMINE OXIDASE A FUNCTIONAL VARIANTS IN A LARGE EPIDEMIOLOGICAL SAMPLE OF CHILDREN

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Functional variations in genes involved in the metabolic pathways of the monoamine neurotransmitters are primary candidates for the genetic basis of normal cognitive variation. Understanding their effects on normal cognitive development, including potential interactions with sex, ethnicity, and maturation, may be fundamental to understanding the abnormal neurodevelopmental processes that precede schizophrenia. This study aimed to assess the cognitive effects of two such candidates, the catechol-O-methyltransferase (COMT) Val158Met polymorphism and a 30bp functional repeat polymorphism in the monoamine oxidase A (MAOA) gene promoter in a large general population sample of children, the Avon Longitudinal Study of Parents and Children (ALSPAC). Cognitive measures of attentional control, verbal and motor inhibition, working memory and IQ were obtained from more than 5000 children at ages 8 and 10 years old. In addition, children's pubertal development was assessed at age 9 years 8 months. COMT genotype significantly affected executive function and IQ scores in boys but not girls. There was an interaction with puberty, with IQ differing by up to ten points across COMT genotypes in boys who were entering puberty. In contrast, MAOA genotype showed little cognitive effect. The cognitive effects of interactions between COMT and MAOA genotypes were also assessed. We conclude that normal variation in children's cognitive function is associated with genes in monoamine neurotransmitter pathways. In the case of COMT, effects may become larger during puberty as the prefrontal cortex becomes optimally functional. Sex-specific effects and the importance of maturational processes are relevant to the aetiology of schizophrenia.

Large samples and longitudinal studies are required to tease out subtle genetic effects on cognitive development at the population level.

ESTIMATING RISK FACTORS FOR DIABETES AMONG SCHIZOPHRENICS WITH EXPOSURE TO ATYPICAL ANTIPSYCHOTICS

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OBJECTIVE: Recent ADA guidelines have identified age >45, BMI >25kg/m2, positive family history, gestational diabetes, physical inactivity, smoking, elevated blood pressure and lipids, and being non-white as risk factors for developing diabetes type II (DM-II). In addition, atypical antipsychotic(AAP) exposure has been shown to be a risk factor for DM-II. The exact relationship between AAP exposure and DM-II remains unclear however, because schizophrenia itself is related to DMII risk factors, including inactivity, smoking, and increased BMI. This study estimates the risk of ADA factors and AAP exposure for DM-II among schizophrenics. METHODS: Data was collected via structured interview for 107 schizophrenic outpatients at a tertiary care center in Iowa City, IA. Data collected included: age, height, weight, waist circumference, blood pressure, lipid level, and random capillary glucose; along with smoking history, level of physical activity, months of typical and atypical antipsychotic exposure, and if previously diagnosed with DMII. Patients not previously diagnosed with DMII who had a random glucose >120mg/dl were followed up with a fasting plasma glucose. Adjusted odds for DM-II were estimated for ADA risk factors and AAP exposure using a multivariate logistic regression model. RESULTS: Fourteen schizophrenics met criteria for a DM-II diagnosis. Compared to non-DM-II schizophrenics (N=93), DM-II schizophrenics (N=14) had higher BMIs (35.7 ± 7.6 vs. 29.6 ± 8.2, P<.01), were more likely to be inactive (86% vs. 58%, P<.01) and were on AAP for more months (83.8 ± 70.7 vs. 47.9 ± 43.9, P<.01). The sample did not differ in age, gender, smoking history (pack years), family history of DM-II, or elevated hypertension and/or lipids. In multivariate analyses, no risk factors were found to be significant (P<.05). CONCLUSIONS: Analyzing a recent sample of schizophrenic outpatients, BMI, physical inactivity, and exposure to AAP were all found to be positively related to DM-II; however in multivariate analyses, none of these risk factors remained significant. These results indicate that AAP exposure may not play as large a role in the development of DM-II among schizophrenics patients as previously thought.

SOCIODEMOGRAPHIC PROFILE OF AMBULATORY PATIENTS WITH SCHIZOPHRENIA: SURVEY ON FUNCTIONAL AND PRAGMATIC FACTORS

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Prevalence data of autonomy and functional measures related to patients with schizophrenia are scarce. Such measures would provide epidemiologic information useful for designing more pragmatic studies. Cross-sectional survey on patients with schizophrenia during a follow-up visit at secondary clinical settings of Mental Health in Spain. Selection criteria included a diagnosis of Schizophrenia and stable drug treatment. Patients without medical records or unable to provide informed consent were excluded. Information regarding clinical profile, sociodemographic data, work and legal disability status was recorded. Patients' daily needs were also assessed by using the Camberwell Assessment of Needs, limited to six areas. A sample of 1,060 was recruited by 359 clinicians from all the Constituted Communities in Spain. Among evaluable patients (894, 84.3%) the majority were men (66.7%) with an average age of 38.7 SD (11.5), and schizophrenia onset at an average age of 25.6 SD 8.2; about sixty percent of patients were assessed as moderately-severely ill according to the Clinical Global Impression scale. The majority of patients were single (74%) and living with their parents (60.2%). Only a few have or ever have had a partner (23%), and live with their own family (16.3). Only a few were actively employed (18.1%) while others were unemployed (20%). All patients showed the need for help in the areas assessed, where the most common and acute needs were with psychotic symptoms (81.1%) and companionship (75%). Other frequently detected needs were related to daytime activities (61%), housekeeping (57.3%), food (37.8%) and self-care (34.6%). However, informal help was addressed at the less acute areas of need. The logistic regression model showed that only the severity of the disease and marital status were associated with the presence of any need in daily life (Chi2=32.1882, p<0.0001 and Chi2=20.3359, p=0.0024 respectively). Measures related to autonomy level and functional status are strong and complementary to clinical assessments in patients with schizophrenia. During stabilization periods, the needs in patient's daily life but informal help provided, gives a pragmatic view of outcome results. This information is representative of efficiency and should be taken into account when specific intervention strategies are assessed. Acknowledgments:Funded by Sanofi-Aventis. The authors thank PSYNCRO, Neuropsychological Research Organization, S.L and EPISOL Study group.

ARE FIRST EVER PSYCHIATRIC SYMPTOMS IN SCHIZOPHRENIA SPECTRUM AND AFFECTIVE PSYCHOSIS INFORMATIVE ABOUT TRAJECTORIES OF AFFECTIVE VS NON-AFFECTIVE PSYCHOSIS?

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Psychotic disorders are often preceded by general psychiatric symptoms some of which develop much earlier in life and may be important for our understanding of trajectories of affective vs non-affective psychoses. We report a retrospective description of first ever psychiatric symptoms in patients with a first episode of psychosis (FEP). One hundred and twenty patients (age 14-30 years) with a diagnosis of a first episode of schizophrenia spectrum (SSP) or affective psychosis (AP) were administered a standardized interview schedule, the Circumstances of Onset and Relapse Schedule (CORS), to assess details of any psychiatric symptoms occurring for the first time prior to the onset of psychosis and WAIS-III-R to assess I.Q. Seventeen different "early" symptoms were grouped into four conceptually relevant categories: "psychotic-like" (e.g. suspiciousness, delusional ideas, unusual perceptual experience, odd/bizarre ideas); "cognitive/behavioural disorganization" (e.g. bizarre behaviour,

impaired concentration, aggressiveness); "mood" (e.g. depression, anxiety, elation) and "negative" symptoms (e.g. loss of energy, hygiene neglect, social withdrawal). Patients' median age of onset of first ever psychiatric symptoms was 17.7 years (range =5.7-29), 80 (66.7%) were males, 98 had a SSP diagnosis and 22 Affective psychosis, 105 were single, 60 had not yet completed high school. The most common category of early symptoms was "mood" (45%) followed by "psychotic-like" (25%), "cognitive/behavioural disorganization" (18.3%) and "negative" symptoms (11.7%). A Chi-square analysis revealed a significant effect (r=8.37; p=0.004) of categories of first symptoms on diagnosis: patients experiencing a "mood" symptom as a first change were more likely to have a SCID diagnosis of affective psychosis. "Psychotic-like" symptoms were associated with significantly older age of first change compared to "cognitive behavioural disorganization" (p=0.036) and "mood" symptoms (p=0.025). Logistic regression showed longer time between onset of first ever psychiatric symptoms and onset of psychosis to be associated with higher verbal IQ (beta=0.20; p=0.046) after controlling for diagnosis and gender. This effect of IQ was almost significant even after age of onset of early symptoms was controlled for (p=0.053). These results suggest that while there is some overlap on "mood" symptoms between SSP and AP, trajectories of affective vs non-affective psychosis may be developed relatively early.

SOCIAL COHESION, RACIAL DISCRIMINATION AND INCIDENCE OF PSYCHOSIS

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Background It has been suggested that social experience contributes to the incidence of psychosis especially in minority groups. Cross-sectional studies and one prospective study have found an association between the experience of discrimination and risk of psychosis but these could not overcome the possibility of response bias by people who were psychotic or at high baseline risk of becoming psychotic. Aims This study aimed to test whether hostility towards minority groups and social cohesion at the ecological (neighbourhood)level predict incidence of psychosis in neighbourhoods in South East London. Method Hostility and social cohesion were measured using the Sampson and McCulloch questionnaires, rated by the general public, and administered so that every adult, in each of nine areas (of approx 10000 people) had an equal chance of being selected. There was an adequate response rate of 60%. Incidence of psychosis was measured in the nine areas using the Camberwell Case Register of all first onset psychosis presenting between 1998 and 2004. Population data was taken from the 2001 Census. Results For the whole area the incidence of psychosis remains elevated in ethnic minority groups (SMR standardised for age and sex was 7.1 for people of Caribbean descent and 5.5 for people of African descent). The areas were amalgamated into three groups by proportion of ethnic minorities. Levels of reported discrimination rose as the proportion of ethnic minorities became smaller. Poisson Regression modelling showed a strong and statistically significant effect of social cohesion in that incidence rose as social cohesion fell (IRR 1.88: 95%CI 1.15-3.08 p= 0.012). The effect of racial discrimination was also strong and statistically significant in that incidence dropped as discrimination fell (IRR 0.32:95%CI 0.12-0.88 p=0.027) Conclusion Levels of racial discrimination and social cohesion as reported by the healthy population in an area predict incidence of psychosis in that area.

RACE AND SCHIZOPHRENIA IN A U.S. BIRTH COHORT

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Background: We compared rates of schizophrenia between whites and African Americans and evaluated whether the association was mediated by socioeconomic status (SES) of family of origin in a U.S. birth cohort. Methods: Study subjects were offspring of women enrolled during pregnancy at Alameda County Kaiser Permanente Medical Care Plan clinics (1959-1966) in the Child Health and Development Study. 12,094 of the 19,044 live births were followed 1981-1997 for schizophrenia spectrum disorders. The analysis is restricted to cohort members whose mothers identified as African American or European white at intake. Stratified proportional hazards regression was the method of analysis. Results: African Americans were more likely than whites to be diagnosed with schizophrenia (Rate Ratio = 3.27; 95% CI: 1.71 - 6.27); adjusting for indicators of family SES at birth, the rate ratio was about twofold (RR = 1.92; 95% CI: 0.86 - 4.28). Conclusion: African Americans were at higher risk of schizophrenia than whites in this cohort. The excess risk was not entirely mediated by family SES. Further studies are required to rule out artifactual explanations.

PRENATAL INFECTION, NUTRITION, AND ANOMALIES OF BRAIN STRUCTURE AND FUNCTION IN SCHIZOPHRENIA

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Prenatal infection and nutrition have been associated with risk of schizophrenia. In a large birth cohort study, we have previously demonstrated relationships between schizophrenia and serologically documented prenatal exposure to influenza and toxoplasmosis, as well as maternal respiratory infection, and maternal genital/reproductive infection. In the Developmental Insult and Brain Anomaly in Schizophrenia study (DIBS), we sought to better understand the relationship between these infections and structural and functional brain anomalies found in schizophrenia. We first examined the relationship between prenatal infection and cavum septum pellucidum (CSP), a developmental brain defect that indicates in utero disruption, in schizophrenia patients in the birth cohort. All patients were assessed for CSP using MRI and standard methodology, including the MP-RAGE sequence which provides 1.4 mm contiguous coronal slices. Estimates of the anterior to posterior length of the CSP were made on each subject. We found that CSP occurred in 11 of 12 (91.7%) schizophrenia cases exposed to prenatal infection, compared to 2 of 5 (40%) unexposed cases. Prenatal infection was associated with a 16-fold increased risk of CSP (OR=16.5, 95% CI=1.1, 250.2, p=.043). We then investigated the relationship between prenatal infection and measures of executive function, including mental set-shifting. We found that exposed schizophrenia cases, compared to unexposed cases, committed significantly greater errors on the Wisconsin Card Sort Test and required significantly longer

time to complete the Trails B Test, but did not differ on other tests of executive function that do not require set-shifting, or on tests of psychomotor or processing speed, including Trails A. Taken together, these results provide the first evidence that prospectively measured prenatal infection is associated with specific structural and functional brain disturbances in schizophrenia. In studies of prenatal nutrition, we have investigated the relationship between gestational hyperhomocysteinemia and schizophrenia. Elevated homocysteine in the third trimester was associated with a greater than twofold, statistically significant increase in schizophrenia risk (OR=2.39, 95% CI=1.18, 4.81, p=.015). This finding may be accounted for by partial antagonism at the glycine site of the NMDA receptor during development. Each of these findings will be discussed in the context of the previous presentations.

PROSPECTIVE COMPARISON OF PREMATURE MORTALITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER: A 7-YEAR STUDY WITHIN AN EPIDEMIOLOGICALLY COMPLETE, HOMOGENEOUS POPULATION IN RURAL IRELAND

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The aim of this study was to compare prospectively premature mortality in schizophrenia and bipolar disorder in a prevalent population followed up 84 months after initial case ascertainment. The index population was identified in 1996. Multiple sources of information were used to identify "all" persons in the study region with the diagnoses of interest. Structured Clinical Interview (SCID) DSM III-R diagnosis, psychopathological and neuropsychological assessments were performed on the cases identified. 84 months following SCID diagnosis, disposition of cases were sought using admission registers, inpatient, outpatient records and death certificates. Mortality data, using age of death by any cause as primary endpoint were analysed actuarially by the life table method, with determination of relative risk (RR) and associated 95% confidence intervals. Survival data from 1996 to death or those alive 84 months later were analysed by Cox proportional hazard modelling. At ascertainment 110 cases of schizophrenia and 75 cases of bipolar disorder were identified. At 84 months follow-up information was available on all but 3 cases (98% follow-up). For all case of psychosis, number of deaths was 38 out of 185 cases: relative risk (RR) 2.29 (95%CI 1.69-2.97; $p < 0.001$). In the schizophrenia group, 24 (22%) cases out of 110 were deceased; RR 2.14 (95% CI 1.48-2.98; $p < 0.001$). In the bipolar group, 14 (19%) of 75 were deceased; RR 2.60 (95%CI 1.55-3.90; $p < 0.001$). Clinical and demographic predictors of reduced survival are in analysis. An approximate doubling of mortality in schizophrenia confirms our previous work in a similar population with schizophrenia followed up over a similar time period. We report now that bipolar disorder is associated with similarly heightened mortality. These findings indicate that factors operating to reduce life expectancy in schizophrenia may be acting similarly in bipolar disorder and suggest a common pathobiological process. These studies were supported by the Stanley Medical Research Institute.

PREDICTORS OF CONVERSION TO PSYCHOSIS IN THE NORTH AMERICAN PRODROMAL LONGITUDINAL STUDY

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Early detection and prospective evaluation of individuals who will develop schizophrenia or other psychotic disorders are critical to efforts to isolate mechanisms underlying psychosis onset and to validate preventive interventions. Prior studies using Structured Interview for Prodromal Syndromes (SIPS) or similar criteria for an ultra-high-risk clinical state, which emphasize onset or worsening of attenuated forms of psychotic-like symptoms in the past 12 months, have detected a 20 to 40% risk for conversion to psychosis within 1 year, but these risk rates are based on relatively small sample sizes ($N \leq 60$) and vary widely across studies. The North American Prodromal Longitudinal Study (NAPLS) is an 8-site consortium involving the single largest sample of longitudinally followed prodromal subjects worldwide (N=370). Risk for conversion in this sample has a monotonic distribution of 17% per year, with an ultimate conversion rate of 40% after 2 and 1/2 years of follow-up. Numerous variables from assessments of prodromal symptom severity, psychosocial functioning, diagnostic co-morbidities, neurocognitive functioning, stressful life events and other risk factors at baseline were found to improve the prediction of conversion to psychosis over and above that associated with prodromal syndrome criteria. In a multivariate model, family history of psychotic illness, history of drug abuse, poorer social functioning, and higher levels of unusual thought content, suspicion-paranoia, disorganized communication, and reduced ideational richness at baseline each contributed uniquely to the prediction of conversion to psychosis. Combining two or more of these variables into risk prediction algorithms resulted in dramatic increases in positive predictive power (>80%), but with correspondingly large compromises in sensitivity. While these findings require replication in other large prospective samples, they nevertheless suggest that the SIPS prodromal criteria have high predictive accuracy, and that their positive predictive power can be improved considerably using clinical, neurocognitive and historical variables assessed at baseline. Over the long run, such improved risk ascertainment algorithms may enable more selective recruitment into preventive intervention programs (minimizing exposure of false positive cases to potential adverse effects) and may facilitate studies attempting to elucidate neural, hormonal, and other changes proximal to the onset of psychosis.

VALIDATION OF THE USE OF THE AUDIT AND DAST AS SCREENING INSTRUMENTS TO ASSESS SUBSTANCE USE DISORDERS IN FIRST-EPISODE PSYCHOSIS

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The Alcohol Use Disorders Identification Test (AUDIT) and the Drug Abuse Screening Test (DAST) are brief self-report instruments, widely used to screen alcohol and drug related disorders, respectively, in the general population; these may have potential utility for identifying substance abuse in early phase of psychotic disorders but

have, however, not been validated in this patient population. A sample of individuals with a first episode of psychosis were divided into two groups based on the presence or absence of a SCID diagnosis of current alcohol (when analysing AUDIT) or drug (when analysing DAST) misuse. The data were analysed to see whether or not AUDIT and DAST scores were predictive of SCID diagnosis. Patients with a SCID diagnosis of alcohol misuse and those with a diagnosis of drug misuse scored significantly higher on the AUDIT and DAST, respectively, than the group without the respective SCID diagnosis ($p < .001$ in both cases). The AUDIT functioned best when the cut off for problem drinking was a score of 10 (compared to 8 in the general population) showing a sensitivity of 85%, a specificity of 91%, a positive predictive value of 65%, and a negative predictive value of 97%. The DAST functioned best when the cut off for problem drug use was a score of 3 (compared to 6 in the general population), showing a sensitivity of 85%, a specificity of 73%, a positive predictive value of 74%, and a negative predictive value of 84%. The area under the receiver operating characteristic (AUROC) curve was 0.86 for the AUDIT and 0.83 for the DAST. These results suggest that the DAST and the AUDIT are effective as relatively quick screening instruments which can reliably identify patients with substance abuse in a population of patients with first-episode psychosis although the cut-off scores may need to be altered in order to increase their utility in this patient population. These findings are important in light of the relatively high prevalence of substance abuse in patients with psychotic disorders which has often been associated with medication non-adherence, symptom exacerbation, and higher rates of relapse. Supported by Valorisation de Recherche de Quebec, through the Douglas Hospital Research Centre, and Canada Research Chair Program support to the senior author (A.M.).

NO IN VITRO ANTI-CANCER EFFECT OF ANTIPSYCHOTIC DRUGS AT DOSES USED IN THE PSYCHIATRIC CLINIC

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Background: There is suggestive evidence in the literature that patients with schizophrenia are at reduced risk of developing cancer compared with the general population. It has been proposed that this reduced risk may be attributable to an anti-neoplastic effect of antipsychotic medication used in patients' treatment. Purpose: The purpose of this study was to determine the effect of antipsychotic drugs on cell viability for two lymphoblastoid and two neuroblastoma cancer cell lines. Methods: Exponentially growing cancer cells (Raji, K-562, IMR32, BE(2)C) were exposed to chlorpromazine, haloperidol, risperidone or olanzapine at concentrations ranging from 0.4 – 400 μM for 72 hours following which cell viability was determined using the Alamar Blue assay. The percent viability of treated cells compared to untreated control cells at each drug concentration was plotted and the 50% lethal dose (LD50) was determined for each individual experiment. Results: The effect of antipsychotic drugs on cell viability expressed as the LD50 is detailed in the results table. Conclusion: Although some of the antipsychotic drugs tested decreased cancer cell viability, this occurred at levels which greatly exceeded the plasma levels obtained with therapeutic doses of these drugs. The study is limited by being carried out in an in vitro cell culture system, which does not allow for any effect of antipsychotic drug metabolites.

Results table

	Cell line				
Drug	Raji μM	K-562 μM	IMR32 μM	BE(2)C μM	Therapeutic plasma level μM (ng/mL)
Chlorpromazine	15.3 ± 1.4	12.3 ± 1.4	6.3 ± 1.7	18.3 ± 0.9	0.84 (300)
Haloperidol	38.0 ± 0.2	40.0 ± 5.3	24.4 ± 8.2	51 ± 12	0.008 (4)
Risperidone	> 200	> 200	150 ± 30	> 200	0.056 (23)
Olanzapine	25 ± 18	51 ± 14	42.8 ± 2.5	155.3 ± 3.2	0.1 (33)

MATERNAL FEVER DURING PREGNANCY AND RISK OF SCHIZOPHRENIA IN ADULT OFFSPRING

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Prenatal exposure to infection, particularly influenza, polio, herpes simplex and rubella, has been shown to be associated with an increased incidence of later schizophrenia among those exposed. However the exact causal mechanism remains unclear. Various candidate mechanisms have been proposed including a direct effect of fever, an immunological mechanism involving cytokines or a secondary effect of the analgesic medication used to treat the symptoms of infection. In this experiment we wished to test whether fever is the primary mechanism for this effect. Acute pyelonephritis is a bacterial infection of the kidneys which is associated with a time-limited high fever. Pregnant women are at higher risk of infection. In this study we examined whether hospital-treated acute pyleonephritis during pregnancy is associated with an increased incidence of schizophrenia among exposed offspring. Data for this analysis was obtained through record linkage between three population-based registers in Finland: the Finnish hospital discharge register, the Medical birth register and the Finnish population register. The sample comprised 9,596 cases exposed to pyleonephritis in utero between 1947 and 1990. The siblings of each case were taken as controls (N = 13,808). Exposure to fever in utero was associated with a very modest increase in the risk of later developing schizophrenia which did not reach statistical significance (OR 1.48, 95% CI: .92-2.3; p=0.09). Adjusting for parental psychiatric history did not affect the estimated risk. There was no significant effect for trimester of exposure (OR 0.9, 95%: .93-1.05). The effect size found here for prenatal exposure to infection on the subsequent development of schizophrenia is very small and suggests that fever may not be the main causal mechanism for the association between prenatal exposure to infection and later schizophrenia. The association may be relatively specific to viral infections rather than bacterial.

SURGERY RATES AMONG VETERANS WITH SCHIZOPHRENIA

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The purpose of this study was to compare the rates of surgery among Veterans Health Administration (VA) patients with schizophrenia to those of patients with other or no serious mental illness. Medical record extracts from VA administrative databases provided data on

patients receiving care in fiscal year 2005. Patients were categorized as diagnosed with schizophrenia, other serious mental illness (SMI), or no serious mental illness. Other SMI included bipolar disorder, post-traumatic stress disorder (PTSD), major depressive disorder (MDD), and other psychosis. We examined overall surgery rates and selected common types of surgeries. In FY05, 4.5 million patients received care in the VA healthcare system. Of these, 81,191 were diagnosed with schizophrenia and 4,041,012 had no serious mental illness, while there were 69,128 bipolar patients, 40,901 with other psychosis, 249,054 with PTSD, and 130,025 with MDD. Among patients with schizophrenia, 2.5% of patients underwent surgery, compared to 1.8% of patients without serious mental illness. Other SMI had higher rates of surgery: bipolar disorder 2.9%, PTSD 2.9%, MDD 3.3%, other psychosis 3.6%. In two major categories of surgery, rates were: cardiovascular system surgeries – 0.37% non-SMI vs 0.32% schizophrenia, 0.36% bipolar disorder, 0.46% PTSD, 0.47% MDD, 0.56% other psychosis; digestive system surgeries – 0.41% non-SMI vs 0.71% schizophrenia, 0.72% bipolar disorder, 0.66% PTSD, 0.78% MDD, and 0.91% other psychosis; and respiratory system surgeries – 0.13% non-SMI; 0.18% schizophrenia; 0.20% bipolar disorder; 0.18% PTSD; 0.21% MDD; 0.26% other psychosis. Regarding access to surgical care, these data suggest that veterans with schizophrenia have similar or higher rates of common types of operations, possibly excepting cardiovascular surgeries, compared to veterans without serious mental illness, but slightly lower rates relative to other serious mental illnesses. Veterans with schizophrenia are a vulnerable population that relies heavily on publicly funded VA healthcare. These patients have high rates of cardiovascular, digestive, and respiratory illness, yet studies of their surgical treatment are lacking. Whether the rates reported here represent under- or over-treatment should be investigated.

A MULTIFACETED WEIGHT LOSS INTERVENTION FOR PERSONS WITH SEVERE MENTAL ILLNESS: RESULTS FROM THE ACHIEVE STUDY

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BACKGROUND: Overweight and obesity are highly prevalent in persons with severe mental illness (SMI); psychiatric rehabilitation programs(PRPs) may provide ideal settings for lifestyle interventions as SMI attend regularly. The objective of this study was to develop and pilot test a multifacted weight loss intervention appropriately adapted for persons with SMI in PRPs. METHODS: We performed a pre/post study at two PRPs where SMI attend three days/week. The 6 month intervention provided nutrition classes (2 45 minute sessions/week) and group physical activity classes (3 45 minute sessions/week) along with healthy modification of on-site meals and vending machines. Nutrition sessions were led by trained nutritionists, used materials adapted to a 5th-8th grade reading level and emphasized repetition of concepts and hands-on activities. The primary outcome was weight loss at 6 months. Paired t-tests were performed. RESULTS: Of potentially eligible SMI at the rehab programs, 60% enrolled. 50(82%) completed the study; others were discharged from the PRP before study completion. Mean participant age was 43 years; 55% were women; 50% African American; 54% had schizophrenia; 25% bipolar disorder; 20% depression; 22% mental retardation; 33% substance use. Over half smoked, a third had hypertension, 20% had diabetes. Average intervention attendance across all classes was 67% (84% on days participants attended the PRP). Participants significantly reduced weight, waist circumference, and improved fitness after the intervention (Table). Blood pressure decreases were not statistically significant. The 57% of participants achieving weight loss had a mean loss of 12 lbs. CONCLUSIONS: SMI in this multifaceted weight loss intervention had high levels of participation and achieved weight loss, decreased waist circumference and improved fitness. These pilot study results, which need confirmation in controlled trials, suggest appropriately tailored healthy lifestyle interventions are feasible and can be effective to decrease cardiovascular risk factors in persons with SMI.

Achieving Healthy Lifestyles (ACHIEVE) Study Results Pre/Post Nutrition and Exercise Intervention (N=50)

	Baseline Mean (SD)	Follow-up Mean (SD)	Mean Change (SD)	P-value
Weight (lbs.)	215.2 (47.3)	210.6 (45.4)	-4.6 (12.6)	0.01
Waist circumference (cm)	112.7 (13.3)	109.6 (14.3)	-3.1 (5.6)	0.0005
6 minute fitness walk (ft)	1348 (295)	1453 (298)	+ 105 (176)	0.0002
Systolic blood pressure (mmHg)	117.4 (21.5)	114.4 (22.2)	-3.0 (14.4)	NS
Diastolic blood pressure (mmHg)	69.4 (13.3)	67.3 (14.4)	-2.1 (9.8)	NS

ARE THERE SYMPTOMS OR DEFICITS SPECIFIC RISK FOR SCHIZOPHRENIA?

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Background: Previous studies led to the hypothesis that poor cognitive abilities in adolescence, depression, anxiety poor or social adjustment are associated with increased risk for the later appearance of schizophrenia. Methods: We utilized the cognitive and psychiatric assessments performed by the Israeli military on all adolescents in the country, and ascertained hospitalization for schizophrenia using a National Psychiatric Hospitalization Registry. In addition we examined consecutive referrals to military mental health professionals and later hospitalizations for schizophrenia. Results: Future schizophrenia patients had cognitive test scores that were 0.4-0.5 SDs below population means. Their un-affected siblings had cognitive test score that were below population norms, but less impaired then their siblings later affected with schizophrenia. However, analysis of cognitive data on adolescents with non-psychotic disorders (depression, anxiety and personality disorders) found that they also had decreased cognitive test scores, and that their un-affected siblings also had cognitive test score that were below population norms, but less impaired then their un-affected siblings. These same cognitive deficits that were associated with increased risk for schizophrenia were associated with risk for imprisonment during military service, which we consider to be an adverse life event. Finally, non of the symptoms reported by recruits to military mental health professional was specific for impending schizophrenia. Discussion: Although cognitive deficits and other symptoms in adolescence are associated with later schizophrenia and some are genetically medicated, it appears that these same symptoms and cognitive deficits are associated with having a non-psychotic disorder, and for adverse life events. Generalized

cognitive deficits might be non-specific risk factors for adverse life events, and are probably not specific for schizophrenia.

PREMATURE DEATH IN INDIVIDUALS WITH SCHIZOPHRENIA

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Individuals with schizophrenia have increased mortality from natural causes. Previous studies indicate that individuals with schizophrenia have increased exposure to a number of infectious agents. We evaluated the relationship between schizophrenia mortality and infectious exposure and clinical and demographic factors. The study population consisted of stable outpatients with schizophrenia who were receiving anti-psychotic medications. At baseline, patients were assessed on symptom severity, smoking status, and self-reported medical conditions. Serological evidence of exposure to infectious agents was assessed by enzyme immunoassay. Genetic polymorphisms were measured by real time polymerase chain reaction methods. At follow-up, mortality status and cause of death were obtained from the National Death Index. The relationship between exposure to infectious agents and mortality was assessed by Cox's Proportional Hazard function. The sample included N=420 individuals who were evaluated for a total of 23,613 person-months (mean=56, range=2–93). Mean age at baseline was 40.3 years (s.d. 11.3); n=259 (62%) were male and n=298 (71%) were Caucasian. There were n=11 deaths from natural causes, yielding a mortality rate of 4.67 per 10,000 person-months. Serological evidence of infection with Toxoplasma gondii was associated with a more than five-fold increase in death from natural causes, independent of age, race, gender, education, smoking status, and medical conditions at baseline (Cox Proportional Hazard =5.6; 95% CI 1.6, 20.5. p<.008). Mortality was also associated with a history of a hematologic condition at baseline (p<.02). Mortality during the study period was not associated with other medical comorbidities such as diabetes or cardio-pulmonary disease or serological evidence of exposure to other infectious agents such as herpes or influenza viruses. Increased mortality was also not associated with polymorphisms in cytokines genes or other genes associated with the immune response. The reasons for the increased mortality among individuals with evidence of Toxoplasma infection are not known with certainty but may be related to organ system dysfunction or immune suppression associated with Toxoplasma infection. Future studies should be directed at elucidating the mechanisms of Toxoplasma-associated mortality and devising early interventions to prevent premature death in this population. This work was supported by the Stanley Medical Research Institute

PSYCHOPATHOLOGY AND FAMILY HISTORY IN CANNABIS USERS VS. NON USERS WITH FIRST EPISODE SCHIZOPHRENIA

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There is now considerable evidence that cannabis use is relevant in the aetiology of psychosis. It has been suggested that the psychosis resulting from cannabis use (termed "cannabis psychosis") is distinct from idiopathic schizophrenia. Several studies have investigated differences in psychopathology and family history in schizophrenia according to cannabis use. We wanted to test the hypotheses arising from these studies that cannabis use is associated with a different symptom profile, in particular fewer negative symptoms and a stronger family history of schizophrenia. We used a case register that contained 757 sequential cases of first onset Research Diagnostic Criteria Schizophrenia, from a defined geographical area, 182 (24%) of whom had used cannabis prior to first presentation. 552 (73%) had not and 23 (3%) had missing data. We investigated differences in the proportion of people with distractibility, bizarre behaviour, positive formal thought disorder, delusions of reference, well organised delusions, any first rank symptom, persecutory delusions, abusive/accusatory hallucinations, blunted affect, negative thought disorder, any negative symptoms (any one of catatonia, blunted affect, negative thought disorder, deterioration), lack of insight, suicidal ideation and a positive family history of schizophrenia, using chi square tests. Logistic regression modelling was then used to determine whether cannabis use affected the presence of the characteristics after controlling for age, sex and ethnicity. There was no statistically significant effect of cannabis use on the presence of any of the above. There remained however a non significant trend towards more insight (OR 0.65, p=0.055) amongst the cannabis users and a finding of fewer abusive or accusatory hallucinations (OR 0.65, p=0.049) of borderline significance at the p <0.05 level again amongst the cannabis users. These were in the hypothesised direction. There was no evidence of fewer negative symptoms or a greater family history amongst cannabis users despite adequate power. We found no evidence to support the existence of "cannabis psychosis" as a distinct entity and few appreciable differences between symptomatology in cannabis users and non-users despite adequate power. There were no differences in the proportion of people with a positive family history of schizophrenia between cannabis users and non-users.

SEROLOGICALLY CONFIRMED PRENATAL INFLUENZA B EXPOSURE DIFFERENTIALLY AFFECTS COGNITIVE PERFORMANCE AMONG PRESCHIZOPHRENIC CHILDREN VERSUS CONTROLS

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Previous studies have linked prenatal influenza exposure to increased risk of schizophrenia, particularly during early-mid gestation; however, no study has explored the neurodevelopmental sequelae of this prenatal insult among preschizophrenic individuals using serological evidence of infection. This study sought to examine the effects of prenatal influenza B exposure on childhood cognitive performance among preschizophrenic children versus controls. Subjects were 70 schizophrenic patients and 213 matched controls followed from gestation until age 7 through the Philadelphia site of the National Collaborative Perinatal Project. WISC IQ tests were administered at age 7 and psychiatric morbidity was assessed by an algorithm that combined medical records review and (for a subsample) diagnostic interviews. Assays were conducted from archived prenatal maternal sera collected at birth. Infection status was considered positive if IgG antibody titers > 75th percentile. Scaled scores were used for WISC subscales and all analyses controlled for ethnicity, SES, mother's education, and child's gender. Results indicated a marginal reduction in full-scale IQ scores and a significant reduction in verbal scale scores among preschizophrenics exposed prenatally to influenza B com-

pared to those not exposed. Among preschizophrenic children, prenatal influenza B exposure versus no exposure led to significant reductions in scores on vocabulary and digit symbol coding, marginal reductions in scores on information and comprehension, and no differences in scores on digit span and picture arrangement. There were no differences in cognitive performance among controls exposed and not exposed to influenza B prenatally. Lastly, once an influenza B by case-control interaction term was included in the models, some previously found case-control differences in cognitive performance became insignificant, with only one significant difference found between probands and controls on full-scale IQ scores. These results suggest that prenatal influenza B exposure led to worsened cognitive outcomes among preschizophrenics, but not controls, with the most pronounced deficits among the verbal scale scores, as well as the subscale scores for digit-symbol coding and vocabulary. These findings suggest that a genetic and/or an environmental factor associated with schizophrenia rendered the fetal brain particularly vulnerable to the neurally disruptive effects of influenza B.

SOCIAL EXPERIENCE, ETHNICITY AND PSYCHOSIS

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Research has consistently suggested that the risk of psychosis is higher in African-Caribbean and Black African populations in the UK, compared with the White population. This study sought to investigate whether indicators of adverse social experiences in childhood (parental separation and death) and adulthood (social exclusion) were associated with an increased risk of psychosis, and, if so, whether these might partly account for the high rates of psychosis in the African-Caribbean and Black African populations. The ÆSOP study identified all individuals presenting to services for a first time with a psychotic mental illness over a two-year period. A group of randomly selected, population-based controls were recruited over the same time period. We obtained data from cases and controls on clinical presentation, ethnicity and a range of potential social risk factors. ICD-10 and DSM-IV diagnoses were determined by consensus, blind to the subject's ethnicity. In total, 535 cases and 391 controls were included in the analyses. 1) Compared with the White British population, the incidence of all psychoses was significantly higher in both African-Caribbean (Incidence Rate Ratio (IRR) 6.7, 95% CI 5.4-8.3) and Black African (IRR 4.1, 95% CI 3.2-5.3) populations. 2) Separation from, and death of, a parent before the age of 16 were three times more common in cases compared with controls (Separation: Odds Ratio (OR) 3.36; Death: OR 3.19). Separation from (but not death of) a parent was more common among African-Caribbean (but not Black African) controls than White controls (31% v. 18%, p=0.03). 3) Using an index of adult social exclusion, there was strong evidence that the risk of psychosis increased as levels of social exclusion increased (Test for trend: OR 2.0, 95% CI 1.7-2.2). There was evidence that African-Caribbeans and Black Africans were more socially excluded than Whites. These findings provide strong evidence for an association between indicators of early and later social adversity and risk of psychosis. The greater prevalence of social adversity over the life course in the African-Caribbean, and to a degree the Black African, populations, may partly explain the high rates of psychosis in these groups.

GENDER SPECIFIC EFFECTS OF CHILDHOOD MALTREATMENT ON RISK FOR PSYCHOSIS

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Previous literature has demonstrated that adverse experiences in childhood are associated with increased risk of developing psychotic symptoms in adulthood but these studies employed extremely brief questionnaires, small sample sizes and often lacked healthy controls for comparison. Therefore, this study sought to explore the prevalence of childhood maltreatment amongst those with and without a psychotic disorder using detailed assessments of a large epidemiological case-control sample. Information relating to different types of maltreatment in childhood (parental neglect and antipathy, physical and sexual abuse) was obtained via a semi-structured interview using the Childhood Experiences of Care and Abuse Questionnaire (CECA.Q). Data were collected on 181 first-presentation psychosis cases and 246 epidemiologically-matched controls drawn from 2 UK centres as part of the ÆSOP study. Analysis revealed that females with psychosis were three times more likely to have experienced severe childhood physical abuse compared to female controls (OR = 3.00, 95% CI 1.61-5.57, $p<0.01$). In terms of reports of severe sexual abuse, female cases had almost a two-fold increase relative to female controls although this failed to reach significance (OR = 1.75, 95% CI 0.90-3.42, $p>0.50$). However, no significant differences were found for males on either type of abuse. In relation to parental antipathy and neglect, only maternal antipathy was reported significantly more often by cases than controls with both male and female cases showing a two-fold increase although this was only significant for females ($p<0.05$). As adverse events in childhood have previously been linked to affective disorders the results for females were also analysed according to diagnosis made using the Schedules for Clinical Assessment in Neuropsychiatry. This revealed that the rates of severe physical abuse were elevated in both affective and non-affective female psychosis cases thereby suggesting that affective diagnosis does not explain the high prevalence amongst female psychosis patients relative to controls. In conclusion, the initial results of this study provide more comprehensive evidence of the association between childhood adversity and development of psychosis in adulthood and point to a gender-specific pathway that involves hostility & physical abuse. Further analyses are planned to explore the potentially mediating role of familial susceptibility and specific candidate genes.

EARLY INTERMODAL INTEGRATION IN OFFSPRING OF PARENTS WITH SCHIZOPHRENIA

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Objective: Early intermodal integration (EII) is the infant's ability to link motility and perception and to relate perception across modalities. According to developmental psychology, EII occurs from birth on and is at the basis of complex mental and motor functions later in life, which are typically disturbed in patients with schizophrenia. The present study determined whether abnormalities in EII are indicators of the genetic vulnerability for schizophrenia by studying children of

parents with schizophrenia. We also determined the specificity of these abnormalities to the offspring of parents with schizophrenia. To our knowledge, there is no published study on EII and the genetic vulnerability for schizophrenia. Method: The study sample included offspring of parents with schizophrenia (n=58) or affective psychoses (n=128) and offspring of control parents (n=174) who were enrolled in the New England Family Study. We chose 54 items that typically measure EII from the Bayley scales assessed in eight-month-old infants. These items were grouped into three domains that characterize different aspects of an infant's development. These domains of intermodal experience are in relation to 1) one's own body, 2) an object, and 3) social interactions. Generalized linear models were used to assess the relationship between the EII scores and the high-risk status of the offspring. Results: Body-related EII abnormalities were significantly increased in infants of parents with schizophrenia compared to control infants (OR=3, p=0.04). The mean score for object-related EII abnormalities was 36% higher among infants whose parents had schizophrenia compared to control infants (p-value=0.006). There was no significant association between body- and object-related EII abnormalities in infants of parents with affective psychoses. EII abnormalities in relation to social interactions were significantly increased in infants born to parents with schizophrenia or with affective psychoses. Conclusion: Body-related and object-related EII abnormalities were specific to infants of parents with schizophrenia. This novel approach adds a developmental perspective to the neurodevelopmental hypothesis of schizophrenia, both at the psychological and at the biological level. It is in line with neuropathological findings associated with schizophrenia emphasizing on abnormalities in cortical connectivity and impaired binding. Further studies are needed to confirm and extend the results.

GENDER DIFFERENCES ON BEHAVIOR PROFILE OF CHILDREN OF SCHIZOPHRENIC MOTHERS

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The aim of the study was to investigate whether there are differences between the sexes in the behavioral profile of children and adolescents born to women with schizophrenia. The prevalence of behavioral problems detected by the Child Behavior Checklist (CBCL) was compared between male and female children born to mothers with diagnosis of schizophrenia according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), treated at the Psychiatric Institute of the University of São Paulo. The CBCL was also administered to a comparison group of children born to women without serious mental disorders, recruited at the gynecology outpatient department of the same university. Group comparisons were performed using chi-square tests and t-tests, and a logistic regression analysis was performed to control for the variables: socio-economic level, educational delay and residing with the mother. Male children of women with schizophrenia had a lower prevalence of aggressive behavior compared to girls (4% x 36%;p=0.005). No gender differences regarding aggression were detected in the comparison group (24% x 32%;p=0.53). Logistic regression analyses showed that the presence of aggressive behaviour in the children was associated with belonging to the female sex regardless of socio-economic status and whether they were living with the schizophrenic mother (OR= 3.09;p=0.03), and also regardless of educational delay and socio-economic status (OR= 3.37;p= 0.02). Regarding the interaction between child gender and group of study, being a male child of a woman with schizophrenia was found to be a protective factor against the presence of aggressive behaviour (OR=0.09;p=0.03). The lower prevalence of aggressive behavior in male children of women with schizophrenia could be related to traits of withdrawal and avoidance, which may be present in these children who are genetically vulnerable to schizophrenia. The low prevalence of aggressive behavior in the sons of schizophrenic mothers is notable, because these are children raised in an environment of Sao Paulo surrounded by poverty and violence, factors which are generally associated with aggressive behavior in children and adolescents. The differences between the sexes reported herein may be related to the known gender differences in the development of schizophrenia, whereby a younger age-at-onset and a less favorable course of illness are more frequent among men.

RESULTS FROM OBSERVATIONAL STUDIES COMPARED WITH THOSE OF RANDOMIZED CLINICAL TRIALS: DIFFERING PERSPECTIVES

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Background: Observational data on atypical and typical antipsychotics available from the EuroSC offers additional insight into data from the CATIE study. Objectives: 1) to show that observational data can assist clinicians on drug effectiveness and questions concerning essential outcomes pertaining to relapse, suicide and mortality and 2) that tolerability is the main factor differentiating treatments. Methods: Patients with schizophrenia (N=1,208) aged 18–64 from France, the UK and Germany were interviewed at 6-monthly intervals over 2 years. Switch, use of co-medication, polypharmacy and dosage were evaluated. Relapse, suicide and the reduction of mortality used were used as real measurers of effectiveness. Tolerability and efficacy were also assessed using classic clinical scales as well as the Subjective Side Effects Scale (SSES). Results: The EuroSC revealed high rates of relapse, switch and dropout as well as numerous co-prescriptions and frequent use of polypharmacy. Adverse effects were shown to be highly distressing, with weight gain and EPS being the two most likely to contribute to non-compliance. Treatment setting was shown to affect most outcomes. Conclusion: The majority of patients over the study period switched medications, had polypharmacy and was prescribed numerous co-medications. The meaningful differences in between-drug effectiveness were due to the high magnitude of and variance in adverse events. Since all individuals react differently to treatments, therapeutic strategies need to be individualized. This study was funded by a research grant from H. Lundbeck A/S and a grant from the German Federal Ministry of Education and Research.

AGE DOES NOT EXPLAIN THE HIGH RATES OF MINOR PHYSICAL ANOMALIES IN SCHIZOPHRENIA PATIENTS

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Minor physical anomalies (MPAs) are subtle structural alterations, of little general physiological or cosmetic importance, but reflecting aberrant development of various bodily structures. These deviations develop during a time of major brain development in the first and

possibly early second trimesters of gestation, and researchers have assumed that detrimental factors that negatively influence the morphogenesis and differentiation of the brain also produce readily identifiable MPAs in the head, face and limbs. Significantly increased rates of total MPAs in schizophrenia patients represent a very robust finding across the many studies in this field. However, Lloyd et al. (2003) questioned these findings, suggesting that age might be a confounding factor for the observations of increased rates of MPAs among schizophrenia patients. We thus investigated the association between age and MPA rates in four independent studies from different European countries (Ireland, Norway and Sweden), three having found significantly increased rates of MPAs in schizophrenia patients. The four samples included a total of 401 subjects (298 psychosis patients, both first-episode and chronically ill; 103 mentally healthy controls), with both sexes and a broad age span. In all four independent samples, no significant association was found between MPA rate and age in patients or controls across the total age span, but patients over 60 years had increased MPA rates, compared with younger patients. Nevertheless, few studies of MPAs in psychosis have included old subjects, and the consistent and robust findings of increased rates of MPA in schizophrenia patients are not a result of uncontrolled age.

Spearman rank correlation between total MPA score and age

Study	Group	Correlation		
		n	r's	p**
Ismail et al. Sweden	Male patients	44	-0.004	0.981
	Female patients	16	-0.038	0.888
Kelly et al. Sweden	Male patients	24	-0.072	0.737
	Male controls	16	-0.336	0.204
	Female patients	4	0.200	0.800
	Female controls	11	0.394	0.231
Lane et al. Ireland	Male patients	122	0.126	0.165
	Male controls	51	-0.093	0.516
	Female patients	43	-0.168	0.280
	Female controls	25	-0.158	0.452
Nesvåg et al. Norway	Male patients	24	0.126	0.559
	Female patients	21	0.004	0.985

statistical significance ($p<0.05$)

MATERNAL IRON DEFICIENCY AND THE RISK OF SCHIZOPHRENIA IN ADULT OFFSPRING

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Iron deficiency is the most common nutritional deficit during pregnancy. This condition can induce chronic hypoxia in a developing fetus, a widely replicated prenatal risk factor for schizophrenia. Previous studies indirectly quantified fetal hypoxia based on summary scales of obstetric complications; however, a more refined approach is to examine its relation with schizophrenia through the use of direct indicators of blood oxygenation. We hypothesized that iron deficiency, assessed by maternal hemoglobin (Hb) concentration, increases the susceptibility to schizophrenia in the offspring. The data were drawn from a large birth cohort with prospectively collected data on maternal Hb during pregnancy. Subjects were born between 1959 and 1967 to women enrolled in a pre-paid health plan. Adult offspring belonging to the health plan from 1981 to 1997 were followed up for schizophrenia. Maternal Hb was available on the vast majority of cohort members (N=6,872); 57 were diagnosed with schizophrenia. Mean maternal Hb was the primary measure of exposure. Results were analyzed by Cox proportional hazards regression. Offspring with mean maternal Hb less than or equal to 10.0 g/dl had a nearly four-fold increased risk of schizophrenia (adjusted rate ratio=3.73; 95% CI 1.41- 9.81) compared with offspring having mean maternal Hb greater than 12.0 g/dl. Adjusting for maternal education and ethnicity, for every one g/dl increase in mean maternal Hb, a twenty seven percent decrease in the rate of schizophrenia was observed (adjusted rate ratio=0.73: 95% CI 0.55-0.96). A statistically significant interaction between maternal Hb and sex of the offspring was apparent, that is, the risk was essentially limited to the female offspring. Since the primary cause of low maternal Hb is iron deficiency, these data suggest that a deficit of maternal iron during pregnancy, resulting in fetal hypoxia, may be a risk factor for schizophrenia. If replicated, this finding offers the potential for reducing the risk for this disorder. Thus, further investigation in independent samples is warranted.

SYSTEMS VIEW ON SEPARABLE DEVELOPMENTAL TRAJECTORIES IN SCHIZOPHRENIA FROM FETAL PERIOD TO ACUTE ILLNESS

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Systems or organizational theory is an attempt to create wholes out of parts. Its principles are based on the observation that nature is organized in patterns of increasing complexity, and that these larger wholes cannot be identified through their component parts. From a systems perspective, the clinical features of schizophrenia are surface-level markers indicating partial failure of the complex and poorly-understood systems involved in higher cognitive functioning. Our aim was to examine the pre- and postmorbid life-span development for schizophrenia from a systems theory perspective. Based on the Northern Finland 1966 Birth Cohort, we studied developmental pathways across diagnostic groups using developmental markers at birth, at ages 1, 16, 31, and 34 (brain morphology, cognitive capacity, clinical status). The main results were: the schizophrenia group achieved developmental milestones later and showed altered patterns of development over time when compared with non-psychotic controls. The pattern of associations between early development and post-onset cognition/brain morphology differed in schizophrenia contrasted to non-psychotic controls. Furthermore, we have identified evidence of dysfunction in a distributed network involving a fronto-striatal-cerebellar circuit. We conclude that individuals who subsequently develop schizophrenia follow a developmental trajectory that partly and subtly differs from that of the general population; this trajectory lacks flexibility and responsiveness compared to control subjects, at least in the early stages. We propose a descriptive, lifespan, multilevel systems model on the development and course of schizophrenia. We believe that systems theory provides a heuristic framework that can help researchers navigate the hidden layers of complexity underpinning schizophrenia. Funding source: This work was supported by the grants from the Finnish Academy, Sigrid Juselius Foundation and the Stanley Medical Research Institute References: Isohanni M, Miettunen J, Mäki P, Murray G, Ridler K, Lauronen E, Moilanen K, Alaräisänen A, Haapea M, Isohanni I, Ivleva E, Tamminga C, McGrath J, Koponen H: Developmental pathways of schizophrenia from gestation to the course of illness. The Northern Finland 1966 Birth Cohort Study. World Psychiatry 2006 (in press)

SUBSTANCE USE DISORDERS AMONG LATINO POPULATIONS WITH SCHIZOPHRENIA

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There is little data on dual diagnosis of schizophrenia (SC) and substance use disorders (SUD) among Latino populations. Dual diagnosis has been associated with incompliance with treatments, more frequent relapses, poorer prognosis, increased use of health services and more severe symptoms of the illness. The aims of this study were: estimate the frequency of the dual diagnosis among Latino patients; describe their clinical characteristics; ascertain associated risk factors. Methods. We studied 534 subjects with SC recruited for a genetic study from the Southwest United States, Mexico, and Central America (Costa Rica y Guatemala), of which 156 were sib-pairs. Subjects were diagnosed according with the DSM-IV by consensus using a semi-structured interview (DIGS), an interview with a close relative (FIGS) and review of all available medical records. We defined SUD as either alcohol/substance abuse or dependence. Results. Out of 534 patients with SC, 130 (24.4%) had also SUD, of which 59 (45.4%) met criteria for only alcohol abuse or dependence, and 71 (54.6%) met criteria for abuse or dependence of illegal substances alone or in combinations among themselves and with alcohol. Subjects with dual diagnosis were mainly male (90%), never married (78%), unemployed (66%), and residents of the USA (45%). Age-adjusted rates by country of residence were 46.5% for USA, 23.6% for Central America and 15.5% for Mexico; sex-adjusted rates were 44.5% for USA, 23.2% for Central America and 15.8% for Mexico. The mean age of onset of psychosis was similar in patients with dual diagnosis compared with those with SC only. Seventy two subjects (64%) met criteria for SUD earlier than for SC. Sib pair concordance for alcohol was 62% (k=0.092), for cannabis 82% (k=0.215), and for any substance 58% (k=0.169). Sib-pair concordance rates among non-users were higher than those among users, for alcohol and other substances. Conclusion. The rates of dual diagnosis among Latino patients were similar to those reported in other countries. The substance more frequently used was alcohol either alone or with other substances. This study provides data suggesting that younger age, unemployed and male sex were risk factors for SUD in schizophrenia. Adjusted by age and sex showed that rate for dual diagnosis was significantly higher in the USA compared with Central America and Mexico. We found that concordance between sib-pair with or without dual diagnosis was small.

A REVIEW OF THE SOCIO-SPATIAL EPIDEMIOLOGY FINDINGS FROM THE ÆSOP STUDY: IMPLICATIONS AND FUTURE DIRECTIONS FOR PSYCHOSES

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Introduction: The role of socioenvironmental risk factors [SERF] in the etiology of psychoses remains unclear, despite accruing evidence of a causal relationship between urbanicity and psychosis risk. Objective: To provide a review of research from the ÆSOP study elucidating potential SERFs for psychoses at individual- and neighborhood-levels that may underpin the 'urbanicity' effect. Methods: Incidence data from the ÆSOP study (1997-9) was collected in Southeast [SE] London, Nottingham and Bristol (UK) to investigate spatial variation in the incidence of psychoses between and within centers. Age, sex, ethnicity, ethnic density, ethnic fragmentation (cohesiveness of ethnic groups), socioeconomic deprivation, population density and social capital were considered as risk factors. Measures of social capital were obtained from a sample of 5% of the adult population in SE London (n=16,549) received a questionnaire about social disorganization and social cohesion and trust [SC&T] in their neighborhood. Data was analysed using multilevel Poisson or Bayesian spatial models. Non-affective and affective psychoses were considered separately. Results: Non-affective psychoses varied between centers (greatest in SE London: RR=1.7; 95%CI: 1.4-2.5) and neighborhoods, independent of age, sex and ethnicity. No such variation was observed for affective psychoses. In SE London, 25% of this variation was attributable to the neighborhood-level. For schizophrenia, increased deprivation (RR=1.3; 95%CI: 1.0-1.7) and ethnic fragmentation (RR=1.7; 95%CI: 1.3-2.0) explained some of this variation. Schizophrenia was also higher in high (RR=2.5; 95%CI: 1.3-4.8) or low (RR=2.0; 95% CI: 1.2-3.3) SC&T wards, compared with medial SC&T wards. Similarly, ethnic minorities were at greatest risk of schizophrenia in neighborhoods with highest (RR=3.7; 95%CI: 1.8-7.5) or lowest (RR=6.6; 95%CI: 3.0-14.2) proportions of ethnic minority residents. Results were similar for other non-affective psychoses. Conclusion: Non-affective, but not affective psychoses, showed variation at neighborhood and center levels. Social capital may underpin the urbanicity effect; potentially in a U-shaped way, as evidenced by SC&T and the ethnicity/ethnic density interaction. Social capital may buffer against social stress, mediating psychosis risk. However, social capital-rich neighborhoods may elicit psychoses for excluded individuals, or if psychotic cases are more likely to present to services in such neighborhoods.

THE RISK OF SCHIZOPHRENIA IN OFFSPRING OF WOMEN EXPOSED ANTENATALLY TO SEVERE LIFE EVENTS

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Objectives: To estimate the risk of schizophrenia in offspring of women exposed to severe life events periconceptionally or during pregnancy. The study focuses on the effect of timing of exposure, and individual, rather than population level exposure, on subsequent risk of schizophrenia. Methods: All women delivering live births in Denmark between 1 January 1973 and 30 June 1995 (N=1.38m) were linked to information about their partners/spouses, their parents, siblings and their older children. Exposure was defined as death of one or more of these relatives. Exposure was further classified by timing: 6 months before pregnancy, first 12 weeks' gestation, 13 to 24 weeks' gestation, 25 weeks' gestation until birth. Offspring were followed until 30 June 2005. Relative risks (RRs) were modelled using log-linear Poisson regression adjusted for maternal age, offspring age and sex, unknown spouse (legal father of the child), family history of mental illness, place of birth and calendar year. Results: The risk of schizophrenia was significantly elevated in offspring of women exposed to death of a relative during the first trimester (n=16, adjusted RR 1.67 [95% CI 1.02-2.73]). Death of a relative during the second, or third trimesters, or before pregnancy, was not associated with

elevated risk of schizophrenia. Relative risks by death of specific relatives did not reach significance, but the observed risk of schizophrenia associated with death of a child was greatest (2.02[95% CI 0.65-6.26]) although small numbers (n=3) precluded significance. Conclusions: The offspring of mothers experiencing an incontrovertibly severe stressfull event early in pregnancy appear to have a nearly twofold increased risk of the neurodevelopmental disorder, schizophrenia. This risk is confined to the first trimester, coinciding in magnitude and timing with other adverse pregnancy exposures conferring increased risk, such as famine. The mechanisms of stress-related effects on risk of neurodevelopmental disorder may include gene mutation in specific genes associated with neurodevelopment or effects on fetal programming of somatic and fetal growth.

VISUAL ACUITY IN SUBJECTS WITH SCHIZOPHRENIA

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Objective: To investigate in a general population the prevalence of impaired habitual visual acuity (VA) and self-reported difficulties in vision among subjects with schizophrenia. Method: The study was based on a nationally representative sample of persons aged 30 or older. Diagnostic assessment of schizophrenia according to DSM-IV criteria combined SCID interview and case note data. Results: After adjusting for age and sex, schizophrenia was associated with significantly increased odds of having visual impairment (VA <0.5 = 20/40) for distance (OR 4.89, P<0.0001) and for near vision (OR 6.06, P<0.0001). Of subjects with schizophrenia, 14.7 % reported problems in reading television text and 14.8 % in reading newsprint, compared with 5.2 % and 7.4 % in the total sample. Conclusions: Regular ocular evaluations should be a part of somatic health monitoring in schizophrenia.

DIFFERENTIAL STABILITIES AND PROGNOSTICANDS AMONG INITIAL PSYCHOTIC DIAGNOSES OVER 6 YEAR FOLLOW-UP OF A FIRST EPISODE POPULATION

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Introduction: As the diagnosis of psychosis relies principally on assessment of psychopathology, understanding the long-term stability and prognostic import of the diversity of diagnostic categories encountered at the first episode is essential for: (i) assessing the validity of these categories, (ii) clarifying the boundaries of psychotic disorders, (iii) understanding the nature of psychosis, and (iv) provision of optimal patient care. The present study documents long-term diagnostic stabilities and prognosticands for, inter alia, the following inception diagnoses: schizophrenia [SZ], schizoaffective disorder [SA], schizophreniform disorder [SZP], brief psychotic disorder [BrPD], delusional disorder [DD], bipolar disorder [BP], major depressive disorder with psychotic features [MDD-P] and psychotic disorder not otherwise specified [PNOS]. Method: The Cavan-Monaghan First Episode Psychosis Study is an epidemiologically complete incidence study in a rural catchment area in Ireland. The present study presents interim data on the first 104 of a total of 202 patients incepted over the first 8 years of the study. They were followed up over a mean of 6 years [range 31 -125 months post-inception. Diagnosis at follow-up utilised the Structured Clinical Interview for DSM-IV-TR [SCID]. Results: Over 6-years of follow-up: among SZ, SA and BP, inception diagnoses were substantially stable [81%, 100% and 76% sustained, respectively]; among SZP, 78% had been rediagnosed with SZ; among BrPD, 100% had been rediagnosed with a diversity of more serious psychotic disorders; among DD, 83% had been rediagnosed with SZ/SA; among MDD-P, 32% were deceased and 36% had been rediagnosed with a diversity of alternative psychotic disorders, particularly SZ/SA; among PNOS, 80% had received specific psychotic diagnoses. Of the total of 104 subjects, 10% were deceased, with 4% of these having died by suicide; of these 10 deceased subjects, 70% had an inception diagnosis of MDD-P. Conclusion: A particular implication of these interim data is that, in contrast to relative stability over the first six months, (i) initial diagnoses of BrPD and DD are usually the harbingers of a more serious psychotic process in the long-term, and (ii) initial diagnosis of MDD-P is associated with high mortality.

THE RELATIONSHIP BETWEEN SCHIZOPHRENIA AND NEIGHBOURHOOD-LEVEL SOCIAL CAPITAL IN AN URBAN AREA: FINDINGS FROM THE ÆSOP STUDY

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Context: Social capital is has been proposed as potentially important in the etiology of psychosis but relatively little empirical evidence has tested this hypothesis. Objective: To test whether social capital, measured at the neighborhood-level, is associated with the incidence of schizophrenia [ICD-10 F20]. Design: Cross-sectional. Incidence rates of psychosis, using data from the ÆSOP study, were calculated for 33 neighborhoods (wards) (n~6000) in South London, UK (1997-9). In a separate study, 16,459 randomly sampled individuals in the study area (5% of the adult population) received a questionnaire containing validated items regarding social disorganization [SocD] and social cohesion & trust [SC&T] (2004-6). Wards were categorized as having low, medium or high levels of SocD and SC&T. Multilevel Poisson regression was used to test for the effects of social capital after controlling for individual- and neighborhood-level confounders. Results: 148 cases were identified during 565,576 person-years at-risk from the ÆSOP study. Response from the survey was 25.7%. Twenty-six percent of variation in incidence rates was attributable to neighborhood-level effects. SocD was not associated with the incidence of psychosis. The association between SC&T and schizophrenia was U-shaped. Compared with medium SC&T wards, wards with low [IRR: 2.0; 95% CI: 1.2, 3.3] or high [IRR: 2.5; 95% CI: 1.3, 4.8] levels of SC&T had increased rates of psychosis, independent of age, sex, ethnicity, ethnic density, ethnic segregation and socioeconomic deprivation. The rate of psychosis for black & minority ethnic [BME] individuals was conditional upon ethnic density (p=0.07) and also U-shaped. The BME group were at greatest risk compared with the White British group when they made up a lower [IRR: 6.6; 95% CI: 3.0, 14.2] or higher [IRR: 3.7; 95%

CI: 1.8, 7.5] proportion of the ward population, compared with medium-level ethnic density wards [IRR: 2.1; 95% CI: 1.2, 3.8]. Conclusion: Neighborhood variation in SC&T and ethnic density were associated (nonlinearly) with the incidence of psychosis within an urban area. High SC&T neighborhoods may either have more informal social control resulting in greater reporting of psychotic individuals, or may increase the risk of psychosis for residents unable to access SC&T. Further prospective studies of factors related to social capital are required to elucidate the exact role of the neighborhood in the etiology of psychosis.

GENERAL COGNITIVE IMPAIRMENT AND LATE-ONSET OF PSYCHOTIC SYMPTOMS

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Background: Cognitive impairment is a risk factor for early-onset psychosis (onset before the age of 45 years) and is associated with negative and disorganised symptoms in particular. For the late-onset counterpart (onset after the age of 45 years), associations with symptom dimensions have rarely been reported. The present study investigated the aetiological and phenomenological relevance of general cognitive impairment for late-onset of psychotic symptoms in a general population sample. Method: At the three measurement points of the Netherlands Mental Health Survey and Incidence Study, psychotic symptoms were studied by means of the Composite International Diagnostic Interview. The Mini-mental state examination (MMSE) was administered at baseline to all individuals aged 55 to 64 years (N = 1231). Associations between errors on MMSE and lifetime positive psychotic symptoms at baseline and current and incident symptoms up to three years thereafter (all symptom outcomes defined dichotomously) were analysed in a logistic regression model corrected for age, gender and education. Results: Lifetime positive psychotic symptoms were present in 167 (13.6%) of the total sample, current positive symptoms were present in 50 subjects (4.1%) and incident positive symptoms were present in 17 subjects (1.4%). Errors on MMSE (range: 0-10) were not significantly associated with lifetime positive symptoms (OR = 1.03, 95%CI = .94,1.12), but predicted current positive symptoms (OR = 1.16, 95%CI = 1.01,1.34) and incident positive symptoms (OR = 1.18, 95%CI = 1.02,1.37). The association with current positive symptoms was present for hallucinations (OR = 1.52, 95%CI = 1.04,2.22) but not for delusions. In addition, MMSE error scores were associated with current negative symptoms (OR = 1.35, 95%CI = 1.08,1.67) and current thought disorder(OR = 1.41, 95%CI = 1.03,1.92).Conclusion: General cognitive impairment often accompanies psychotic symptoms in older individuals and may act as a risk factor for late-onset psychosis.

COGNITIVE DECLINE IN SCHIZOPHRENIA FROM CHILDHOOD TO MIDLIFE: A 35-YEAR LONGITUDINAL BIRTH COHORT STUDY

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A sizeable body of research supports the notion that cognitive deficits are present both long before as well as after the onset of schizophrenia. However, there are exceedingly few studies that have included childhood and post-onset cognitive assessments using the same measures at both times. Moreover, we are unaware of any study that has employed this design in a population-based sample in which participants were selected neither for having shown signs of illness in childhood nor for being at risk for schizophrenia. The present study fulfills all of those criteria. Analyses are based on 26 cases with schizophrenia and 25 controls who participated in the longitudinal Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, a birth cohort investigation of neurocognition and neuroimaging in a population-based sample. The Peabody Picture Vocabulary Test (PPVT) was administered to participants at either age 5 or 9 and was then repeated at an average age of 40 years; in the PPVT, the identical test is used in both young children and adults. The use of standard scores, based on age group, permitted us to combine the age 5 and 9 scores. For participants with scores at both the child and adult time points (10 cases, 15 controls), cases scored significantly lower than controls in childhood (d=.94, p<.03) and as adults (d=1.66, p<.005). After adjusting for parental (maternal) education, the effect sizes were 1.13 (p<.02) and 1.83 (p<.0002), respectively. Residualized scores were calculated to indicate the number of standard deviations (SDs) above or below the predicted adult score, given one's childhood scores. On this measure, the mean case-control difference was -1.47 SDs after adjusting for maternal education, consistent with significant relative decline over time among the cases (p<.0009). These findings indicate that individuals who developed adult schizophrenia demonstrated impaired receptive vocabulary during childhood and manifested further deterioration sometime between childhood and midlife. The results are consistent with both reduced IQ in children who later develop schizophrenia as well as continued neurocognitive decline; however, we cannot be certain whether the continued deterioration took place before and/or after the onset of illness. Future analyses will examine possible relationships between decline in cognitive performance and perinatal complications.

THE EFFECT OF 9/11 ON THE INCIDENCE OF PARANOID DISORDERS AND CONTENT OF PARANOID DELUSIONS

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The content of paranoid delusions is the subject of sparse research. Historically changes in technology have been incorporated into paranoid delusions (e.g., pneumatic devices, radar, x-rays, computer chips). Further, certain organizations are commonly involved in such delusions including the government and their spy organizations (e.g., CIA), the Masons, Vatican, etc. Unanswered is whether historic events can infiltrate the content of paranoid delusions. Moreover, are historic events risk factors that might increase the number of cases of paranoid disorders. The events of 9/11 provide an ideal model for answering these questions. A randomly selected number of 196 hospitals and community mental health centers throughout the U.S. were contacted and asked if they had seen changes in the content of paranoid delusions (e.g., terrorists, Islamic Jihad) in patients admitted post-9/11 and if the number of cases of paranoia, broadly defined, had increased since 9/11. Given that the number of cases of other mental illnesses (e.g., PTSD) increased in the New York City area, hospitals in that city plus Washington, D.C. were over-sampled. Results indicate approximately 90% of facilities observed no significant changes in either the content of paranoid delusions or the incidence of paranoid dis-

orders. This is despite the fact that recent polls indicate that 69% of residents in NYC and many individuals throughout the country feel unsafe and very concerned about possible terrorist attacks. Although 30% of facilities had at least one case in which terrorist themes were prominent these tended to have occurred in the period soon after 9/11. These findings suggest that the risk factors for paranoid disorders do not appear to include historic traumatic events, which are clearly risk factors for other types of mental illnesses.

PREVALENCE AND CORRELATES OF PSYCHOTIC-LIKE EXPERIENCES AND OTHER DEVELOPMENTAL ANTECEDENTS OF SCHIZOPHRENIA IN CHILDREN AGED 9-12 YEARS

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Population surveys and cohort studies have demonstrated an association between schizophrenia and socio-demographic variables such as ethnicity and migration. Within the United Kingdom, the incidence of schizophrenia among the African-Caribbean and Black African populations is raised relative to the White British population. These socio-demographic variables are similarly associated with self-reported psychotic symptoms in the general adult population. Using questionnaires, the present study sought to determine whether ethnicity and migrant status were associated with 9-12 year-old children's experience of a triad of putative antecedents of schizophrenia, including motor and language developmental delays, emotional and behavioural problems, and psychotic-like experiences. Participants were recruited through General Practitioners and schools. Children and parents completed the Strengths and Difficulties Questionnaire to rate behaviour and emotional adjustment, and questions (extended and revised from the Diagnostic Interview Schedule for Children) to assess psychotic-like experiences. Parents reported developmental lags, child's ethnicity, and child and parent migrant status. 2592 children and 602 parents completed questionnaires. 10% of boys and 7.3% of girls experienced a triad of antecedents comprising at least one psychotic-like experience, emotional or behavioural problem, and motor and/or speech delay. Ethnicity was significantly related to children's experience of the triad of putative antecedents of schizophrenia. Relative to White British children, African-Caribbean children were significantly more likely to experience the antecedent triad. There were also non-significant trends for Black African children to be more likely, and for South Asian and Oriental children to be less likely, to experience the triad. There was no evidence of association between migrant status and experience of the antecedent triad. Among a community sample of children aged 9-12 years, child and parent responses to questionnaires identified a group who present a triad of putative antecedents of schizophrenia, and who may thus experience increased risk for developing the illness. Ethnicity was related to children's experience of the antecedent triad in a manner similar to that observed for self-reported psychotic symptoms in general U.K. adult population samples, and for schizophrenia. Supported by NARSAD, U.K. Department of Health, and the BMA Margaret Temple Award.

A COMPARISON OF SELECTED RISK FACTORS FOR UNIPOLAR DEPRESSIVE DISORDER, BIPOLAR AFFECTIVE DISORDER, SCHIZOAFFECTIVE DISORDER, AND SCHIZOPHRENIA

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Objective: Growing evidence of an etiologic overlap between schizophrenia and bipolar disorder has become increasingly difficult to disregard. In this study we examined paternal age, place of birth, small for gestational age, and parental loss as risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia, focusing on a comparison between schizophrenia and bipolar disorder. Furthermore, we examined the incidence of the disorders in a population based setup and evaluated our results in the context of the dichotomization of bipolar disorder and schizophrenia. Method: We established a register-based cohort study of more than 2 million persons born in Denmark. Relative risks for the 4 psychiatric disorders were estimated by survival analysis, using Poisson regression. Results: Differences were found in age specific incidences. Loss of a parent (especially by suicide) and high paternal age were risk factors for all four disorders. Urbanization at birth had a major impact on the risk of schizophrenia. Children born preterm had an excess risk of all four disorders if they were born small for gestational age. Conclusions: An overlap in the risk factors examined in this study was found, and the differences between the phenotypes where quantitative rather than qualitative, that is, only the magnitude, and not the direction of the risk factors, differed. This could suggest a genetic and environmental overlap between the disorders. However, large gender differences and differences in the age-specific incidences in the four disorders were present and the results call for further research examining multiple risk factors at the same time, and comparing bipolar disorder and schizophrenia in the same setup.

RESOLVING THE LATENT STRUCTURE OF SCHIZOPHRENIA ENDOPHENOTYPES USING EM-BASED FINITE MIXTURE MODELING

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Prior research has focused on the latent structure of endophenotypic markers of schizophrenia liability, also known as schizotypy. This work supports the existence of two relatively distinct latent classes and derives largely from the taxometric analysis of psychometric values. The present study used finite mixture modeling as a technique for discerning latent structure and employed the laboratory-measured endophenotypes of sustained attention deficits and eye tracking dysfunction as endophenotype indexes. Using a large, adult community sample (N = 311), finite mixture analysis of the sustained attention index d' and two eye tracking indexes (gain and catch-up saccade rate) revealed evidence for two latent components. A putative schizotypy class accounted for 27% of the subjects. A supplementary maximum covariance taxometric analysis of these data yielded highly consistent results. The subjects in the schizotypy component displayed higher rates of schizotypal personality features and an increased rate of treated schizophrenia in their first-degree biological relatives as compared to subjects in the

other component. Substantive implications of these results are examined in light of major theories of schizophrenia liability, and the methodological advantages of finite mixture modeling for psychopathology research, with particular emphasis on genomic, are discussed.

RECRUITMENT SOURCE IMPACTS IN SCHIZOPHRENIA RESEARCH

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Over the past few years, members of our schizophrenia research group have conducted a variety of analyses examining differences between recruitment sources, including comparisons between: samples with different patterns of substance use recruited for clinical and epidemiological studies (Baker et al., 2005); samples recruited from general practices and public mental health services (Carr et al., 2002); and samples recruited from non-treatment (Research Register) and treatment settings (Loughland et al., 2004, 2007). These findings generally reinforce the notion that a severity/functioning gradient exists across schizophrenia recruitment sources, which has important implications for research design, recruitment, analysis and generalizability. This paper attempts to synthesize the findings from these studies and to provide a methodological context or framework for viewing recruitment source impacts. Since random sampling is rarely possible, a greater focus needs to be placed on purposive sampling strategies and on the preliminary identification of potential threats to (internal, construct and external) validity, prior to subject recruitment. By being more explicit about the factors that could impact on the key inferences we hope to draw, better sampling templates might be able to be devised, which achieve greater heterogeneity on the characteristics of interest.

SUPERIOR ACADEMIC PERFORMANCE AT AGE 16 PREDICTS ADULT BIPOLAR DISORDER, BUT POOR PERFORMANCE PREDICTS SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: A NATIONAL COHORT STUDY

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BACKGROUND: Prospective cohort studies using cognitive test scores have demonstrated clear premorbid deficits in schizophrenia, but it is not known whether these are reflected in school performance. Furthermore, it is not certain whether bipolar disorder is associated with premorbid cognitive deficits. We therefore investigated whether school performance at age 16 is associated with adult bipolar disorder, schizophrenia and schizoaffective disorder. METHOD: National population registers were used in a historical cohort study. 715,401 Swedish children completing compulsory education between 1988 and 1997 were followed up using national registers until Dec 31, 2003. Their school grades at age 16 were examined as predictors of hospital admission for schizophrenia, bipolar disorder, schizoaffective disorder and other psychoses, controlling for potential confounders. Cox proportional hazard models were used to calculate Hazard Ratios (HR), using 95% confidence intervals (CI). RESULTS: Children with excellent school performance (>2 standard deviations above the population mean) were at increased risk of bipolar disorder. Poor performance predicted schizophrenia and schizoaffective disorder, and no students with excellent school performance developed either of these disorders. Receiving the lowest (E) grade was significantly associated with risk of future schizophrenia at the p<0.001 level for every school subject. By contrast, achieving an A grade was a significant predictor of later bipolar disorder in almost half the school subjects. CONCLUSION: School performance has opposite associations with schizophrenia and bipolar disorder, suggesting important differences in aetiology.

Hazard ratios with 95% confidence intervals for schizophrenia and bipolar disorder at 5 levels of school performance

School performance	Schizophrenia	Bipolar Disorder
Excellent	0.00	2.71 (1.41, 5.21)
Good	0.81 (0.59, 1.11)	1.26 (0.90, 1.80)
Average (reference)	1.00	1.00
Poor	1.94 (1.53, 2.46)	1.35 (0.94, 1.94)
Very poor	3.87 (2.80, 5.34)	2.15 (1.19, 3.78)

All hazard ratios are adjusted for socioeconomic group, gender, paternal and maternal age >40 at birth, parental education, spring birth, low birth weight, length and head circumference for gestational age, preterm delivery and neonatal hypoxia.

SCHIZOPHRENIA IN THE OFFSPRING OF ANTENATALLY DEPRESSED MOTHERS AND FAMILIAL RISK – OVER 30-YEAR FOLLOW-UP OF THE NORTHERN FINLAND 1966 BIRTH COHORT

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Objective: Maternal depression is common during pregnancy. The aim was to study the association between mothers' antenatal depressed mood and schizophrenia in their offspring with special consideration to Familial Risk for psychosis. Methods: In the Northern Finland 1966 Birth Cohort mothers of 12 058 babies were asked at mid-gestation at the antenatal clinic if they felt depressed. This general population birth cohort of the children was followed up for 31 years being record-linked with the FHDR covering the years 1982-97. Mothers and fathers appearing on the FHDR between 1972-2000 for any psychosis (i.e. ICD-8 290-299, DSM-III-R diagnoses 290-299, and ICD-10 F 20-29) were identified. Results: Of the mothers of the cohort members, 14 % felt depressed during pregnancy. The cumulative incidence of hospital-treated schizophrenia was 1.3% among the offspring of depressed mothers and 0.9% among the descendants of non-depressed mothers (RR 1.5; 95%CI 0.9-2.4). Of the offspring, 4,4% had had a mother and/or a father being psychotic. The elevated level of maternal depressed mood in pregnancy among schizophrenia patients was connected to Familial Risk for psychosis. Conclusion: Mothers' depressed mood in pregnancy per se is unlikely to increase the risk for schizophrenia in the offspring, but seems to be connected to Familial Risk for psychosis in the close relatives of schizophrenia patients. Acknowledgements: This work was supported by grants from the Signe and Ane Gyllenberg Foundation. References: Rantakallio P. (1969) Groups at risk in low birth weight infants and perinatal mortality. Acta Paediatr Scand 193:1-71 Mäki P et al. (2004) Schizophrenia in the offspring of antenatally depressed mothers – a 31

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DEVELOPMENTAL AGE AND THE SPECIFICITY OF INSULTS FOR SCHIZOPHRENIA VERSUS OTHER PSYCHIATRIC DISORDERS

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Data from a large prospective birth cohort will be presented to demonstrate that later paternal age is a specific risk factor for schizophrenia, vis-à-vis other psychiatric disorders. Additional information form this population cohort shows that prenatal stress in specific early gestational weeks is only associated with schizophrenia risk, while adversity in other periods is related to the risk for other conditions. Both late paternal age and early gestational fetal stress may influence gene expression during key stages of prenatal development. By contrast, insults occurring after infancy appear to similarly increase illness risk across the spectrum of psychiatric disorders. These include traumatic brain injury and early childhood loss. These exposures may exert their illness promoting effects via nonspecific pathways, such as an increase in HPA stress axis functioning, or by interactions with otherwise latent susceptibility alleles.

RATE AND TIME TO RELAPSE AND THE ROLE OF PREDICTORS OF RELAPSE IN THE FIRST TWO YEARS OF TREATMENT OF FIRST EPISODE PSYCHOSIS (FEP) IN A SPECIALIZED EARLY INTERVENTION (EI) SERVICE

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Risk of relapse following treatment of a first episode psychosis is relatively high in the first one to five years and is reported to be determined largely by non-adherence to treatment and, to a lesser degree, pre-morbid adjustment. Specialized treatment in early intervention services may improve outcome including a reduction of risk of relapse of psychosis. Whether the predictors of relapse are the same in EI services remains unexplored. The objective of this study was to examine risk of relapse in an epidemiological sample of FEP patients treated in a speiclaized EI service for two years. Method: Relapse was based on monthly ratings on the Scale for Assessment of Positive Symptoms and weekly ratings based on Life Chart Schedule (WHO). Predictor variables included gender, duration of untreated psychosis (DUP) and of total length of any psychiatric symptoms (DUI), age of onset, pre-morbid adjustment, co-morbid diagnosis of substance abuse at one year, time taken to achieve remission of psychotic symptoms and adherence to medication. Univariate analyses were followed by logistic regression for rate of relapse and survival analysis with Cox proportional hazard analysis was used for time to relapse as the dependent variable. Results: Of the 207 patients offered treatment 199 accepted, 161 showed remission of positive symptoms and were, therefore, at risk for relapse. We observed a considerably lower rate of relapse (21.6% at one year and 29.3% at two years) with 33 weeks as the mean time to relapse. Relapse rates were significantly higher for patients with a co-morbid diagnosis of substance abuse (24% vs 9%, Chi sq. 5.98, p=.01) and those with shorter DUI (Mann Whitney U, Z= -2.44, p=.01). Gender, adherence to medication, age of onset, time to remission and pre-morbid adjustment were not associated with risk of relapse. Logistic regression confirmed the influence of substance abuse diagnosis (B= 1.06,, p=0.03) and shorter DUI on risk of relapse in the 2nd year (Beta= -.003, p=.05) of follow-up. Hazard ratio for time to relapse was associated with only a co-morbid diagnosis of substance abuse (HR= 2.49, p=.01, CI 1.21-5.10). Conclusions: Lower rates of relapse in specialized EI services may be associated with improved adherence to medication. Some of the remaining risk may be associated with continued substance abuse, another malleable predictor.

DIAGNOSTIC AND GENDER DIFFERENCES IN FIRST EPISODE PSYCHOSIS

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Objective: Previous research has found that women present with later age of onset of first psychotic symptoms and milder symptom severity. It is necessary to replicate these differences in new cohorts of first episode psychosis patients. We report here early results of demographic variables and treatment response in first episode psychosis in both schizophrenia and affective psychotic disorders. Method: Seventy-two patients were recruited from the University of Illinois Medical Center. First episode psychosis patients were evaluated free of pharmacological treatment. Lifetime exposure to antipsychotics was less than 16 weeks. Diagnosis was determined using the SCID and consensus diagnosis based on all available information. All patients were assessed on standardized research instruments evaluating symptoms and global functioning at baseline and 4 weeks after treatment with risperidone. Results: In this ongoing study, women with schizophrenia presented for psychiatric treatment an average of 2 years earlier than men. Overall, women with schizophrenia tended to present with greater impairment in global functioning and more severe depression. Men with affective psychotic disorders presented for treatment an average of 3 years earlier than women. Overall, the severity of psychotic symptoms in males was slightly worse at initial presentation. The degree of clinical improvement was not significantly different between schizophrenia and affective psychotic disorders as measured by the PANSS scores. Conclusions: Early data emerging from this study indicate that presentation for initial psychiatric treatment occurs earlier for women in schizophrenia and later for men in affective psychoses. Clinical differences between schizophrenia and affective psychoses at first psychotic episode will be discussed.

SCHIZOID-LIKE FEATURES AND SEASON OF BIRTH IN A NONPATIENT SAMPLE

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Deficit schizophrenia, which is characterized by decreased social interests and a lack of depression, has a well-replicated and relatively strong association with June/July birth. Patients with deficit schizophrenia have elevated scores on Social Anhedonia, compared to other patients with schizophrenia. As some features of schizophrenia are found in subclinical form in nonpatient groups, we hypothesized that June/July birth would be associated with the combination of decreased sociality in the absence of depression in a nonpatient group as well. We administered the Beck Depression

scale, the Chapman Perceptual Aberration and Magical Ideation scales, and the Chapman Social Anhedonia scale to a group of university students. The Perceptual Aberration and Magical Ideation scale scores were combined into a single psychotic-like symptom score (PerMag). Blind to month of birth, each subject (N=425) was given a score that quantified the combination of social anhedonia and an absence of depression. Analyses were then performed in subjects in the upper 50% of PerMag scores who had complete data (N=171, 27.5% male). June/July birth (compared to birth in any other month; F=4.4, p=.037) and male gender (F=9.78, p=.002) were both found to be associated with higher scores on the combination of social anhedonia and a low depression score; the interaction of these factors was not significant (F=1.18, p=.278). These results suggest the same seasonal factor that contributes to risk of deficit schizophrenia affects personality characteristics in the general population.

PATERNAL AGE AND MORTALITY IN THE NORTHERN FINLAND 1966 BIRTH COHORT

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Introduction: Advanced paternal age (APA) is a replicated risk factor for schizophrenia, and is also associated with other adverse health outcomes. Schizophrenia is associated with increased mortality. A previous report from a small, biased sample found APA was associated with increased mortality in females but not males. Hypothesis: We hypothesized that APA is associated with increased mortality in the general population and within psychosis. Methods: The Northern Finland 1966 Birth Cohort is a population-based sample ascertained during mid-pregnancy of 12,068 pregnant women who had 12,058 live-born children. 10,934 offspring who were living in Finland at the age of sixteen were followed until end of the year 2005. Information on cause of death was obtained from death certificates. Results: In the general population, APA (as a continuous variable) was associated with significantly increased mortality in female (p=0.029) but not male offspring. In psychotic subjects (N=155), APA was also associated with increased mortality in females (p=0.049), but not in males. Conclusions: APA is associated with increased mortality in females, but apparently not in males. Although the relatively young age and small number of psychotic subjects limited the statistical power of the analyses, our results raise the possibility that APA contributes to increased mortality within schizophrenia.

OBSTETRIC COMPLICATIONS AS A RISK FACTOR FOR FIRST PSYCHOTIC EPISODES IN ADOLESCENCE

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INTRODUCTION: There are reports of significant association between Obstetric Complications (OC) and childhood psychosis. HYPOTHESIS: The risk of presenting a first psychotic episode in adolescence will be significantly higher in subjects with records of OC. METHOD: Case-control study with 102 adolescents diagnosed of first psychotic episode, and 94 healthy controls, matched by sex, age (mean age was 15) and years of education. The Obstetric Complications Scale (OCS, 15 items) was administered to parents, and completed with medical records when possible. Socio-demographic variables and family history of mental disorders were also collected. A logistic regression was performed to quantify the risk of psychosis in adolescence, based on OC, adjusting for confusion factors. RESULTS: OC appeared more frequently in the records of patients than in the records of controls (34.3 % vs. 22.3%, p=.064). Significant differences between patients and controls were found in the group of Prenatal OC (15.7% vs. 5.3%, p<0.05). Among Prenatal OC, bleeding in pregnancy (item 4) appeared as the most significant (12.7% vs. 2.1%, p<0.01). In the logistic regression, bleeding in pregnancy showed an Odds Ratio of 6,7 (CI 95%=1.4–30.6) and, after being adjusted by Socio Economic Status (SES) and Psychiatric Family History, turned to 5,1 (CI 95%=1.0–24.9). CONCLUSIONS: Bleeding in pregnancy is a likely independent risk factor for presenting a first psychotic episode during adolescence. REFERENCES: Owen MJ, Lewis SW, Murray RM. Obstetric Complications and Schizophrenia: A Computed Tomographic Study. Psychol Med 1988; 18: 331-9. Alaghband-Rad J, Hamburger SD, Giedd JN, Frazier JA, Rapaport JL. Childhood-Onset Schizophrenia: Biological Markers in Relation to Clinical Characteristics. Am J Psychiatry 1997, 154: 64-68. Cannon M, Jones PB, Murray RM. Obstetric Complications and Schizophrenia: Historical and Meta-Analytic Review. Am J Psychiatry 2002: 159: 1080-1092. Ordonez AE, Bobb A, Greenstein D, Baker N, Sporn A, Lenane M, Malaspina D, Rapaport J, Gogtay N. Lack of Evidence for Elevated Obstetric Complications in Childhood Onset Schizophrenia. Biol Psychiatry 2005; 58:10-15.

THE EPIDEMIOLOGY OF INTELLECTUAL DISABILITY COMORBID WITH SCHIZOPHRENIA AND OTHER PSYCHIATRIC DISORDERS: CLINICAL MANIFESTATIONS AND AETIOLOGICAL IMPLICATIONS

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Background. The population prevalence of intellectual disability (ID) is estimated at ~1%, and it is reported that ~3% of intellectually disabled persons will have schizophrenia. However, research findings in the area of psychiatric illness comorbid with ID have not been consistent, and there have been few whole-of-population studies. Aims and methods. Two Statewide registers, the ID register and the psychiatric case register, were linked in order to: (i) get estimates of the prevalence of comorbidity; (ii) compare levels of comorbidity across diagnostic categories including schizophrenia and bipolar disorder; and (iii) describe the profile of persons with a comorbid illness. Combining data from both registers produced 245,749 individuals with a psychiatric disorder, ID (including borderline IQ of 70-74) or both. Two birth cohorts (1950-64 and 1965-79) were identified for intensive analysis. Results. Overall, 1 in 3 persons with ID had some psychiatric illness. In the birth cohorts, 5.1% of the older cohort with ID and 3.7% for the younger cohort had a diagnosis of schizophrenia. This is at least 3 times higher than population lifetime estimates for schizophrenia. The percentages for bipolar disorder and unipolar depression were within population estimates. The prevalence of ID among persons with psychiatric illness was higher than population estimates for ID. Among persons with a psychiatric illness, 1.8% of the older cohort and 2.3% of the younger cohort had ID; the per-

centages among persons with schizophrenia were much higher at 5.2% and 4.5% respectively. Compared to those with "ID only", comorbid cases were significantly less likely to have a biomedical or genetic basis to their ID or to have Down syndrome, and were significantly more likely to have pervasive developmental disorder. Compared to those with "psychiatric illness only", comorbid cases had a more serious illness as indicated by: earlier age at first contact with psychiatric services; more inpatient admissions; more inpatient days. The aetiological implications of the findings and the challenges of researching comorbid disorders will be discussed. Conclusions. The facility to integrate records held in separate administrative jurisdictions has had a marked impact on our capacity to estimate the extent of comorbidity and its prevalence across diagnostic categories, to understand its clinical manifestations and to start to untangle aetiological implications.

THE PREVALENCE, AND CORRELATES, OF SELF-REPORTED PSYCHOTIC SYMPTOMS IN A HEALTHY POPULATION BASED SAMPLE: FINDINGS FROM THE AESOP STUDY

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There is increasing evidence that psychotic symptoms occur in the general population on a continuum of severity. We sought to investigate the prevalence, and correlates, of self-reported psychotic symptoms in a population based sample of healthy controls drawn from the MRC AESOP study. Data were collected from a group of randomly selected community control subjects, recruited as part of the AESOP study, a three-centre population based incidence and case-control study of first episode psychosis. All control subjects completed the Psychosis Screening Questionnaire and the MRC Sociodemographic Schedule. The prevalence of self-reported psychotic symptoms was calculated, and associations were investigated using odds ratios and logistic regression. Data are presented for two of the study centres only (Nottingham and south-east London, UK). A total of 372 control subjects were recruited. The proportion reporting one or more psychotic symptom was 19.4% (n = 72). The variables associated with self-reported psychotic symptoms were: 1) Age 16-25 (OR 1.93, 95% CI 1.05-3.55); 2) African-Caribbean ethnicity (OR 2.00, 95% CI 1.06-3.77); 3) Black African ethnicity (OR 3.82, 95% CI 1.38-10.59); 4) Living in rented accommodation (OR 2.22, 95% CI 1.30-3.81); 5) Living alone (OR 1.94, 95% CI 1.14-3.30); 6) Being single (OR 1.75, 95% CI 1.04-2.94); and 7) Long-term separation from a parent before the age of 16 (OR 2.60, 95% CI 1.44-4.69). There was weak evidence that psychotic symptoms were more common in the London sample (OR 1.63, 95% CI 0.97-2.74). There was no association between gender and self-reported psychotic symptoms. When these variables were simultaneously adjusted for, only Black African ethnicity (Adj. OR 3.29, 95% CI 1.00-10.81) and separation from parents (Adj. OR 2.01, 95% CI 1.03-3.92) retained a significant effect. The prevalence of self-reported psychotic symptoms in our sample was very similar to that reported in previous studies. The variables associated with such symptoms (age, ethnicity, living in rented accommodation, living alone, being single, separation from parents) have been previously found to correlate with clinically treated psychosis in both AESOP and other studies. These findings are consistent with a continuum view of psychosis.

RISK FACTORS FOR SCHIZOPHRENIA AND BIPOLAR DISORDER: THE SAME BUT DIFFERENT

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Data will be presented from cohort, first episode and family studies concerning the similarities and differences concerning risk factors for schizophrenia and bipolar disorder. The data indicate that obstetric hazards, childhood cognitive problems, widespread grey matter deficits, and urban living are significant risk factors for schizophrenia but not for bipolar disorder. On the other hand, certain susceptibility genes such as neuregulin and G72 appear to influence risk of both schizophrenia and bipolar disorder as does drug abuse (especially cannabis) and the migration of black individuals to European countries.

EPIDEMIOLOGICAL EVIDENCE CONCERNING THE DIAGNOSTIC STATUS OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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Data from cohort, first episode and family studies concerning the similarities and differences concerning risk factors for schizophrenia and bipolar disorder. The data indicate that obstetric hazards, childhood cognitive problems, widespread grey matter deficits, and urban living are significant risk factors for schizophrenia. It is also clear from studies of the general population that a proportion of normal individuals have minor delusions or hallucinations; furthermore the same risk facts are associated with these as are associated with schizophrenia itself. This suggests that schizophrenic is better seen as a continuum rather than a discrete category. Other risk factors eg drug abuse and the migration of black individuals into European countries seem to be shared with bipolar disorder, and certain susceptibility genes such as neuregulin and G72 appear to influence risk of both schizophrenia and bipolar disorder. Thus schizophrenia and bipolar disorder should be seen as overlapping conditions but with developmental impairment largely confined to the former

RISK OF SCHIZOPHRENIA AND ANTIBODIES TO *TOXOPLASMA GONDII* AMONG U.S. MILITARY PERSONNEL

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A number of studies report an association between *Toxoplasma. gondii (Tg)* infection and schizophrenia (SCZ). *Tg* infection prevalence in the US is about 20% in adults. *Tg* is neurotropic. Infection of glial cells may result in an alteration in levels of dopamine and other neurotransmitters. Acute *Tg* infection can cause symptoms compatible with SCZ, and chronically infected persons may have behavior and personality profile changes. Most previous studies of *Tg* risk employed small samples, single post-diagnosis specimens, and retrospectively determined control populations. We conducted a pilot case-control study of *Tg* antibodies among a cohort of military personnel, using stored serum samples obtained before and after the onset of symptoms. Cases (n=200)

were military personnel discharged for SCZ. Controls (n=591), matched on several factors, were personnel not discharged with SCZ. We used microplate enzyme immunoassay to measure IgG antibody levels in serum samples obtained pre- and post-diagnosis. Each subject had 1-3 specimens with at least 1 sample obtained pre-illness onset. We employed 2 logistic regression models: IgG as a continuous variable with each serum specimen IgG level an independent observation, and IgG as a categorical variable to assess the single highest level per subject occurring before illness onset. Both methods evaluated the effect of matched and un-matched covariates. Both analyses found significant increases in SCZ risk associated with higher levels of antibody. The odds ratio (OR) for continuous IgG was 1.40 ($p<.05$); the OR for categorical IgG was 2.15 ($p<.05$). Both models found increases in risk associated with IgG levels drawn shortly before onset of illness, while the continuous model also found an association for specimens drawn after onset. The categorical model also found that those who had 3 or more years of service had a substantially higher odds ratio of schizophrenia risk associated with elevated antibody levels. Our 2 different modeling approaches indicate that SCZ is associated with increased levels of *Tg* IgG antibodies measured prior to and after diagnosis. *Tg* does not appear to explain a large proportion of SCZ, but those with high IgG levels are at a significantly higher risk of developing the disease. These findings will be used to design and execute a larger study of military personnel, to better understand the role of Tg infection in SCZ, and to develop new methods of preventing and treating some cases of SCZ.

COMPARISON OF BASELINE METABOLIC VARIABLES BETWEEN DRUG-NAIVE FIRST-EPISODE PSYCHOSIS PATIENTS AND HEALTHY CONTROLS

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Background. Schizophrenia is suspected to be associated with an increased risk for diabetes mellitus. It is unclear whether patients suffering from schizophrenia are prone to develop diabetes due to a shared vulnerability for the two disorders or due to previous exposure to neuroleptics and the life style associated with the disease. Studies involving previously untreated patients, likely to provide more accurate information, have been rare and have yielded contradictory findings. Objective and method. Drug-naïve first-episode psychoses patients (N=42) with a life-exposure to antipsychotic medication of less than 7 days and matched controls (N=38) were compared on a number of glucose metabolic parameters, including oral glucose tolerance, and lipid profiles. Results. There were no significant differences between the controls and patients on age, gender, ethnicity, waist circumferences, BMI, family history of diabetes mellitus, hypertension and obesity. The curves of glucose (AUC P =26,8 AUC C=25,5 p=0,27) and insulin (AUC P=353,8 AUC C=331,1 p=0,58) and grade of insulin resistance (HOMA) also showed no significant differences (IR P = 3,65 IR C=3,73 p=0,86). One control and none of the patients had impaired fasting glucose level while three patients and one control had impaired glucose tolerance. HDL cholesterol in the control group was significantly higher than in the patient group (1,25 versus 1,05, p=0,009) but levels of total cholesterol, LDL and triglycerides were not different between the two groups. Conclusions. Our results suggest that, compared to normal matched controls, previously untreated first-episode psychosis patients do not show any evidence of increased vulnerability to diabetes or abnormal lipid metabolism.

SUBJECTIVE EXPERIENCE OF COGNITIVE FAILURES PREDICTS SUBCLINICAL NEGATIVE SYMPTOMS IN THE GENERAL POPULATION

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Objective: Previous studies have shown that the association between cognitive dysfunctions and psychotic symptoms in schizophrenia also exists at the level of the subclinical phenotype. The aim of this study was to extend this finding by examining the relationship between subjective cognitive functioning and the subclinical psychosis phenotype in the general population using a) a cross-trait within relative approach, and b) a cross-trait between relative approach. Methods: At baseline, the Cognitive Failure Questionnaire (CFQ) and the Community Assessment of Psychic Experiences questionnaire (CAPE) were administered in a general population sample of genetically related individuals (n=768). Individuals scoring high (>75th pct) or average on the CAPE (between 40th and 60th pct) (n=488) were re-interviewed with the Structured Interview for Schizotypy-Revised (SIS-R) at follow-up (mean interval 7.7 months, SD 4.8 months). Results: Cross-trait within relative analysis showed a significant association between the CFQ and negative symptoms, assessed with the CAPE (cross-sectional association, beta=0.356, p=0.000, adjusted for the other CAPE dimensions) and with the SIS-R (longitudinal association, beta= 0.37, p=0.000, adjusted for the other SIS-R dimensions). The longitudinal association was only slightly reduced after adjustment for baseline negative symptoms. No association was found between the CFQ and positive psychotic experiences($p>0.7$). Cross-trait between relative analysis showed that subjective experience of cognitive failures in one relative was not associated with any of the dimensions of the subclinical psychosis phenotype in the other relative. Conclusion: Negative subclinical symptoms were strongly linked with subjective experience of cognitive failures in the general population, both cross-sectionally and longitudinally, whereas positive symptoms showed no such relationship. The overlap between the negative symptoms of psychosis and subjective experience of cognitive failures was due to individual effects rather than familial liability.

SPIRITUAL BELIEFS AND RELIGIOUS PRACTICES AMONG PERSONS WITH SCHIZOPHRENIA IN RURAL COMMUNITY

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Given spirituality of persons with schizophrenia in rural community is rarely studied, the aim of the study was to explore the relation between spiritual beliefs or religious practices and outcome of persons with schizophrenia in rural China. A 10-year follow-up investigation among a 1994 cohort (n=510) of patients with schizophrenia, who met ICD-10 criteria, was conducted in Xinjin, Chengdu,

China(1). Five hundred patients (98.0%) and their informants were followed up in 2004 using Patients Follow-up Scale (PFS). Among the 500 patients, 109 subjects (21.8%) once participated in various religious practices and 82 subjects (16.4%) believed in afterlife during the follow-up period. Females were significantly more likely to take part in religious practices and believe in afterlife (31.8%, 23.6%) than males (10.3%, 8.2%) ($p<0.001$). Single patients (4.6%) were less likely to participate in religious practices than married patients (25.5%) ($p<0.001$). There were no relations between religious practices and antipsychotic medication or hospitalization ($p>0.05$). Patients who participated in various religious practices were more likely to believe in afterlife (50.5%) than those who did not participate in religious practices (6.9%) ($p<0.001$). Patients who believed in afterlife had significantly more suicide attempts (23.2%) than those who did not believe in afterlife (12.2%) ($p<0.01$). The results of this study indicate that religious practices are relative common in persons with schizophrenia in rural community. Spiritual beliefs may influence the patient's suicidal behavior. The spiritual factors of mental disorders should be taken into account in developing mental health interventions. Acknowledgments This work was supported in part by China Medical Board in New York (CMB, 92-557) and NIH/FIC 1 R01 TW007260-01 (M.S. Ran, PI). References 1. Ran MS, Chan CLW, Chen EYH, Xiang MZ, Caine ED, Conwell Y. Homelessness among patients with schizophrenia in rural China: A 10-year cohort study. Acta Psychiatr Scand 2006; 114: 118-123.

PREMORBID INTELLECTUAL DECLINE IN SCHIZOPHRENIA: EVIDENCE FROM A POPULATION BASED MULTIGENERATIONAL STUDY

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Background: Evidence suggests that some future schizophrenia patients experience intellectual deterioration from childhood through adolescence. It has been recently proposed that patients may fail to reach their expected level of cognitive functioning based on familial potential. Methods: The study used a nested case-control design. The cohort comprised of all adolescents over 5 consecutive years who received a mandatory assessment by the Israeli Draft Board for intellectual performance and educational attainment at age 17. Cases were 159 individuals with a diagnosis of schizophrenia. Data on intellectual performance and educational attainment of the fathers of cases was also obtained from the Draft Board. Each case-father pair was individually matched to 5 control-father pairs by gender, birth year of the case, school attended at time of testing and father's year of assessment by the Draft Board. Results: Fathers of future patients had significantly lower IQ scores compared of fathers of controls ($p<0.001$; Effect Size: 0.31). As expected, future patients also had significantly ($p<0.001$) lower IQ scores compared to controls. However, the magnitude of effect was 30% larger than that of their fathers (Effect size: 0.42). The increase in impairment over generations was significant ($p<0.05$) after accounting for changes over generations in education. Both low paternal IQ and low IQ in the offspring were independently associated with increased risk of schizophrenia in the offspring (OR=1.2 and 1.4 over 5 categories for fathers and offspring, respectively). Conclusions: Premorbid intellectual impairments in schizophrenia are familial. A large proportion of patients experience cognitive function decrement before the onset of psychotic disorder as defined by a failure to reach the expected level of cognitive functioning.

PREMORBID INTELLECTUAL AND BEHAVIORAL FUNCTIONING AND RISK OF DEVELOPING SCHIZOPHRENIA, NON-PSYCHOTIC OR PSYCHOTIC BIPOLAR DISORDER: A POPULATION LONGITUDINAL STUDY

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Background: Epidemiological studies indicate that a lower IQ score and abnormal social functioning increase risk for schizophrenia. Preliminary evidence suggests that lower IQ score also increases risk for manic-depressive psychosis. In contrast, it has been suggested that superior intellectual abilities may be associated with bipolar disorder. To our knowledge, there are no prior population-based longitudinal studies comparing premorbid functioning and risk of developing psychotic as compared to non-psychotic bipolar disorder requiring hospital admission. Methods: Participants were 600,000 adolescents born in Israel, and mandatory assessed by the draft board at age 17. Data were available on intellectual functioning at age 17 for both males and females, and on behavioral functioning in males. Data regarding psychiatric history was obtained using record linkage for psychiatric hospitalization during a 10-year follow-up period. Results: Hi IQ (>115) was associated with risk of non-psychotic bipolar disorder (Adjusted HR: 2.1). Extreme social behaviors (1SD or more above the mean) were associated with risk of psychotic bipolar disorder and with schizophrenia with a history of a bipolar episode (adjusted HR:1.7). Neither low or high IQ were associated with risk for these disorders. Conclusions: The associations between intellectual and behavioral functioning differs between bipolar disorders and schizophrenia, suggesting different neurodevelopmental etiologies.

IS MORTALITY RISK IN SCHIZOPHRENIA RISING? A SYSTEMATIC REVIEW

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Background: Mortality in schizophrenia is increased compared to the general population. It has been suggested that this excess has increased over time. The aim of this review is to systematically identify and collate studies related to the mortality of schizophrenia, to describe key features of these studies, and to explore the distribution of mortality estimates using various criteria. Methods: A broad search string: (schizo* or psych*) AND (mortality OR outcome OR follow-up) was used in MEDLINE, PsychINFO, Web of Science, and Google Scholar to identify studies in all languages that investigated mortality in schizophrenia between 1980 and 2006 . References were also identified from review articles, reference lists and by writing to authors. We examined the distributions of Standardized Mortality

Ratios (SMR) when sorted by various criteria, and undertook a random-effects meta-analysis in order to pool data for all cause mortality. In particular, we examined the data with respect to sex, cause of death, economic status of nation, and secular trends. Results: We identified 42 papers drawn from 19 different nations. The median (10-90% quantile) SMR for all-cause mortality for persons was 2.56 (1.41-5.98), with a corresponding pooled SMR (95% CI) of 2.55 (2.09, 3.11). No sex difference was detected. Suicide was associated with the highest SMR (12.3), however, most of the major causes of death categories were found to be elevated in schizophrenia. When assessed by several different methods, all-cause SMR has increased significantly over the last three decades. When sites were grouped by economic status, SMR for all-cause mortality from "less developed" countries was significantly higher than those from "developed" countries ($p<0.005$). Conclusions: Overall, schizophrenia is associated with a two to three-fold increased risk of mortality. Apart from suicide, the increased mortality associated with schizophrenia involves many different disease categories. Despite improvements in aspects of care for people with schizophrenia, paradoxically their mortality risk has increased over recent decades. As it is feasible that the second generation antipsychotics may contribute to additional morbidity and mortality in the decades to come, the increasing risk of mortality in schizophrenia is a cause for concern.

HYPOTHESIS: CHRONIC EXPERIENCE OF SOCIAL DEFEAT IS MAJOR RISK FACTOR FOR SCHIZOPHRENIA

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The purpose of the hypothesis is to explain a number of findings in the epidemiology of schizophrenia and to outline a biological mechanism that may underlie these findings. It is proposed that the chronic experience of social defeat, defined as inferior position or outsider status, leads to disturbed dopamine (DA) function in the brain and puts the individual at increased risk for schizophrenia. The hypothesis is derived from: (A) Epidemiological findings of increased risks (1) for migrants, especially those from developing countries and those with black skin color, (2) for subjects raised in urban areas (high levels of competition) (3) for subjects with low IQ, who are socially at a disadvantage (4) for subjects with hearing impairments (5) for subjects with a history of physical or sexual abuse. (B) Animal experiments. An important paradigm is the resident-intruder paradigm, whereby a male rat (the intruder) is put into the cage of another male (the resident). Repeated exposures to social defeat lead to sensitization, i.e., enhanced behavioural and DA response to DA agonists. (C) Research on neuroleptic-naive schizophrenic patients, which shows that their mesolimbic DA system is sensitized. Thus, patients resemble in some aspects defeated animals. The hypothesis can be tested. Firstly, using PET one can compare amphetamine-induced DA release in defeated and non-defeated individuals. Secondly, one can compare amphetamine-induced DA release in healthy migrants from a superhigh risk group to that in healthy natives. Thirdly, randomized studies of non-human primates can be used to examine whether exposed animals will develop greater subcortical DA activity. It is important to note that exposure to social defeat is neither a sufficient cause nor a specific risk factor for schizophrenia. It is also a risk factor for depression, addiction and antisocial behavior. Genes will determine which disorder the patient develops. Conclusion: The hypothesis explains some important findings in the epidemiology of schizophrenia, provides a mechanism whereby social factors impact on brain function, and is testable. Ref: Br J Psychiatry 2005, vol. 187, pp.101-102.

SUBCLINICAL PSYCHOTIC EXPERIENCES AND COGNITIVE FUNCTIONING AS A BIVARIATE PHENOTYPE FOR GENETIC STUDIES IN THE GENERAL POPULATION

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Cognitive deficits may be vulnerability markers for the development of schizophrenia. This study examined whether cognitive deficits are related to specific dimensions of subclinical psychotic experiences and whether associations between these variables are caused by additive genetic, common environmental and/or individual-specific environmental factors. A general population sample of 298 female twin pairs completed the Community Assessment of Psychic Experiences and a neuropsychological test battery. Associations between subclinical positive and negative psychotic dimensions and neuropsychological factors (episodic memory and information processing speed) were examined. Univariate correlation and structural equation analyses were performed to explore the role of genetic and environmental factors in the phenotypes separately. Bivariate correlation and structural equation analyses were applied to examine the causes of association. There were significant correlations between information processing speed and both the positive ($r = .11$; $p < .05$) and the negative dimension ($r = .10$; $p < .05$). For the negative dimension and for speed of processing, the data suggested a model that included genetic factors. The observed phenotypic correlation between the negative dimension and information processing speed could be solely explained in terms of additive genetic factors. Negative symptoms and information processing speed are associated at the subclinical level and this association appears to be influenced by genetic factors exclusively. This finding may guide the search for specific genes in samples characterized by both subclinical negative symptoms and slow information processing.

A LIFE-HISTORY STUDY OF FIRST-EPISODE PSYCHOSIS

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The identification of causal chains of risk factors has advanced our understanding of complex medical disorders. These chains frequently include genetic, biological, social and environmental risks. A life-history research approach provides a model in which the links between sequential risks can be identified. Multiple risk factors of small effect size occur in schizophrenia but the ways in which these risks interact are largely unknown. This paper describes a life-history methodology and the risks and developmental abnormalities found in patients with first episode psychosis (FEP). A detailed history of risks and abnormalities was obtained for 106 patients with FEP who were ascertained from a catchment-area population. This history included familial data and information about each of five time periods: gestation-birth, 0-5 years, 6-11 years, 12-15 years and 16 years to the onset of psychosis. Included were familial risks (familial psychiatric history, socioeconomic position, immigrant status and eth-

nicity), obstetrical events, and events during childhood and adolescence (head injury, physical illness, psychosocial stress and drug use). Childhood abnormalities included delayed milestones, poor social functioning, low academic achievement and emotional problems. Clinical assessments were completed at referral and at 9 to 12 months. Comparisons were made between patients and normal volunteers (N=47) and, where possible, with census data. A second-degree family history of psychosis was evident in 27% of patients. The rate of paternal but not patient immigration was elevated. Significantly high rates of maternal stress and tobacco use occurred during gestation and the rate of neonatal complications was high. Patients were more likely to have a minor head injury before 5 years and between 12 and 15 years. Tobacco and cannabis use were increased and, in the majority of cases, this began before 16 years. No delayed milestones were evident but patients were more likely to have speech difficulties and anxiety problems during childhood. Educational achievement was significantly low throughout school and poor social adjustment began after 11 years. The methodology of a life-history study of schizophrenia is described. Increased rates of several distinct risk factors were evident in a community sample of those with first episode psychosis. These risks occurred throughout childhood and adolescence, as did several developmental and behavioral abnormalities.

PREDICTORS OF 'DEFICIT-SYNDROME' SCHIZOPHRENIA

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The Manchester first-episode psychosis cohort 10 year follow-up study (Stirling et al, 2003) has indicated that outcome in schizophrenia is varied and difficult to predict. Nested within our cohort are a sub-group of individuals (n=19) who fulfill most of the criteria for the deficit syndrome (Carpenter et al, 1999); characterised by persistent primary negative symptoms [excluding inattention]. We have compared this group with the remaining members of the non-affective psychosis cohort. As expected, the deficit group could be distinguished from the non-deficit group on a raft of clinical, functional and cognitive 10 year outcome indices. Of more interest were the limited number of onset and pre-morbid measures that distinguished between groups. These included neurological signs, negative symptoms, and pre-morbid adjustment, but excluded duration of untreated psychosis, earlier non-psychotic episodes, neurocognition and positive symptoms at onset. A positive family history of mental illness also failed to predict the syndrome. The deficit syndrome is pernicious for the sufferer and costly for mental health and social services, yet accurate prediction of it remains illusive. Neurological signs and a preponderance of negative symptoms at first episode appear to be the strongest markers. Stirling et al: (2003), Schizophrenia Research, 65, 75-86 Carpenter et al: (1999), Biological Psychiatry, 46, 352-360

METABOLIC SYNDROME AMONG PERSONS WITH PSYCHOTIC DISORDERS IN A GENERAL POPULATION SURVEY

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Objective: To determine the prevalence of metabolic syndrome and investigate its components in individuals with psychotic disorders and individuals using antipsychotic medication in a general population study. Method: A nationally representative two-stage cluster sample of 8028 persons aged 30 or over from Finland. Laboratory and other measurements related to metabolic syndrome were taken in a health examination. We used SCID interview and case note data when making diagnostic assessments according to DSM-IV-TR criteria. Metabolic syndrome was diagnosed according to ATP- III criteria. Subjects who had not fasted the required four hours were excluded from the analysis. Prevalences of metabolic syndrome, adjusting for age, sex, and hours of fasting, were estimated by calculating predicted marginals, evaluated at eight hours of fasting. Results: The prevalence estimates of metabolic syndrome were 36.2%, 41.7%, and 24.9% among subjects with schizophrenia, other nonaffective psychosis, and affective psychosis, respectively, compared with 30.1% in subjects without psychotic disorders. Subjects with schizophrenia had significantly lower HDL and higher triglyceride and glucose levels and larger waist circumference, but also lower systolic blood pressure than the remaining study population. While all markers of metabolic syndrome were elevated among subjects with other nonaffective psychotic disorders, only the difference in waist circumference was statistically significant. The prevalence of metabolic syndrome was significantly elevated among users of high-potency (52.4%) but not low-potency (38.7%) and atypical (23.4%) antipsychotic medication. Conclusion: Glucose and lipid abnormalities and abdominal obesity are common in subjects with nonaffective psychotic disorders. In contrast, subjects with affective psychoses may not differ from the general population in the prevalence of metabolic syndrome or its components. Use of typical antipsychotics is associated with increased prevalence of metabolic syndrome. Regular monitoring of weight, glucose, and lipid values is essential in subjects with psychotic disorders and also in subjects using antipsychotic medication regardless of the indication.

METABOLIC DYSFUNCTION IN SCHIZOPHRENIA : A POSSIBLE ENDOPHENOTYPE

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Epidemiological studies reveal that the leading cause of death in schizophrenia prior to de-institutionalization was tuberculosis. Today, leaving aside suicide, natural causes such as cardiovascular disease (CVD) account for the vast majority of deaths in schizophrenia. Approximately, 40% of patients with schizophrenia die of atherosclerotic-related reasons. Autopsy studies show that this figure has not changed for over 30 years. Many studies implicate certain atypical antipsychotics in the pathogenesis of obesity and related metabolic dysfunction which can lead to the development of CVD. Yet, schizophrenia is may be inherently associated with a large number of predisposing factors for the cardiovascular illnesses, which include insulin resistance, impaired fasting glucose, impaired glucose tolerance and abnormal body fat distribution. For instance, we have shown that the rates of impaired fasting glucose (IFG), (a precursor) to type 2 diabetes mellitus, in drug naïve patients with schizophrenia are 15% as compared to 0% in age-, sex- and lifestyle-matched healthy controls. One may miss up to 60% of cases of type 2 diabetes using IFG as a sole diagnostic. Therefore, we performed oral glucose tolerance tests in a similar population and found that over 10% of the patient group and 18% of their first degree relatives had abnormal glucose tolerance tests. Many reasons other than medication might explain this greater

propensity to have indices of abnormal glucose metabolism, including age, race, family history, lifestyle issues (poor diet & lack of physical activity) and obesity. The latter is of interest, as we have recently shown that patients with first episode, dug naïve schizophrenia have 3.4 times as much intra-abdominal fat deposition, a key feature in the development of obesity-related illnesses. Finally, using Doppler ultrasound, we have also shown that drug naïve first episode patients with schizophrenia have greater intima media thickening in their common and internal carotid arteries than matched control subjects in the absence of frank type 2 diabetes. Therefore in drug naïve first episode patients with schizophrenia a variety of factors, which range from poor lifestyle choices, an inherent vulnerability to the such physical illnesses, may be responsible the higher than expected rates of CVD-related deaths.

LACK OF SEX DIFFERENCE IN AGE-AT-ONSET OF PSYCHOSIS IN SCHIZOPHRENIA: RESULTS FROM A COMMUNITY-BASED STUDY

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Background: Studies from the industrialized countries have consistently reported later age-at-onset of schizophrenia (AAO) in females. However, Indian (Gangadhar et al 2002) and Pakistani (Naqui et al 2005) studies have reported no sex-difference in AAO. An important limitation of the latter reports was that these were from treatment-seeking subjects and their generalizability was a problem. In this paper we report replication of our earlier findings from a community-based sample that included treated and untreated patients. Methods: Data for this report comes from the Community Intervention in Psychotic Disorders (CoInPsyD) study. Health workers identified schizophrenia patients (N=202; 103 males and 99 females) living in a rural community within a defined geographical area (with a population of 143,000) in southern India. A trained psychiatrist interviewed the patients, caretakers, and healthcare workers to assess AAO using modified Interview for the Retrospective Assessment of Onset of Schizophrenia (IRAOS). Excellent inter-rater reliability was established for the assessment of AAO of psychosis (Intraclass correlation = 0. 8592). Results: The mean AAO (SD) in males was 29.2 (8.8) years and that in females was 30.8 (11.4) years (t=1.12; p=0.22). AAO was classified as early or late with the median of 29 years as cut-off. The AAO difference was significant only in the late AAO group [Mean (SD) AAO in males (n=54) = 35.9 (5.8) years; in females (n=44) = 41.6 (7.6) years; t=4.2; p<0.001)]. There was no sex-difference in AAO in the early AAO group [Mean (SD) AAO in males (n=49) = 21.8 (4.5) years; in females (n=55) = 22.2 (4.4) years; t=0.43; p=0.67)]. Conclusions: This study replicates, in a representative community sample, the finding of no difference between the sexes in AAO of schizophrenia in India. In particular, there is no sex-difference in AAO in early onset schizophrenia. Greater loss of male infants with perinatal insults who could have contributed to early AAO, lower prevalence of illicit substance use among subjects and delayed puberty in Indian females are hypothesized as the causes of this finding. Gangadhar, B.N., Panner Selvan, C., Subbakrishna, D.K., Janakiramaiah, N., 2002. Age-at-onset and schizophrenia: reversed gender effect. Acta Psychiatr. Scand. 105 (4) 317-319. Naqvi, H., Khan, M.M., Faizi, A., 2005. Gender differences in age at onset of schizophrenia. Coll. Physicians Surg. Pak. 15 (6) 345-348.

A PROSPECTIVE STUDY OF ADOLESCENT TOBACCO USE AND EARLY ADULTHOOD PSYCHOTIC SYMPTOMS

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There is considerable evidence that as a group, individuals with schizophrenia smoke tobacco more than those without the disorder. Few studies, however, have prospectively assessed whether tobacco use is increased among such individuals before illness onset. Thus data from 731 male participants of the prospective population-based Pittsburgh Youth Study were examined to determine whether tobacco use as assessed annually from ages 13 to 17 was increased among those who developed full psychotic symptoms by young adulthood compared to those who did not, and if so, whether this association was maintained when controlling for adolescent schizophrenia-like positive symptoms, also assessed annually by parent, teacher, and child report. The Diagnostic Interview Schedule was administered at a mean age of 22. Sixteen boys reported at least one psychotic symptom that persisted for at least one month (psychosis group), 50 met criteria for antisocial personality disorder (APD), and 22 for a depressive and/or anxiety disorder (depression/anxiety group). These groups were compared to the 643 boys not reporting psychotic symptoms nor meeting criteria for APD or an anxiety or depressive disorder (controls). Total frequency of tobacco use from ages 13 to 14 (early adolescence) did not discriminate the psychosis and control groups; however, total tobacco use from ages 15 through 17 (late adolescence) was increased among the psychosis group compared to controls (p=.003, one-tailed), even when controlling for late adolescent cannabis and alcohol use. When controlling for late adolescent schizophrenia-like positive symptoms, this association was maintained but substantially reduced (p=.033, one-tailed). Tobacco use did not differ significantly between the psychosis and other clinical groups. These results suggest that late adolescent tobacco use is related to early adulthood psychosis but that it is not specifically predictive of psychosis relative to APD or depressive and/or anxiety disorders. Furthermore, findings that the late adolescent tobacco-adulthood psychosis association was partially mediated by late adolescent schizophrenia-like positive symptoms may reflect that some individuals who later develop full psychotic symptoms use tobacco to self medicate for symptoms and dysfunction present before full psychosis onset.

DIABETES MELLITUS DURING PREGNANCY AND SCHIZOPHRENIA IN OFFSPRING: EVIDENCE AND PUTATIVE MECHANISMS

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Epidemiologic data suggests that complications of gestation and delivery, including diabetes mellitus (DM) during pregnancy, increase the risk of schizophrenia in offspring (Cannon et al., 2002). Whether the neurodevelopmental diathesis to schizophrenia resulting from DM in pregnancy is mediated by genetic or epigenetic factors such as intrauterine conditions, or is due to a combination of the two, is unknown. The mechanisms underlying this relationship have

not been formally investigated but are likely triggered by hyperglycemia and include hypoxia, inflammation and oxidative stress. These conditions are known not only to adversely affect neurodevelopment, but have been implicated in the pathophysiology of schizophrenia (Lieberman et al., 2006). Moreover, a number of the physiologic changes seen in the offspring of diabetic mothers have also been observed in adults with schizophrenia, providing evidence for the specificity of this relationship. We will discuss the mechanisms by which schizophrenia risk is increased, limitations of the current findings and propose future studies directed at strengthening and exploring this relationship further. Should DM in the mother during pregnancy prove to increase schizophrenia risk, even among a subgroup of patients, it will have important implications for the prevention and treatment of this devastating neuropsychiatric disorder.

NON-SPECIFIC ENVIRONMENTAL ADVERSITY BECOMES SPECIFIC THROUGH GENE-ENVIRONMENT AND ENVIRONMENT-ENVIRONMENT INTERACTIONS

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Data will be presented showing that social adversity is strongly associated with negative behavioural outcomes, and that the study of specific person-environment, environment-environment and gene-environment interactions over development is the only way to clarify the pathways linking adversity to specific psychiatric outcomes. Results show interaction between ethnicity at the individual level and ethnic density at the societal level in predicting psychosis, interaction between childhood trauma and adult momentary stress exposures in predicting general adult stress sensitivity, and interaction between genes and social stress in predicting paranoia in the flow of daily life.

EXPERIMENTAL AND OBSERVATIONAL ECOGENETIC STUDIES OF CANNABIS AND PSYCHOSIS

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Results from two studies examining genotype x THC interactions will be presented. In the first, effects on cognition and psychotic symptoms of experimental THC administration in a double-blind, randomised setting was examined as a function of COMTval158met genotype in patients and controls. In the second, momentary assessment technology was applied in order to examine fluctuations of subtle psychotic experiences in the flow of daily life as a function of THC use and COMTval158met genotype. Results from both studies suggest that THC induces impairment of cognition and psychotic experiences in those with the val/val genotype, associated with lower resting dopamine tone and greater phasic dopamine release following stimulation. In addition, the gene x THC interaction was further conditional on general background genetic risk, suggesting that higher order interactions may explain why only relatively few individuals exposed to THC develop schizophrenia.

DISCRIMINATION, ETHNIC DENSITY, AND THE INCIDENCE OF PSYCHOTIC DISORDERS

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Introduction: It is increasingly recognized that the incidence of psychotic disorders varies in terms of place and ethnicity. Notably, the incidence is increased in several non-Western immigrant groups in Western Europe. While this finding may offer clues to the etiology of psychotic disorders, thus far it has defied explanation. Because it is inherent to immigration that it has a different meaning and different consequences depending on the context in which it takes place, social factors may influence the rates of psychotic disorders among immigrants. We sought to determine whether group-level experience of discrimination and neighborhood ethnic density contribute to their increased incidence. Methods: Incidence data were collected in a seven-year first contact incidence study of psychotic disorders in The Hague, the Netherlands, which included 1,870,435 person years and yielded 621 cases. Results from population surveys provided measures of group-level experience of discrimination. We used population data from the municipal authorities to calculate neighborhood ethnic density, and to compare risks of immigrant groups with that of native Dutch. Results: The incidence of psychotic disorders increased with degree of discrimination. The incidence rate ratio (IRR) was 1.27 (95% CI = 0.99-1.63) for ethnic groups experiencing low, 1.82 (1.51-2.20) for those experiencing medium, and 3.44 (2.69-4.40) for the group experiencing the highest degree of discrimination. In a multilevel Poisson regression model, there was a strong interaction between individual ethnicity and the proportion of own ethnic group in the neighborhood on the incidence of psychotic disorders ($\chi 2$ = 12.99, df=1, p=0.0003). The IRR for immigrants living in high ethnic density neighborhoods was 1.24 (0.66-2.36), for those in low density neighborhoods the IRR was 2.37 (1.89-2.96). Conclusions: These results suggest that the social context strongly influences the incidence of psychotic disorders. Belonging to a group experiencing a high degree of discrimination appears to increase the risk of psychotic disorders, whereas a culturally cohesive social environment may provide protection from the pathogenic effects of factors such as discrimination.

RISK FACTORS FOR SCHIZOPHRENIA: ARE THEY SPECIFIC FOR MENTAL ILLNESS OR FOR UNDESIRABLE EVENTS IN GENERAL?

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Background: Previous studies have identified various risk factors for schizophrenia, including low cognitive and social abilities, having a non-psychotic psychiatric diagnosis in adolescence (anxiety, depression, personality disorders), and fewer years of formal education. Some but not other studies indicated that cigarette smoking and low socio-economic status (SES) also increase risk. Many of these studies indicate that these risk factors have relatively low sensitivity or specificity. We examined the specificity of these risk factors by assessing their effect on risk for going to jail during military service, as a proxy for.an undesirable life event. Methods: We identified 627,103 male adolescents for whom data were available from the assessments performed by the Israeli draft board, and examined the effect of these putative risk factors for schizophrenia on risk for going to jail for 7 days or more during their military service. Those adolescents diagnosed with psychotic disorder during draft board assessment or later hospitalized with any psychotic disorder (N=3,839) were excluded, leaving 623,264 adolescents in the analysis. All potential risk factors were dichotomized to low (more than 1 SD below population mean or higher), and normal-high (1 SD below population means or higher) Results: Low social functioning (OR=1.14), low cognitive functioning (OR=3.48), low SES (OR=2.09), less education (OR=6.26), having a non-psychotic psychiatric diagnosis (anxiety, depression, personality disorder, OR=2.01) and cigarette smoking (OR=3.55) were associated with going to jail. Discussion: Some of the risk factors associated with schizophrenia are associated with risk for undesirable life events such as going to jail during military service. One might hypothesize that in persons with these risk factors, the presence or absence of other environmental and/or genetic risk factors causes mental illness to manifest in some, while others have undesirable life events, such as going to jail, without suffering from psychosis.

REDUCTION IN TRANSITION RATE IN AN ULTRA HIGH RISK (PRODROMAL) SERVICE DUE TO EARLIER DETECTION

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Recently it has become possible to identify people experiencing the prodrome of schizophrenia and related disorders. This has led to the possibility of preventing or delaying onset of such disorders. Detection has been achieved by the application of Ultra High Risk (UHR) criteria, which combine subthreshold psychotic symptoms and risk factors such as family history and age. Using these criteria, several groups have reported rates of transition from prodromal or UHR state to psychosis of 35% to 50% within 12 months. However, a reduction in transition rate has been suspected lately. Our recent data showed a 6 month transition rate of 9.2%. Although meeting UHR criteria was associated with significantly greater odds of becoming psychotic, the apparently decreasing transition rate needed examination. Method: We examined UHR data for subjects recruited from 1995 to 2000 to ascertain if transition rate had reduced and to examine associated factors. Results: 142 UHR subjects were recruited, 51 became psychotic. For each successive year, the Kaplan-Meier estimates of the transition rate were respectively 0.50, 0.33, 0.32, 0.29, 0.21 and 0.12. Estimated risk for each year was 0.80 times that of the previous year (p=0.027). Year was no longer associated with transition rate once duration of symptoms was adjusted for. Given that long duration of symptoms was associated with transition to psychosis in previous cohorts, we suspected that duration of symptoms was decreasing over time. This was confirmed by examination of the duration of symptoms data, which showed significant and successive reduction ($p < 0.001$), from mean 559.6 days in 1995 to 46.5 days in 2000. Conclusions: Given that UHR individuals are being treated earlier than in the past, three possible explanations for the reduction in transition rate arise. First, lead time bias may explain the findings, so that the ultimate level of transition may higher if patients are followed for longer. Second, a length time bias may be responsible, ie the apparent UHR phenotype may have a number of different outcome trajectories, including rapid spontaneous remission, and early detection may increase the probability that those not truly at risk will be identified. Finally, it may be that earlier detection enables intervention to be more effective and preventative. This is consistent with a staging model, which proposes that the earlier disorder is identified, the more benign the treatment and the better the outcome.

4. Neuroanatomy, Animal

NEUROANATOMICAL ABNORMALITIES OF THE BASAL GANGLIA AND THALAMUS IN INFANT MONKEYS EXPOSED TO IRRADIATION IN UTERO: A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

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BACKGROUND: Schizophrenia has been associated with disturbances in early neurodevelopment that alter the structure of a variety of brain regions in adulthood. An animal model designed to investigate the developmental origin of the changes in brain structure associated with schizophrenia has been developed by applying low-dose radiation to rhesus monkeys in early gestation. Here we examine the temporal emergence of abnormalities in the thalamus and basal ganglia in irradiated animals. METHODS: Magnetic resonance scans were collected in Rhesus monkeys exposed to irradiation during thalamic neurogenesis (E30-41) and in sham-irradiated control animals at 6 and 12 months of age. High dimensional brain mapping was used to compare the volumes of three basal ganglia structures (caudate, putamen, nucleus accumbens) and the thalamus in the two groups of animals. RESULTS: Animals exposed to irradiation showed a bilateral loss of volume in each of the four structures as compared with controls at both 6 months and 12 months of age. Differences in volume ranged from 7% to 16% at 6 months of age (thalamus: left 5%, right 16%; caudate: left 8%, right 7%; putamen: left 11%, right 16%; nucleus accumbens: left 14%, right 13%). At 12 months, these volume differences ranged from 9% to 30% (thalamus left 14%, right 27%; caudate: left 10%, right 16%; putamen: left 25%, right 30%; nucleus accumbens: left 30%, right 19%) . These results show that the differences in volume between the irradiated and nonirradiated animals were amplified at 12 months relative those exhibited at 6 months. CONCLUSIONS: Disruption of thalamic neurogenesis during early gestational development in the nonhuman primate results in progressive volume loss in the thalamus and basal ganglia during the first postnatal year. Low-dose irradiation of the fetal primate may be useful for modeling key features of the pathology described in schizophrenia patients. Supported by MH071616.

THE H3 ANTAGONIST THIOPERAMIDE IMPROVES SPATIAL WORKING MEMORY IN AN ANIMAL MODEL OF REDUCED HIPPOCAMPAL VOLUME IN SCHIZOPHRENIA

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Rats with experimental excitotoxic injury to the hippocampus show deficits in spatial working memory. As such, these animals may serve as a face valid model of the reduced hippocampal volume and working memory impairment reported in schizophrenia. Recent work in other animal models of memory has demonstrated that antagonists at H3-type histamine receptors exhibit cognitive enhancing properties. The present experiments determined if one such H3 antagonist, thioperamide, could alleviate spatial working memory deficits in rats with experimental excitotoxic injury to the hippocampus. Stereotaxic surgery was performed on adult male Long-Evans rats, and half of them received direct infusions of the excitotoxin, N-methyl-D-aspartate (NMDA), into the dorsal hippocampus. Infusions of NMDA decreased hippocampal area by 50%. Four weeks after surgery, animals were trained and tested in a discrete-trials, rewarded delayed spatial alternation task. After two weeks of testing, animals received injections of saline or thioperamide (3.0 or 9.0 mg/kg) 30 minutes before testing. Animals were tested in each drug condition for two consecutive days in an order that was counterbalanced within the injured and uninjured groups. After saline treatment, rats with hippocampal injury demonstrated significant impairments in choice accuracy in the alternation task when compared to uninjured controls. However, choice accuracy in the injured rats was identical to uninjured controls after treatment with either dose of thioperamide. These data suggest that the H3 receptor may be a promising target of future drug development for memory impairments in schizophrenia associated with reduced hippocampal volume. This work was funded by the Kentucky Biomedical Research Infrastructure Network through a grant from the National Center for Research Resources - Institutional Development Award (IDeA) Program (NIH Grant Number 2 P20 RR-16481).

DOES BRAIN VOLUME CHANGE AFTER WITHDRAWAL OF ANTIPSYCHOTIC MEDICATION IN FIRST-EPISODE SCHIZOPHRENIA?

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Although influence of antipsychotic medication on brain morphology has been demonstrated many questions remain unanswered. Ideally, the impact of antipsychotic treatment should be assessed with studies performing sequential MRI scans in patients on and off antipsychotic medication. We conducted a longitudinal structural MRI study in which changes in brain volume were compared between schizophrenia patients who discontinued and those that continued antipsychotic medication. Of 30 remitted, stable first-episode schizophrenia patients 20 were randomized to continuation or discontinuation of antipsychotic medication while 10 patients continued or discontinued medication without having been randomized. All were included in a 2-year follow-up. On a 1.5T scanner 112 brain scans, 3-5 scans per patient, (25 medication-free scans and 89 on medication), were made in 26 patients at baseline and at 6, 12 and 24 months of follow-up as well as after a relapse occurred. Thirty-six healthy controls were also scanned twice with a 1-year interval. Preliminary analyses were performed in a selection of scans, with patients divided in three subgroups: A discontinuation group (antipsychotic treatment discontinued at the second scan, n=12, ≤ 6 months scan-interval), a continuation group (patients continued medication, n=14, 6 months scan-interval) and an age-matched healthy control group (n=15, 1-year scan-interval). A one-way between-groups analysis of variance was conducted to explore the impact of medication discontinuation on total brain, third and lateral ventricle, cerebellar, cerebral gray matter (GM) and white matter volume changes, after correction for intracranial volume and age. A statistically significant difference in cerebral gray matter (GM) volume change for the three subgroups [F(2, 38)=4.7, p=.015] was found (Eta squared effect-size=0.2). Post-hoc pair-wise comparisons indicated that the GM volume change in the discontinuation group (Mean

(M)=-14.7ml, SD=16.2) was significantly different from the change in the control group (M=8.8ml, SD=21.2). The continuation group (M=-.9ml, SD=24.3) did not differ from the controls or the discontinuation group. This study suggests that continued use of atypical antipsychotics is associated with less decrement of cerebral GM volume in schizophrenia patients. A time-series analyses is planned including all scans, to enhance the robustness of the analyses.

CHARACTERISTICS OF RATS WITH REDUCED SOMATOSENSORY INPUT DURING DEVELOPMENT – A POTENTIAL ANIMAL MODEL OF ASPECTS OF SCHIZOPHRENIA

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In a previous study we showed that treatment of neonatal rats with capsaicin, which destroys portion of the somatosensory input to the CNS, resulted in reduced brain weight, reduced hippocampal and cross-sectional area, reduced cortical thickness and increased neuronal density at 5-7 weeks of age [1]. The aim of the present project was to determine the characteristics of mature rats treated as neonates with capsaicin. Wistar rats under ice anaesthesia were treated on neonatal day 2 with capsaicin 50mg/kg s.c. or vehicle. Some rats were given a lethal dose of sodium pentobarbitone at 8-14 weeks of age, brains removed, fixed in formalin and coronal sections, 50 µm, cut and Nissl stained. In other groups of rats locomotor behaviour, pre-pulse inhibition to acoustic startle, and cutaneous plasma extravasation responses to methylnicotinate were tested. Plasma extravasation was measured in control and capsaicin treated rats anaesthetized with sodium pentobarbitone, 40mg/kg, and given Evans blue 50mg/kg into a tail vein. Intracutaneous injections (0.05ml) of methylnicotinate (5x10-8 to 5x10-6mol), PGD2 (5x10-10 to 5x10-8mol) and vehicles were given into the abdominal skin. Rats were killed 20min later, and the blue dye was extracted from the skin areas and measured spectrophotometrically. The structural brain changes previously observed in capsaicin treated rats at 5-7 weeks [1] were maintained into adulthood, with the exception of the motor cortex where neuronal density was not increased. Behaviour of treated rats was similar to controls on measures of distance travelled, ambulatory counts, vertical counts and stereotypy. Capsaicin pre-treatment resulted in increased startle amplitude in 12 week old rats ($P<0.05$) but not in 8, and 14 week old rats. PPI was not disrupted at 8, 12 or 14 weeks of age in rats treated as neonates with capsaicin, and indeed, in preadolescent rats, PPI was significantly enhanced ($P<0.01$). Plasma extravasation responses to methylnicotinate and PGD2 were reduced in capsaicin treated rats ($P<0.05$; $P<0.01$). The structural brain changes and reduced plasma extravasation responses to methylnicotinate in capsaicin treated rats are those expected for an animal model of schizophrenia. PPI responses in capsaicin treated rats require further investigation. Thus the neonatal capsaicin treated rat is a potential model of aspects of schizophrenia. [1]. Newson, P. et al (2005). Br. J. Pharmacol., 146, 408-418.

ACTIVATION OF THE CLAUSTRUM BY ANTIPSYCHOTIC DRUGS

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Antipsychotic drugs exert their effects across a wide number of brain regions, rather than a single site. How antipsychotic drugs act across distributed neuronal networks of brain sites to give rise to therapeutic effects remains unclear. Francis Crick and Christof Koch (2005) posited that the processes underlying the integration of multimodal information to give rise to conscious perceptions requires a nodal site overseeing various cortical regions in a top-down manner. They suggested that the claustrum, with its extensive interconnections with virtually all cortical areas, may be such a site. They noted that an "appropriate analogy for the claustrum is that of a conductor coordinating a group of players in the orchestra, the various cortical regions. Without the conductor, the players can still play but they fall increasingly out of synchrony with each other. The result is a cacophony of sounds." The claustrum has been difficult to study because of its shape and orientation. However, the use of anatomical methods to follow immediate-early gene expression is ideally suited to determine if antipsychotic drugs (APDs) activate the claustrum. We therefore examined the effect of acute administration of typical and atypical antipsychotic drugs on Fos induction in the claustrum of the rat. The typical APDs haloperidol and fluphenazine did not have any effect on Fos induction in the posterior claustrum (at the level of the crossing of the anterior commissure) or the more anterior claustrum (at the level of the genu). In contrast, the atypical APD clozapine strongly activated the more rostral claustrum, as did ziprasidone; our preliminary data suggest that olanzapine may have some effect. The effects in the more caudal claustrum were less marked but of similar direction. The data suggest that atypical APDs preferentially activate the claustrum. Because the claustrum projects extensively to diverse cortical areas, but has very few subcortical projections (to the mediodorsal and midline intralaminar thalamic nuclei), the claustrum may be ideally positioned to orchestrate coordinated responses in cortical regions and may be a key site at which atypical APDs target cognitive deficits. Crick FC and Koch C (2005) Phil. Trans. R. Soc. B 360:1271–1279

INCREASED ACTIVITY IN ADULT MACAQUES EXPOSED TO EARLY GESTATIONAL IRRADIATION: A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

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Adult macaque monkeys exposed to x-irradiation during the first trimester of gestation (E30-E41) exhibit deficits in cognitive performance (Friedman and Selemon, Soc. Neurosci. Abst., 2006). Incidental observation of these monkeys during testing on the Delayed Response (DR) task suggested that fetal irradiation may also increase motor activity. Motor stereotypies such as repetitive pivoting were observed in 5/5 irradiated monkeys (IRRs). To verify these observations we videotaped IRRs and sham-irradiated controls (CONs) during performance of the DR task in infancy (12-30 mo) and adulthood (4-5y) and subjected 2 min segments of each taped performance to scoring by 2 naïve raters and one of us (HRF). In a first pass, we measured the inverse of activity, i.e., inactivity as represented by sitting. During each clip, raters counted 1) bouts of sitting (5 uninterrupted sec = 1 bout) and 2) vocalizations as a control for rater disparity. As correspondence in scoring among the raters was high, mean scores are reported here. Bouts of sitting ranged from 0 to 23 (115 /120 sec). Overall, the CONs engaged in 7.0 bouts or 2X the bouts observed in the IRRs (3.5). Infants had fewer bouts of sitting (2.7) than adults (7.8). Infant IRRs had the fewest (1.5), and adult CONs the most (10.1). Note that the 2 infant IRRs who did not learn DR task had the highest activity, i.e., did the least sitting (< 1, or <5/120sec). Conversely, the only adult IRR who achieved criterion on the DR

task exhibited 14 bouts, ~ 3X more than the next closest IRR adult. The adult CONs, all of whom learned the task, had 2X the number of bouts as the adult IRRs (10.1 vs. 5.4), meaning that the CONs spent nearly 50% of the 2 min segment not moving while IRRs were inactive < 25% of the time. Mean vocalization scores inversely paralleled those for inactivity: IRRs vocalized 2X as much (12) as CONs (6). All infant IRRs vocalized during the test clip whereas only 3/5 infant CONs vocalized. Thus, IRRs exhibited increased motor activity in DR during infancy and adulthood relative to the CONs. This hyperactivity appears to be linked to deficient cognitive performance on the DR task only in adulthood although this relationship needs to be examined in more detail. The increase in activity and presence of motor sterotypies in IRRs may indicate that striatal mechanisms are abnormal and could be related to deficits in caudate volume in these same animals (Aldridge et al., this meeting). Support:MH59329,MH71616

HETEROZYGOUS NEUREGULIN-1 MUTANT MOUSE: PHENOTYPIC RELATIONSHIP TO SCHIZOPHRENIA

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Human genetic studies have implicated the gene coding for neuregulin-1 (NRG1) as a candidate susceptibility gene for schizophrenia. In the present study, the functional role of the gene as it relates to cognitive and social processes known to be disrupted in schizophrenia were assessed in heterozygous NRG1 knockout mice vs. wildtype (WT)controls. Both genotypes were compared using the resident / intruder and sociability and preference for social novelty paradigms. In the former task, the experimental animal was isolated for one week and then confronted with a group-housed stranger in the isolate's home cage, whereupon agonistic and non-agonistic social interactions were assessed. In the latter task, time spent by the animal in a cage quadrant inhabited by an unfamiliar conspecific rather than an empty quadrant (sociability) or a second unfamiliar conspecific (social novelty) was the dependent variable. Spatial learning and memory was assessed using the Barnes maze paradigm, while spatial working memory was assessed using the continuous variant of the spontaneous alternation task. Results from the resident / intruder task revealed an increased number of aggressive behaviours in the NRG1 mutants relative to WT mice. Social interaction data from the sociability and preference for social novelty paradigm revealed that NRG1 mutants failed to display the wildtype profile of preference for spending time with the new stranger as opposed to the first unfamiliar mouse. These results suggest that NRG1 mutants show a selective impairment in their response to social novelty. The Barnes maze data revealed intact spatial learning performance in NRG1 mutants compared to WT. Significantly elevated baseline latency to enter the escape hole was observed in male NRG1 mutants, which may be due to increased baseline activity levels. Spontaneous alternation was unaffected in NRG1 mice although, consistent with their reported hyperactive phenotype, NRG1 mutants made a significantly greater number of overall arm entries. While NRG1 mutants display altered patterns of social behaviour compared to WT counterparts, spatial learning and working memory processes appear to be unimpaired following partial loss of NRG1 gene function. These data inform on the functional role of a gene that has been associated with risk for schizophrenia at a novel phenotypic level. This work was funded by Science Foundation Ireland.

EXCESSIVE AMOUNT OF NERVE GROWTH FACTOR IN THE DEVELOPING BRAIN MAY LEAD TO SCHIZOPHRENIA- AND AUTISM-LIKE FEATURES IN RATS

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Nerve growth factor (NGF) is a target-derived neurotrophic factor, essential for the development and survival of certain types of neurons in the brain. NGF exerts its effects via trkA and p75 neurotrophin receptors. NGF acting simultaneously on both types of receptors leads to survival response whereas stimulation of p75 receptor alone leads to apoptosis. In addition to neurons, immune cells especially activated macrophages secrete large quantities of pro-NGF, a precursor to NGF, which also possesses over 1000-fold higher affinity to p75 receptors compared to NGF. Activated macrophages are seen in the developing cerebral cortex in certain types of viral infections. Maternal viral infections are thought to be associated with increased incidence of schizophrenia in offspring. In the present study, we infused recombinant human NGF into the lateral ventricles in rat pups at postnatal days 1 and 2. NGF injections caused a large number of activated caspase-3 positive cells in the subplate layer of the developing cerebral cortex. NGF-injected rats appeared comparable in bodyweight to saline-injected controls during development. However, NGF-injected rats showed adult emergence of behavioral features of subcortical dopaminergic hyperactivity, and a number of neuropathological changes described in postmortem brains of schizophrenia, including, loss of neuropil and GABAergic synaptic abnormalities in the prefrontal cortex, neuronal abnormalities in the hippocampus and enlargement of ventricles. They also showed decreased prefrontal cortical activity following stress or amphetamine challenge, suggesting a task-induced hypofrontality in these animals. Neonatally NGF-injected animals also showed marked deficits in social interaction, a feature shared by both schizophrenia and autism. Interestingly, these animals showed neuronal abnormalities of the entorhinal cortex, and enlarged lateral and basolateral nuclei of amygdala containing increased number of small, densely packed neurons, features described in postmortem brains of autistic patients. We propose that the presence of excessive amount of NGF during a critical window of brain development may facilitate future manifestation of schizophrenia or autism-like features in genetically predisposed individuals. [Supported by the Ontario Mental Health Foundation].

CYCLIN-DEPENDENT KINASE 5-MEDIATED INCREASED SYNAPTIC VESICLE ENDOCYTOSIS AT MESOLIMBIC DOPAMINERGIC TERMINALS MAY FACILITATE CHRONIC DOPAMINERGIC HYPERACTIVITY IN A NEURODEVELOPMENTAL RAT MODEL OF SCHIZOPHRENIA

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Schizophrenia is a complex psychiatric disorder characterized by increased mesolimbic dopamine release in response to non-salient

stressors. Such repeated release may require a process of rapid recycling and endocytosis of released dopamine back in synaptic vesicles. Once transported back into the terminals, dopamine is packaged into vesicles by the process of endocytosis that is controlled mainly by the phosphorylation status of dynamin in synaptic terminals, and the main kinase responsible for this event is cyclin-dependent kinase 5 (cdk5). In a neurodevelopmental rat model of schizophrenia (Rajakumar et al., Biol. Psychiat. 55:797-803; 2004), employing gene arrays and western blotting, we recently identified and confirmed marked up-regulation of cdk5 mRNA and protein, in the nucleus accumbens and the ventral tegmental area (VTA). Present study was undertaken to determine whether the increased cdk5 may facilitate rapid replenishing of dopamine in presynaptic vesicles in the nucleus accumbens in these animals. Western blotting and immunohistochemical studies revealed that adult rats that received neonatal lesions possessed increased levels of cdk5, its activators p35 and p25, and increased levels of dynamin-1 phosphorylated at Serine 774 and 778 without any changes in total dynamin-1 levels in dopaminergic neurons of the VTA. When rats were challenged with 2 successive injections of amphetamine (1mg/kg) one hour apart in order to deplete dopamine, the second injection of amphetamine continue to elicit locomotion and rearing only in the lesioned rats indicating a continued availability of dopamine vesicles for release at the terminals. This suggests a possible rapid re-packaging of dopamine facilitated by cdk5-mediated phosphorylation of dynamin-1. Ultrastructural studies are currently underway to determine whether this prolonged locomotion is associated with increased number of vesicles in dopaminergic terminals in the nucleus accumbens. Studies are in progress to determine whether blocking cdk5 activity will suppress the continued effect of amphetamine. [Supported by the Ontario Mental Health Foundation]

OVERVIEW: SEVERAL TYPES OF DISC1 GENETICALLY-ENGINEERED MICE

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DISC1 is a promising susceptibility gene for major mental illnesses, such as schizophrenia and bipolar disorder. DISC1 protein has multiple isoforms with many distinct functions. Several groups have tried to generate DISC1 genetically-engineered mice, including transgenic mice expressing a dominant-negative form of DISC1 and mice with RNAi injection via in utero gene transfer. In addition, mice of 129 strain has reportedly a robust genetic variation in a coding exon of DISC1, although systematic Western blotting indicates that majority of DISC1 isforms are intact in the mice. In this presentation, I plan to overview several types of DISC1 genetically-engineered mice in a comparative manner, especially focusing on their behavioral and anatomical deficits.

5. Neuropathology, Biochemistry

DYSBINDIN-1 IS A SYNAPTIC AND MICROTUBULAR PROTEIN THAT BINDS TO BRAIN SNAPIN

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Genetic variation in the gene encoding dysbindin-1 has frequently been associated with schizophrenia. Recent studies indicate that the protein also plays a general role in cognition, perhaps by affecting synaptic glutamate release. How dysbindin-1 might affect such release is unknown without discovery of the protein's neuronal binding partners and its subcellular locus of action. Tissue fractionation and immunoprecipitation, Western blotting, and immunohistochemistry were used to examine the regional and subcellular localization and expression of dysbindin-1, snapin, NMDAR1£a, actin, PSD-95, Rab3, and synaptophysin in mouse and postmortem human brain tissue. Immunoelectron microscopy was used to examine the ultrastructural localization of dysbindin-1 in mouse and macaque hippocampus. We found that snapin is a binding partner of dysbindin-1 in vitro and in the brain. Tissue fractionation of whole mouse brains and human hippocampal formation revealed that both dysbindin-1 and snapin are concentrated in synaptic tissue, including synaptic vesicle and postsynaptic density fractions. It is not detected in a presynaptic fraction lacking synaptic vesicles. Immunoelectron microscopy showed that dysbindin-1 is located in or on (1) synaptic vesicles in axospinous terminals of the dentate gyrus inner molecular layer and CA1 stratum radiatum and (2) postsynaptic densities and microtubules of dentate hilus neurons and CA1 pyramidal cells. The labeled synapses are often asymmetric with thick postsynaptic densities suggestive of glutamatergic synapses, most likely deriving from dentate mossy cells and CA3 pyramidal cells. The function of dysbindin-1 in presynaptic, postsynaptic, and microtubule locations may all be related to known functions of snapin.

LOWER SNARE PROTEINS IN DISTINCT REGIONS OF FRONTO-STRIATAL CIRCUITS IN SCHIZOPHRENIA

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Background/Aims: A basic level of connectivity in the brain lies at the synapse. Neurotransmitter release is regulated in part by the interaction of SNARE proteins (SNAP-25, syntaxin and VAMP). Several studies have shown alterations in presynaptic proteins, including SNAREs, in schizophrenia (1). Because SNAREs are integral to synaptic function and because fronto-striatal circuit functions are abnormal in schizophrenia we investigated SNARE protein levels in three circuits known to be abnormal in patients: orbitofrontal-ventromedial caudate [OrF-VMC], anterior cingulate-nucleus accumbens [AnCing-NAcc] and dorsolateral prefrontal cortex-dorsal caudate [DLPFC-DCd]. Methods: SNARE protein immunoreactivities were quantified in OrF, VMC, AnCing, NAcc, DLPFC and DCd of patients with schizophrenia (n=15) and control subjects (n=13) using ELISA. To test if connectivity in different circuits is altered, we employed a nested ANOVA with main effects of diagnosis, circuit and fronto-striatal area (nested within circuit) and interaction effects. Results: Levels of each SNARE protein differed between cortical and striatal regions ($p<0.0001$). A circuit effect was found only for VAMP protein levels, with levels in the OrF-VMC circuit different from the other two circuits. No overall diagnosis effect was evident for any protein, but significant BrainArea by diagnosis interactions were found for all three SNAREs ($0.022>p>0.004$). Significant interactions were followed up with contrasts between diagnostic groups in each region. This showed significantly lower amounts of SNAP-25 in the VMC and NAcc. (32%, 25% respectively), syntaxin in the VMC (26% lower) and VAMP in the DLPFC (31% lower). Conclusions: Levels of SNARE proteins were altered in all three of the fronto-striatal circuits investigated, in particular SNAP-25 and syntaxin levels were lower in the VMC, SNAP-25 was lower in NAcc, and VAMP levels were lower in DLPFC. This is the first study to identify abnormalities in SNARE protein levels in the striatum in schizophrenia. Further investigation is necessary to determine how these changes affect neurotransmission. References: 1. Honer WG & Young CE. (2004). Presynaptic proteins and schizophrenia. Int Rev Neurobiol. 59: 175-199.

EXCITATORY AMINO ACID TRANSPORTER AND TRANSPORTER INTERACTING PROTEIN DYSREGULATION IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

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The excitatory amino acid transporters (EAATs) are a family of molecules responsible for synaptic glutamate reuptake. Expression and regulation of these transporters facilitate clearance of glutamate from the synapse and thus play a pivotal role in long-term potentiation and synaptic plasticity. Compelling evidence has implicated cortical abnormalities of glutamate transmission in schizophrenia, but the precise role of EAATs in schizophrenia remains unknown. We hypothesized that expression and regulation of EAATs are altered in the prefrontal and anterior cingulate cortices in schizophrenia in a pattern consistent with increased glutamate reuptake. In postmortem tissue from patients with schizophrenia and a comparison group, EAAT1, EAAT2, EAAT3, and the EAAT interacting protein g-protein suppressor pathway 1 (GPS1) transcript and protein levels were measured using in situ hybridization and Western blot analysis, respectively. Interactions between EAAT2 and GPS1 will be measured using co-immunoprecipitation. To determine whether typical antipsychotic exposure regulates these molecules, transcript expression for EAAT1, EAAT2, EAAT3, and GPS1 were measured in the frontal, parietal, and retrosplenial cortices of rats treated with haloperidol (2mg/kg/day) or vehicle. EAAT1 and EAAT3 transcript levels were increased in the anterior cingulate cortex in schizophrenia, while GPS1 protein levels were decreased in this region. No changes were detected for EAAT1 or EAAT3 protein expression, and no changes were detected for GPS1 transcript. No changes were detected for EAAT1, EAAT3, or GPS1 in the dorsolateral prefrontal cortex, and no changes were detected for EAAT2 in either region. EAAT1 protein levels and co-immunoprecipitation of EAAT2 with GPS1 data will be presented. In general, none of these

transcripts were regulated by haloperidol treatment in the frontal, parietal, or retrosplenial cortices, with the exception of a down-regulation of EAAT1 transcripts in retrosplenial cortex. Our data support the hypothesis that expression and regulation of EAATs are altered in the prefrontal and anterior cingulate cortices in schizophrenia, but are more consistent with a pattern of decreased glutamate reuptake. These data contribute to a growing body of evidence that glutamatergic signaling may be altered in schizophrenia. Our findings may have important implications for neuronal plasticity in this illness as well as provide targets for the development of novel treatments.

MYELIN-ASSOCIATED PROTEINS AND MRNA IN THE CINGULUM BUNDLE

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Many studies using magnetic resonance imaging have demonstrated cerebral white matter abnormalities, particularly decreased diffusion anisotropy, in schizophrenia. Post mortem studies have shown diminished levels of myelin- or oligodendrocyte-related proteins or their mRNA in grey matter, but white matter has been largely neglected. We report here on the cingulum bundle, one of the first and most consistently reported sites of diminished anisotropy in schizophrenia. White matter from the anterior supracallossal portion of the right cingulate gyrus was sampled from 19 pairs of schizophrenia and nonpsychiatric subjects from the Macedonian/NY State Psychiatric Institute Brain Collection, matched for age (51±4), sex (10F, 9M), and PMI (13±6 h). Clinical diagnoses of all cases and controls were established by application of DSM-IV criteria to data obtained from psychological autopsy interviews and standardized review of medical records. Myelin basic protein (MBP) was assayed by ELISA and 2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNP) by western blot and densitometry. mRNA for MBP, CNP, and myelin-associated glycoprotein (MAG) was quantified by real time RT-PCR, normalized to the expression of 3 "housekeeping" genes. Protein yield was nearly identical from schizophrenia and nonpsychiatric subjects (~165 ± 25 mg/ g tissue). MBP per mg tissue was reduced 19% in schizophrenia (95% c.i. = 0.6% increase to 54% decrease, p = 0.06 by paired t-test). CNP content was virtually identical in both groups, differing by <1%. Analysis of mRNA was restricted to the 7 subjects in each group with Agilent elecrophoresis RNA Integrity Number ≥ 6 (nonpsychiatric M/F = 1/6, age = 52±15, PMI = 14±7; schizophrenia M/F = 3/4, age = 59±12, PMI = 9±3). mRNA for all 3 proteins was 34-35% lower in the schizophrenia group. The differences were statistically significant for CNP and MBP (t=2.2-2.3, p=0.05) but not for MAG (t=1.6, p=0.14). Expression of CNP was significantly correlated with that of MBP (r=0.65, p=0.01) and MAG (r=.931, p<0.001). mRNA for MBP and CNP were not significantly correlated with their respective protein levels (p>0.28). The results are consistent with a mild reduction in compact myelin, or an alteration in its composition, and a more pronounced reduction in oligodendroglial metabolism and, perhaps, myelin turnover. *Support: MH60877, MH64168, MH62185, MH45212, MH64673, NARSAD, Lieber Center for Schizophrenia Research, CIHR, Mind Foundation of BC, VA-MIRECC*

INVESTIGATION OF THE GENE EXPRESSION OF THE DYSBINDIN-1 SUSCEPTIBILITY GENE IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Over the last two decades, important advances have been made in our understanding of the genetic basis of schizophrenia. Neuropathological deficits have been observed in these anterior cingulate cortex with reduced brain volume, glial deficits, decreased neuronal size and density and altered levels of synaptic markers in the schizophrenic brain. Recent evidence from association and linkage studies strongly support a role for candidate susceptibility genes in schizophrenia. Dysbindin-1 is among several strong contenders thought to contribute to the susceptibility of schizophrenia and it is one of the susceptibility genes that are of particular interest to our research group. Dysbindin1 function in the brain is not well known but it forms part of both the dystrophin complex in postsynaptic densities and the BLOC-1 complex in the human brain. It is not known how dysbindin-1 genes contribute to disease pathophysiology but studies so far demonstrate altered expression of dysbindin-1 at the message/protein level in schizophrenia. These studies require further replication in larger and independent brain series. Understanding the altered expression of dysbindin-1 and their molecular pathways may provide a greater insight to the pathogenic role of susceptibility genes in schizophrenia. The Stanley Foundation provided us with total RNA isolated from ACC post-mortem brain (n= 35 per group of control, schizophrenic and bipolar brains). Primers against Dysbindin-1 were generated and ACC RNA from this series was reverse transcribed using gene-specific dysbindin-1 primers and the Roche First Strand cDNA synthesis Kit. Gene-specific dysbindin-1 products were generated by quantitative real-time PCR on the Roche LightCycler System. Gene concentrations were generated by the LightCycler Software and fold change calculated. Statistical analysis was performed using SPSS 13 software. Analysis of covariance, correcting for potentially confounding effects of post-mortem interval and pH, showed significant values between schizophrenia, bipolar disorder and control groups. Posthoc analysis indicated that this was due to significant increases in dysbindin mRNA levels in bipolar disorder (1.90 ± 2.983) compared to control groups (p=0.042). No significant changes were found between schizophrenia (0.52 ± 0.99) and control groups (0.77 ± 1.76). These findings suggest that the human dysbindin-1 gene may play a role in the susceptibility to bipolar disorder.

ABNORMAL MAINTENANCE OF THE GABAERGIC PHENOTYPE IN HIPPOCAMPAL NEURONS OF SCHIZOPHRENICS AND BIPOLARS THROUGH DIFFERENT MOLECULAR MECHANISMS

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Recent in situ hybridization studies of GAD67 transcripts have consistently demonstrated a significant decrease in subjects with schizophrenia (SZ) and bipolar disorder (BD). The presence of a GABAergic defect in both disorders suggests that this change may be related to an environmental factor, such as stress, which is common to both. To increase our understanding of GABAergic dysfunction in SZ and BD, we have used laser capture microdissection (LCM) to disas-

semble the trisynaptic pathway in sectors CA3/2 and CA1; significant alterations in CA3/2, but not CA1 have been observed in SZ and BD. Using a cohort consisting of 7 normal controls, 7 schizophrenics and 7 bipolar subjects matched for age, postmortem interval (PMI), gender, hemisphere, pH, 28S/18S ratios and 3', 5' ratios, samples from the stratum radiatum, stratum pyramidal and stratum oriens were obtained from each sector. Using the U133A human genome chip (Affymetrix), an abundance of gene changes in the SO of sector CA3/2 and CA1 was observed. GAD67 expression was significantly reduced in SO of CA3/2 of BDs (fold change = -9.57; p = 10-5) and SZs (fold change = 2.5; p = 10-4). Using GenMapp biopathways and clusters, groups of cell cycle and neurogenesis genes showed very prominent changes in SO of CA3/2 and CA1. Additionally, in SZs, there was a significant increase in the expression of histone deacetylase 1 (HDAC1; fold change = 1.5; p = 0.02) and DAXX (fold change = 1.25; p = 0.03), a regulator of HDAC1 which can help suppress the GAD67 promoter. In the BDs, however, transcription factors associated with cell differentiation, i.e. Runx2 (fold change = 2.8; p = 0.002), PAX5 (fold change = 1.4; p = 0.027) and LEF1 (fold change = 2.0; p = 0.027) were all significantly down-regulated. Cyclin D2 (Fold-change = 1.4; p = 0.022) and other genes associated with cell cycle regulation and DNA repair were upregulated in SZs, but down-regulated (fold change = -2.2; p = 0.0007) in BDs. These findings suggest that the GABAergic phenotype could be regulated through fundamentally different molecular pathways. Despite the common GABA defect in these two disorders, the underlying mechanisms appear to be different in SZ and BD and may reflect their respective cellular endophenotypes. Supported by MH42261 and MH31862.

EXPRESSION OF POSTSYNAPTIC DENSITY PROTEINS IN GABAERGIC AND GLUTAMATERGIC THALAMIC NEURONS IN SCHIZOPHRENIA

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The glutamate hypothesis of schizophrenia suggests altered glutamatergic function in several brain areas, including the prefrontal and cingulate cortices and thalamus. There is a growing body of evidence indicating dysregulation of components of the synaptic glutamatergic machinery, including metabotropic receptors (mGluR), ionotropic receptors (AMPA, NMDA and Kainate), glutamate transporters (EAAT and VGLUTs), as well as glutamate receptor interacting proteins of the postsynaptic density (PSD proteins). PSD proteins are critical for normal receptor assembly, trafficking, insertion in the plasma membrane, and receptor activation. In this study, we are measuring the molecular expression of the postsynaptic proteins PSD95, PSD93 and SAP102 associated with the NR2 subunits of t he NMDA receptor in GABAergic interneurons and glutamatergic relay neurons from mediodorsal, ventral, anterior, and reticular thalamic nuclei. We are using immunohistochemical methods to specifically label neuronal subpopulations, harvest GABAergic and glutamatergic neurons with laser capture microdissection (LCM), and measure mRNA expression by quantitative PCR (RT-PCR). Data for expression of PSD95, PSD93 and SAP102 in GABAergic interneurons and glutamatergic relay neurons will be presented. These results will increase the knowledge about the role of glutamate receptor interacting proteins in schizophrenia.

DIFFERENTIAL LEVELS OF GLUTAMATE, GLUTAMINE AND THE GLUTAMINE/GLUTAMATE RATIO IN SCHIZOPHRENIA AND AFFECTIVE DISORDERS: A POSTMORTEM STUDY OF PREFRONTAL CORTEX AND CAUDATE NUCLEUS

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Background: Disruption in central nervous system (CNS) glutamatergic functioning has been increasingly implicated not only in the pathophysiology of psychotic symptoms in schizophrenia, but also the well characterized deficits in neurocognition. Methods of directly measuring or estimating levels of CNS glutamate and glutamine by CSF sampling or in vivo molecular imaging have yielded inconsistent results. Methods: Levels of glutamate (Glu), glutamine (Gln), and the glutamine to glutamate ratio (Gln/Glu), were assessed in postmortem brain of patients with schizophrenia (n = 10) and a control group composed of patients who were diagnosed with major depression or bipolar disorder (n = 10). Neuroanatomical areas of interest were prefrontal cortex and caudate nucleus. Levels of Glu and Gln were measured using high performance liquid chromatography. Results: In prefrontal cortex, lower levels of Glu were observed in the brains of patients with schizophrenia (238.3 +/- 7.4 UNITS vs. 261.2 +/- 7.36 UNITS), a difference that nearly reached statistical significance (p = 0.056). There were no significant between groups differences in Gln levels or the Gln/Glu ratio in this region. In caudate nucleus, there were significant between groups differences in schizophrenic and control brain for levels of Gln (780.8 +/- 63.3 UNITS vs. 468.9 +/- 63.3 UNITS, p = 0.025) and the Gln/Glu ratio (2.16 +/- 0.12 UNITS vs. 0.99 +/- 0.12 UNITS, p = 0.0025), but not for Glu. Conclusion: Our data support a role for the glutamatergic system in either the underlying pathophysiology of schizophrenia, or the effects of medication. Our findings in both prefrontal cortex and caudate also provide evidence that glutamatergic dysfunction may provide a basis for neurocognitive dysfunction in schizophrenia, especially for working memory, executive functioning/problem solving and learning.

ALTERED EXPRESSION OF GABAERGIC MARKERS AND NMDA RECEPTOR SUBUNITS IN THE CEREBELLUM OF PATIENTS WITH SCHIZOPHRENIA AND RATS CHRONICALLY EXPOSED TO PHENCYCLIDINE

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One of the most consistent findings in schizophrenia is the dysfunction of specific subsets of GABAergic interneurons. This dysfunction is observed in distributed brain regions including the prefrontal cortex, hippocampus, and cerebellum. Analyses of post-mortem tissue from cerebellar hemispheres from 13 schizophrenic patients and 13 matched controls by quantitative real-time PCR (qRT-PCR) revealed that the mRNA levels of both the 67 kDa and 65 kDa isoforms of glutamic acid decarboxylase (GAD-67 and GAD-65) as well as the presynaptic GABA transporter GAT-1 were decreased the schizophrenic group. In addition to GABAergic alterations, N-methyl-D-aspartate (NMDA)

receptor dysfunction has been proposed in this illness. To investigate this possibility, we measured NMDA receptor subunit mRNA levels in the same samples. No significant changes were observed in NR1, NR2A and NR2C mRNA levels. However, the ratio of NR2D over NR2B was increased in the patients. In an effort to understand the mechanisms for these gene expression changes, we chronically administered the NMDA receptor antagonist phencyclidine (PCP), which elicits schizophrenia-like symptoms in both humans and animal models. Adult rats were given PCP i.p. at a dose of 2.58 mg/kg/day for one month using a chronic intermittent exposure paradigm, after which qRT-PCR was performed. Analyses of PCP-treated rat cerebellum demonstrated similar decreases in GAD-67, GAD-65, and GAT-1 mRNAs, reproducing the molecular GABAergic changes seen in human patients. NMDA receptor subunit analyses did not reveal any major differences in PCP-treated rats, except for a significant decrease in both NR2B and NR2D mRNA levels. Interestingly, these two subunits are present in Golgi cells and colocalize extra-synaptically. Since low doses of PCP preferentially block NMDA receptors in GABAergic interneurons, chronic PCP administration could preferentially affect Golgi cells in the cerebellum. A dysfunction of these and other GABAergic interneurons may lead to unregulated firing of excitatory cells and subsequent neuronal damage in specific brain regions. In conclusion, our results further support the use of rats chronically exposed to PCP as an animal model of schizophrenia. Supported by the MIND Institute.

CHARACTERISING PRE AND POST-MORTEM FACTORS INFLUENCING HUMAN POST-MORTEM BRAIN PROTEOMIC STUDIES

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BACKGROUND: High through-put genomic and proteomic studies of human post-mortem brain are invaluable tools for characterising the molecular processes underlying complex psychiatric disease. There is however a considerable amount of natural variation among human tissue samples due to pre- and post-mortem factors that cannot be controlled for. Evidence from gene expression studies suggests that agonal state and brain ph profoundly effect mRNA expression levels[1, 2, 3] while post-mortem interval(PMI), age, gender, tissue storage time and medication are also know to exert effects. It is imperative that these confounding factors are taken into consideration during analysis as they are likely to mask the effect of disease associated gene/protein changes, which are usually of small effect size. **AIM:** To identify the principle sources of natural variation in the proteomic profiles of human post-mortem brain samples and to understand their impact on downstream analyses. **METHODS:** We employed two dimensional fluorescence difference in gel electrophoresis (2D-DIGE), for measuring changes in protein expression in post-mortem white matter from DLPFC, between 35 Scz, 35 BPD and 35 controls. The tissue was provided by the Stanley Foundation. The gel images were analysed in DeCyder(6.0) statistical analysis carried out(ANCOVA, $P<0.01$) with disease groups and covariates defined a priori as brain pH, PMI, refrigerator interval, age, lifetime alcohol and lifetime drug use. **RESULTS:** Protein spots statistically significant for brain pH(97), PMI(37), Age(62), lifetime Alcohol(8), and lifetime drug effects(17) were excised from preparative gels and are currently being identified by MS. **CONCLUSION:** This is the first study to examine the effects of pre and post-mortem factors on the protein profile of human brain. Our results show that brain ph was the most predictive (43% of significant proteins) source of natural variation among the post mortem samples, a finding in keeping with recent microarray studies ([1,2,3]. Taken together these studies highlight the need for careful interpretation of post-mortem brain expression studies to ensure the chance of finding significant and reproducible changes. **ACKNOWLEDGEMENTS:** Research supported by the Stanley Foundation, NARSAD, and Wellcome Trust. **REFERENCES:** 1.Li, Z. et al. Human Molecular Genetics 2004,13,609-616. 2.Vawter, M. et al. Molecular Psychiatry 2006,7,663-679. 3.Mexal, S. et al. Brain Research 2006,1106,1-11.

EVIDENCE TO SUPPORT ALTERED TRIPARTITE SYNAPSE FUNCTION IN SCHIZOPHRENIA AND BIPOLAR 1 DISORDER

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Schizophrenia and bipolar 1 disorder are serious psychiatric illnesses that affect approximately 4% of the World population. Both illnesses are thought to occur in individuals with a genetic predisposition after they encounter as yet unknown detrimental environmental factors. Postmortem CNS studies have been undertaken to identify the combined impact of these two factors on both cellular and molecular cytoarchitecture. In particular, studies from our laboratories have shown changed levels of the glial derived proteins apolipoprotein E and D in the cortex of subjects with schizophrenia and bipolar disorder1. In addition, we have shown changes in levels of S100β in the dorsolateral prefrontal cortex from subjects with bipolar disorder2. Significantly, it is known that levels of S100β are known to be potently regulated by serotonin via the serotonin1A receptor and receptors for apolipoprotein E are localised on neurons. Our data would therefore support the hypothesis that at least part of the pathology of schizophrenia and bipolar disorder are due to a breakdown in communication between neurons and glia, which occurs most potently at the tripartite synapse. Our published data and recent data from our microarray study has now shown that there is a decrease in the expression of specific apolipoprotein E receptors in the CNS of subjects with schizophrenia, further supporting our hypotheses of altered neuronal glia communication in psychiatric disease will be summarised in this presentation. 1. Digney, A.L., Keriakous, D., Scarr, E., Thomas, E.A. and Dean, B. (2005) Differential changes in apolipoprotein E in schizophrenia and bipolar 1 disorder. Biological Psychiatry 57: 711-715. 2. Dean, B., Gray, L. and Scarr, E. (2006) Regionally-specific changes in levels of critical S100β in bipolar 1 disorder but not schizophrenia. Australian and New Zealand Medical Journal. 40 : 217 – 224

BRAIN DERIVED NEUROTROPHIC FACTOR, TRKB AND P75 IN STANLEY CONSORTIUM BRAINS: DIAGNOSIS-SPECIFIC CHANGES IN HIPPOCAMPAL PROTEIN LEVELS AND EVIDENCE OF FUNCTIONAL POLYMORPHISMS

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BDNF and its associated receptors, TrkB and p75 are important in the structural and functional development of the hippocampus. Altered function of these molecules may underlie hippocampal volume

reductions and cellular changes observed in schizophrenia and mood disorder. Using the Stanley Consortium post-mortem brain collection, the aims of this study are: (i) to determine whether hippocampal (pro)BDNF, trkB and p75 protein density are altered in schizophrenia, bipolar disorder and unipolar depression; and (ii) to analyse the effect of single nucleotide polymorphisms (SNP's) within each gene on protein expression in the hippocampus. Formalin-fixed paraffin-embedded postmortem anterior hippocampal sections from subjects with major depression (MDD), bipolar disorder (BPD), schizophrenia (SCZ) and nonpsychiatric control subjects were stained for (pro)BDNF, trkB and p75 and each protein quantified using immunoautoradiography. In addition, frozen blocks of cerebellum from each subject were genotyped for specific SNP's within each gene to determine whether protein expression levels correlated with genotype. We found that (pro)BDNF density was decreased in the hippocampal pyramidal layer in MDD versus controls. A significant decrease in (pro)BDNF was also seen in stratum oriens in MDD, SCZ & BPD versus controls and in stratum radiatum in schizophrenia and BPD versus controls. No differences were found between diagnostic groups in any of the regions of interest for TrkB-T1. Decreased p75 density was found in BPD relative to other diagnostic groups. No effect of antipsychotic or antidepressant treatment were found on (pro)BDNF, TrkB, or p75 protein. Genotyping studies revealed that individuals expressing the rare allele for two SNPs in the TrkB gene (rs1187326 and rs1187323) expressed lower protein levels of truncated-TrkB in most regions of the hippocampus relative to homozygous dominant allele carriers. In addition, rare allele carriers for a SNP in the p75 gene (rs11466117) had increased p75 protein levels in the hippocampus relative to homozygous dominant allele carriers. In conclusion, we have revealed two novel findings: a decrease in p75 in BPD and functional polymorphisms in the TrkB and p75 genes. We also confirm previous findings of reduced BDNF in hippocampus in schizophrenia and mood disorder.

ALTERATIONS IN CB1 RECEPTOR MRNA AND PROTEIN EXPRESSION IN THE DLPFC OF SUBJECTS WITH SCHIZOPHRENIA: IMPLICATIONS FOR COGNITIVE DEFICITS

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Delta-9-tetrahydrocannabinol (Δ9-THC), the chief psychoactive cannabinoid in cannabis, has profound effects on higher cognitive functions. Exposure to Δ9-THC has been associated with an increased risk of schizophrenia and disturbances in working memory, a core feature of schizophrenia. The working memory deficits associated with schizophrenia are thought to result from alterations in the circuitry of the dorsolateral prefrontal cortex (DLPFC), specifically reductions in markers of GABA neurotransmission. Interestingly, the CB1 receptor, the principal cannabinoid receptor in the brain, is highly expressed in the DLPFC and is preferentially contained in GABA neurons. These findings suggest that the CB1 receptor may play a role in the circuitry that subserves working memory. Therefore, we utilized in situ hybridization and immunocytochemistry to examine the expression of CB1 receptor mRNA and protein in DLPFC area 9 of 23 pairs of subjects with schizophrenia and matched control subjects. CB1 receptor mRNA was expressed across layers 2-6, with the highest expression in layers 2 and superficial 3. Optical density analysis of film autoradiograms revealed that CB1 receptor mRNA was significantly reduced by 14.8% in the DLPFC of subjects with schizophrenia compared to matched controls. Laminar analysis revealed significant reductions in CB1 mRNA expression in layers 2-3a (-15.9%), 5 (-15.5%) and 6 (-17.7%). The expression of CB1 mRNA was not changed in the DLPFC of monkeys chronically exposed to haloperidol or olanzapine, suggesting that the observed decrease in CB1 mRNA expression was not the result of antipsychotic medication. By immunocytochemistry, intense CB1-immunoreactivity was observed primarily in axons and boutons. The density of CB1-IR axons was lowest in layer 1 and progressively increased from superficial to deep across layers 2 and 3. Layer 4 contained a very dense band of immunoreactive axons and varicosities, whereas layer 5 contained a low level of immunoreactivity that sharply demarcated the border with layer 4. Analysis of CB1 immunoreactivity in DLPFC area 9 revealed a significant reduction in the subjects with schizophrenia. A laminar analysis to determine if this overall decrease is due to changes in specific layers is ongoing. The altered expression of CB1 receptor mRNA and protein in the DLPFC of subjects with schizophrenia may inform the identification of novel drug targets for the treatment of cognitive deficits in schizophrenia.

PROTEOMIC ANALYSIS OF WHITE MATTER FROM THE DORSOLATERAL PREFRONTAL CORTEX IN SCHIZOPHRENIA DEMONSTRATED ALTERATIONS IN SYNAPTIC ASSOCIATED PROTEINS

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BACKGROUND: White matter abnormalities in the Dorsolateral Prefrontal Cortex (DLPFC) are implicated in the pathophysiology of Schizophrenia (Scz) and Bipolar Disorder (BPD). Investigations have shown reductions in myelin and oligodendroglial-associated proteins and genes and these findings are in keeping with cytoarchitectural studies that suggest the presence of a glial cell defect in Scz and BPD. These studies provide a strong argument for the examination of DLPFC white matter tissue at the protein level in Scz and BPD. **METHODS:** We employed two dimensional fluorescence difference in gel electrophoresis (2D-DIGE) to measure changes in protein expression in post-mortem deep white matter from DLPFC in 35 Scz, 35 BPD and 35 controls samples. The tissue was provided by the Stanley Foundation Brain Consortium. A total of 53 gels were run (ph4-7) and analysed in DeCyder (6.0). The data was exported for analysis of covariance (ANCOVA) with disease groups and covariates defined as brain pH, PMI, refrigerator interval, age, lifetime alcohol and drug use. Differentially expressed proteins were identified by mass spectrometry (LC-MS-MS).**RESULTS:** 120 proteins were differentially expressed between groups (ANOVA $P<0.05$). After correcting for covariates, 45 proteins were significantly changed between the Scz and control groups while 36 proteins were altered between BPD and controls (ANCOVA $P<0.05$). A total of 6 differentially expressed proteins overlapped between Scz and BPD groups. **CONCLUSION:** This is the first large scale proteomic study to specifically target DLPFC deep white matter Scz and BPD. Of interest, NF-L, Rab GDP, and Bin1 are implicated in synaptic function and were found differentially

expressed in the Scz group only. Moreover, NF-L, a protein involved in localizing the NMDA receptor to the neuronal plasma membrane, was recently found to be decreased in DLPFC Scz patients, a finding in keeping with our study. Altered white matter proteins included 14-3-3 epsilon, important for neuronal migration and previously implicated in multiple sclerosis (MS), and Stathmin, a cytoskeletal protein also implicated in MS. Taken together this study provides important molecular evidence implicating synaptic function in Scz, and white matter abnormalities in both diseases. **ACKNOWLEDGEMENTS:** Research supported by the Stanley Medical Research Institute, the National Alliance for Research on Schizophrenia and Depression, and Wellcome Trust.

PROTEOMIC ANALYSIS OF HIPPOCAMPAL SUBREGIONS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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The hippocampus has critical roles in learning and memory and is centrally implicated in many neuropsychiatric disorders. It is divided into subregions, and these differ with regards to morphology, connectivity, electrophysiology and susceptibility to insults. There is evidence that hippocampal changes are amongst the central components of schizophrenia and precede the onset of the illness and that changes involve the hippocampal subregions differentially. For example, corona ammonis 1 (CA1) is relatively spared but CA2 and CA3 are more vulnerable. The dentate gyrus is also implicated. These different subregions implicated in schizophrenia have distinct roles in regulation of hippocampal circuitry and alterations within them are likely to contribute in a primary way to the clinical presentation. We aim to characterise the differential protein expression in each of these hippocampal subregions in schizophrenia and bipolar disorder compared to control tissue obtained by the Stanley Medical Research Institute. We used laser assisted microdissection, and Difference in Gel Electrophoresis to enrich for these tissues and to compare protein profiles. We have undertaken a pilot study where we used the dentate gyrus of 5 cases of each of the three groups A, B, and C representing schizophrenia, bipolar disorder and controls. 30 laser microdissected sections of each of the dentate (5/5/5)were lysed and 25 µg brain tissue samples were labelled with 200 pmol of one of the two fluorescent dyes Cy3 and Cy5 and mixed with the internal standard that was labelled with Cy2. After reswelling the IPG pH4-7 strips iso-electric focussing (first dimension) was undertaken and proteins separated according to their isolelectric point. The second dimension was performed on 12% slab gels to separate proteins by their molecular weight. Subsequently gels were scanned according to the different wavelength for each of the CyDyes. Image analysis was then carried out using DeCyder 6.5. Samples were grouped according to the different disease /control groups. DeCyder co-detected protein spots from the Cy2, Cy3, and Cy5 images within each gel and spots were matched across all gels via the internal standard. An average of 700-900 spots were matched across all images. These preliminary results confirm the feasibility of this strategy for proteomic analysis of hippocampal subregions in schizophrenia. This study is supported by the Wellcome Trust, Stanley Medical Research Institute and RCSI.

THE EXPRESSION OF PRESYNAPTIC DOPAMINE NEURONAL MARKERS IN POSTMORTEM TISSUE OF SCHIZOPHRENIC SUBSTANTIA NIGRA

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Dopamine (DA) in the basal ganglia is the most prominent neurochemical entity related to the pathology of schizophrenia. The substantia nigra (SN) and ventral tegmental (VTA) are basal ganglia structures that house the majority of DAergic neurons in the brain. At the DAergic synapse, different levels of alterations in dopamingergic transmission can occur. Both pre- and post-synaptic processes may contribute to the abnormal DA system in the basal ganglia. DA levels are affected by DA synthesis, release and uptake processes at the dopaminergic synapse. In subjects with schizophrenia, alterations in the DA synthesis enzyme tyrosine hydroxylase (TH) and the dopamine transporter (DAT) in synaptosomes have been found in the dorsal striatum and nucleus accumbens, respectively. Previously, our electron microscopic studies of postmortem tissue have shown the abnormalities in the morphology of DA neurons in the substantia nigra (SN) and in the number of TH positive striatal synapses in schizophrenia. In this study, we selected presynaptic DA neuronal markers to test the general hypothesis that the DA system is perturbed in the basal ganglia in schizophrenia. Using in situ hybridization we will examine the transcription levels of TH, DAT and vesicular monoamine transporter (VMAT-2) in postmortem SN. We used serial sections from the rostrocaudal axis of the SN obtained from matched postmortem tissue in six individuals with schizophrenia (SZ) and six normal controls (NC). Age = 54.3 +/-14.7 yr (SZ) and 57.7 +/- 14.2 yr (NC). Postmortem interval = 18.8 +/- 4.9 h (SZ) and 18.8 +/- 2.4 h (NC). The quantification of three presynaptic protein mRNAs in the SN will be reported. We will assess how these neurochemical findings relate to protein levels and changes in synaptic structures. Supported by MH 66123 and MH 60744.

VASCULAR ENDOTHELIAL CELLS OF THE PREFRONTAL CORTEX INVESTIGATED BY LASER CAPTURE MICRODISSECTION AND MICROARRAY HYBRIDISATION

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Previous studies from our laboratory and others point towards the role of compromised brain metabolism in schizophrenia. We were therefore interested to investigate vascular endothelial cell function in schizophrenia patients. The application of laser capture micro-dissection to human post-mortem tissue provides a unique means to accurately dissect individual cell populations from complex tissue. Amplified RNA from captured cells can subsequently be investigated with regards to cell-type specific and/or disease-specific gene expression profiles using microarray technology. This represents a major advance in molecular profiling technology over tissue homogenate based studies, in which the cellular heterogeneity of brain tissue is an inherent confounding factor. Rapid immunostaining was used to identify vascular endothelial cells and neurons in human post mortem brain tissue (DLPFC) from subjects with schiz-

ophrenia, and controls (endothelial cells n=15, neurons n=12). These cell types were isolated by laser microdissection and the extracted RNA amplified, labeled and hybridized to gene microarrays. Both Codelink and Affymetrix microarray platforms were used, in order to maximize the amount of information that could be extracted from this RNA population, and also in order to cross-validate results. Initial investigation of the data confirmed that gene expression profiles from each cell type showed the predicted biological signal based on markers of endothelial and neuronal cell function. Gene ontology analysis was then used to identify functional categories of genes altered in schizophrenia in each cell type. Results showed that different classes of gene were altered in neurons and endothelial cells in schizophrenia; thus further investigation of the vasculature of schizophrenia patients may be warranted. This research is part of the Molecular Evolution of Human Cognition project which is funded by an EU Sixth Framework Programme grant, and was also supported by the Stanley Medical Research Institute.

SUSCEPTIBILITY GENES AND SYNAPTIC PLASTICITY IN SCHIZOPHRENIA

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Synaptic dysfunction, particularly affecting glutamatergic transmission and NMDA receptors, has been advocated as a key component in schizophrenia pathophysiology. The talk will consider the more recent proposal that schizophrenia susceptibility genes may impact in a convergent fashion upon these processes. First, results of a bioinformatics study which suggests there is indeed a convergence of the genes upon glutamatergic synapses and NMDA receptor signalling will be presented. Other evidence for, and against, the proposal will be summarised. Discussion will then be broadened to the key issues, and the limitations, of the attempts to link genetic susceptibility to synaptic and circuitry dysfunction in schizophrenia. The problems range from the complexities introduced by non-coding polymorphisms and alternative splicing, to the need to specify more precisely what is meant by synaptic plasticity and to identify the actual molecular pathways involved. The talk will be illustrated by recent data for several putative susceptibility genes.

REGIONAL SURVEY OF GABA-RELATED GENE EXPRESSION IN THE NEOCORTEX OF SUBJECTS WITH SCHIZOPHRENIA

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In the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia, GABA neurotransmission appears to be altered as indicated by decreased expression of the mRNAs for GAD_{67}, an enzyme for GABA synthesis, the neuronal GABA membrane transporter 1, and the $\alpha 1$ and δ subunits of the $GABA_A$ receptor. Furthermore, these alterations appear to involve specific subclasses of GABA neurons because parvalbumin (PV) and somatostatin (SST) mRNAs, which are expressed in separate subclasses of GABA neurons, were decreased, whereas calretinin (CR) mRNA, which is expressed in a third subclass of GABA neurons, was unchanged in subjects with schizophrenia. Given the critical roles of the affected GABA neurons in regulating distinct aspects of cortical activity, these alterations are likely to make a major contribution to DLPFC dysfunction in schizophrenia. However, it remains to be determined whether similar abnormalities underlie the dysfunction of other cortical areas in the illness. Thus, we systematically assessed the expression of eight mRNAs encoding proteins involved in GABA neurotransmission in the DLPFC, anterior cingulate cortex (ACC) and primary visual cortex (V1) from 12 matched pairs of schizophrenia and control subjects using real-time quantitative PCR. For each mRNA, the pair-wise expression changes were determined by the comparative threshold cycle (δCt) method using the geometric mean of three internal control genes, GAPDH, cyclophilin, and beta-actin. Our preliminary analyses detected decreased expression for several mRNAs including those encoding GAD_{67}, PV, and SST mRNAs across the DLPFC, ACC, and V1 of subjects with schizophrenia, without a disease-related difference in CR mRNA levels in any region. These findings suggest that the local inhibitory circuitry is affected in a similar manner, with selective involvement of the PV- and SST-containing subclasses of GABA neurons, across cortical regions with different functional properties. These alterations may reveal a common mechanism for altered information processing in diverse areas of the neocortex in individuals with schizophrenia. Supported by NIH grants MH 045156, MH 043784, and by NARSAD Young Investigator award.

ABNORMAL AMPA RECEPTOR TRAFFICKING PROTEIN TRANSCRIPT EXPRESSION IN THE THALAMUS IN SCHIZOPHRENIA

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The glutamate hypothesis of schizophrenia is based, in part, on the observation that NMDA receptor antagonists can trigger schizophreniform symptoms in non-psychotic subjects. In addition, AMPA receptor positive modulators, AMPAkines, can improve cognitive functions in schizophrenia and enhance antipsychotic efficacy. In basal conditions, synaptic activation of NMDA receptors require partial depolarization of the neuron mediated by co-localized AMPA receptors. Trafficking of AMPA receptors is regulated by subunit specific protein-protein interactions that modulate receptor cell surface expression, regulating their response to glutamate and subsequent signalling cascades. Specifically, GluR1 trafficking is mediated by the protein SAP97, that transports newly-synthesized GluR1-containing AMPA receptors from the Golgi apparatus to the membrane. GluR2 trafficking is regulated by several postsynaptic density (PSD) proteins, including NSF (constitutive recycling of GluR2-containing AMPA receptors), PICK1, Syntenin, GRIP1, and ABP (intracellular storage and vesicular recycling mediated by GluR2 and GluR3). Binding all four subunits, the transmembrane protein Stargazin mediates AMPA receptor lateral translocation and clustering at the synaptic membrane. Using in situ hybridization, we investigated the transcript expression of all four AMPA subunits and these trafficking proteins in the thalamus of schizophrenic and control subjects. Decreased expression of GluR1 and GluR4 transcripts was detected throughout all thalamic nuclei investigated. However, GluR1 associated protein, Sap97, remained unchanged. While transcript expression of the GluR2 subunit was unchanged in schizophrenia, the transcript expression of the GluR2-trafficking-associated-proteins, NSF and Syntenin, was diminished in multiple thalamic nuclei. Stargazin mRNA expression was also reduced in the thalamus in schizophrenia. Taken together, these alterations suggest abnormal glutamate receptor function, resulting in disturbances in signalling

pathways associated with glutamate neurotransmission, in the thalamus in schizophrenia.

POSTNATAL MK-801 EXPOSURE AND SYNAPTIC DEFICITS IN SCHIZOPHRENIA

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N-methyl-D-aspartate (NMDA) receptor hypofunction has increasingly been implicated in the pathophysiology of schizophrenia (SCZ), based in part on evidence that phencyclidine (PCP) can reproduce multiple symptom domains of SCZ in healthy volunteers and exacerbate symptoms in patients. Behavioral deficits associated with animal models of SCZ are also found in adult rats and mice treated neonatally with NMDA antagonists, including MK-801 and PCP. Synaptic deficits (including altered dendritic spine density) in hippocampus and prefrontal cortex are thought to represent primary neuropathological features in schizophrenia. Postnatal MK-801 exposure in a rodent model is known to produce synaptic deficits in hippocampus and thalamus, possibly acting via a caspase-3 mediated apoptotic pathway. The effect of MK-801 on synapses in this model has not been examined in frontal cortex. The current study examined the impact of MK-801 1 mg/kg i.p. q8 hrs x 3 in Sprague-Dawley rats at postnatal days (PD) 1, 7, 14, 21 followed by sacrifice after 24 hours. Western blot and immunohistochemistry was used to ascertain caspase-3 activation. Western blot was used to quantify spinophilin, a well established dendritic spine marker. Golgi impregnation was used to determine dendritic spine density. We found robust increases (2.5-fold) in activated caspase-3 levels in medial frontal cortex by Western blot at PD8 but not at other timepoints. Spinophilin levels were significantly higher (3-fold) at PD22, but not at other timepoints. Data on Golgi impregnation will also be presented. These data suggest that early postnatal MK801 can alter synaptic connectivity within a narrow developmental window as evidenced by the substantial increase in spinophilin content at PD22 but not at earlier ages. This effect appears to be dissociated from the pro-apoptotic response which is confined to the first postnatal week. Altered dendritic spine content associated with postnatal NMDA antagonism provides a potential mechanism that could contribute to the evidence for synaptic deficits in schizophrenia. Future studies will need to examine long term consequences of early NMDA exposure on dendritic spines.

EXPRESSION OF THE NMDA RECEPTOR TRAFFICKING PROTEINS CASK, VELIS, MINT1 AND KIF17 IN PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Both clinical and experimental evidence suggest abnormal functioning of the N-methyl-D-aspartate (NMDA) glutamate receptor in schizophrenia. Analysis of expression of NMDA receptor subunits and their interacting proteins of the postsynaptic density (PSD) in postmortem tissue suggest that, in addition to regional changes of expression of these molecules, cellular processing including dendritic trafficking of the receptor might also be compromised in this illness. In neurons, the cellular mechanism for NMDA receptor trafficking has recently been described. Following assembly of the NMDA receptor, a protein complex consisting of the mLin7/Velis (1-3) and mLin10/Mint1 adaptor proteins associated with the Shank related mLin2/CASK anchoring protein, links vesicles containing newly synthesized NMDA receptors to the microtubule associated kinesin related KIF17 motor protein. NR2B-containing NMDA receptors in particular rely on this protein complex for dendritic targeting as cellular knockdown of KIF17 selectively affects trafficking of NR2B containing NMDA receptors, whereas NR2A containing receptors that rely on different trafficking mechanisms are unaffected. Altered expression of the KIF17-associated NMDA receptor trafficking complex in schizophrenia could therefore cause a changed composition of NMDA receptor subtypes at the PSD in schizophrenia, resulting in altered signaling properties at excitatory synapses. To study the hypothesis of compromised dendritic trafficking in schizophrenia, we have in this study measured expression of the Velis, Mint1, CASK, KIF17 molecular complex at both transcript and protein levels in dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) in brains from patients with schizophrenia and a comparison group. At present we have measured Velis3 and Mint1 transcript expression and have found expression of Mint1 in DLPFC significantly increased in schizophrenia, whereas Velis3 was not altered. Expression of Mint1 and Velis3 in ACC were not altered. Our results indicate that altered NMDA receptor trafficking, in addition to alterations in expression of the receptor and associated PSD proteins, might be involved in the pathophysiology of schizophrenia.

SMOKING AND SCHIZOPHRENIA: EVIDENCE FOR SELF MEDICATION

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The prevalence of smoking in schizophrenia is much higher than in the general population (>80%). This may represent a form of self-medication. Nicotine normalizes the auditory evoked potential deficit (P50) seen in most all schizophrenics and also improves cognition. Surface nicotinic receptors, the first point of response for nicotine in the brain, are reduced in number in schizophrenic smokers, compared to control smokers. We have recently completed a study of global gene expression differences in postmortem hippocampus of control and schizophrenic smokers and non-smokers. A total of 34 subjects were studied. Our findings show that the expression of more than 250 genes is changed in smokers. The two most significantly altered gene groups were genes of the NMDA postsynaptic density and genes functioning in the immune system. When the effects of smoking were compared in controls and schizophrenics, we found that smoking in schizophrenics differentially regulated 77 genes. The pattern of regulation was the same: the expression levels in schizophrenic non-smokers were different from control non-smokers, but brought to control expression levels or normalized in the schizophrenic smokers. The normalization of gene expression in these systems in the patients by smoking is consistent with a self-medication hypothesis. Genes in the NMDA postsynaptic density, including the alpha 7 nicotinic receptor, fell into this class. Alpha 7 mRNA and protein were significantly lower ($P<0.05$) in schizophrenic non-smokers, compared to controls, and were brought to control levels or normalized by smoking in the patients ($P<0.01$). The alpha 7 nicotinic receptor is genetically linked to schizophrenia and to the P50 auditory deficit. Alpha 7 also plays a role in nicotine addiction and in cognition. An agonist for the alpha 7 receptor, DMXB-A improves both the P50 deficit and cognition in schizophrenic subjects. Drugs such as DMXB-A, therefore, hold promise for improvement of both sensory and cognitive deficits in schizophrenia, without the side

effects of smoking. They may also be useful in smoking cessation programs in the disorder.

TOOLS FOR TRANSLATIONAL RESEARCH

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Human postmortem brain tissue is an essential resource that facilitates translational research. It serves as a bridge allowing for discoveries in animals to feed forward into the clinical setting and vice versa. With the advent of modern neuroscience tools, human post mortem research will become increasingly important in translation neuroscience. The Dallas Brain Collection (DBC) was established in 2003 and is an integral part of the Division of Translational Neuroscience Research in Schizophrenia (DTNRS) at UTSW. The DTNRS is comprised of several sections including neuroimaging, post mortem tissue analysis and a Stanley Center for Early Drug Development. The DBC is designed to collect high quality human post mortem research to facilitate translation of research findings within the DTNRS. One strategy that we employ is to use data from imaging studies to inform our human post mortem studies, specifically in terms of identification of important brain regions involved in the pathophysiology of schizophrenia. For example, functional imaging studies in our group have identified the anterior medial temporal lobe as a brain region associated with cognitive deficits and psychosis in schizophrenia. Based on these findings, we have directed our human post mortem research to the neurochemical characterization of the anterior hippocampus. We have now identified several presynaptic trafficking proteins and markers of glutamate neurotransmission that are abnormal in this brain region. In this manner, functional in vivo data combined with higher resolution post mortem molecular findings provide a stronger research strategy. In addition, the relevant molecular targets identified in our post mortem studies can inform animal studies where experimental manipulations can unravel the molecular mechanisms involved in pathophysiology.

IDENTIFICATION OF ROBUST DISEASE CHANGES IN MICROARRAY STUDIES OF PSYCHIATRIC DISORDERS

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Schizophrenia (SZ), bipolar disorder (BD) and depression (D) are severe psychiatric disorders with a strong genetic component. They may form a spectrum of disorders and have some shared features, including psychosis and depression. Microarray technology has the potential to help elucidate the pathophysiology of these complex disorders, but diverse genes and processes have been implicated by the numerous microarray studies undertaken to date. The brain collection held by the Stanley Medical Research Institute (SMRI) is considered one of the best in the world and post-mortem brain tissue from subjects with schizophrenia, bipolar disorder, depression as well as controls has been distributed to a number of laboratories, including the Bahn laboratory. SMRI has recently analysed the raw data from 12 of these studies and created the open source SMRI Online Genomics Database (Higgs et al, 2006) to enable researchers to investigate further the changes in gene expression identified in these disorders. The studies use tissue samples from either the Array Collection (n=35 for each patient group) or Consortium Collection (n=15 for each patient group) and include six different brain regions, primarily prefrontal cortex BA46. A total of six microarray platforms were used, the majority being Affymetrix GeneChips. All datasets were analysed in the same way and included an assessment of the effects of over 40 demographic variables on gene expression. We used this unique resource to identify genes that were consistently altered across different studies and generated a list of robust genes for each disorder (SZ, BD and D). We excluded one study that did not use a commercial microarray platform and considered eleven BD, ten SZ and five D studies in total. We functionally profiled the lists of consistently altered genes to characterise each disorder as well as investigate similarities and differences between disorders. We also used a custom statistical algorithm to assess the distribution of genes for each disorder across the genome and then identify chromosome regions containing clusters of genes. We gratefully acknowledge funding support from SMRI.

MRNA EXPRESSION OF GABAA RECEPTOR δ AND α4 SUBUNITS IN THE DORSOLATERAL PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA

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Disturbances in inhibitory neurotransmission appear to play a prominent role in the dysfunction of the dorsolateral prefrontal cortex (DLPFC) in schizophrenia. In a recent microarray study, we found decreased expression levels of the GABAA receptor subunits δ and α4 in the DLPFC of subjects with schizophrenia. In order to understand the potential functional significance of these changes, we utilized in situ hybridization to assess the anatomical localization and expression pattern of δ and α4 transcripts across layers of the DLPFC in 23 subjects with schizophrenia, each individually matched with a control subject for age, sex and postmortem interval. In all subjects, the mRNA levels of both δ and α4 subunits were high and uniform across layers 2, 3 and superficial layer 5, whereas in deep layer 5 and layer 6, the expression levels were low. The mRNA levels of δ were reduced by 19% in the DLPFC of subjects with schizophrenia, whereas those of α4 were reduced by 9%. In addition, the mRNA levels of δ were significantly reduced in layers 3-6 in the DLPFC of subjects with schizophrenia, whereas those of α4 were significantly reduced only in layers 5 and 6. However, α4 mRNA levels were reduced only in subjects with schizophrenia receiving benzodiazepines and/or mood stabilizers at the time of death, suggesting that the observed changes represent an effect of medications and not of schizophrenia. In order to determine whether the reduction in δ subunit mRNA could be downstream of the reduced signaling through either TrkB or NMDA receptors previously reported in schizophrenia, we are analyzing δ mRNA levels in the PFC of mice genetically engineered to express low levels of TrkB or NMDA receptors. In contrast to the phasic inhibition mediated by synaptic GABAA receptors containing γ subunits, those containing δ subunits mediate a slower form of inhibitory transmission (tonic inhibition) that results in a persistent increase of a cell's input conductance, making it less likely that an action potential will be generated. A reduction in GABA neurotransmission mediated by these receptors would result in decreased inhibition, as observed in GABAA δ knockout mice. Consequently, the reduced expression of GABAA δ subunit in subjects with schizophrenia could contribute to altered inhibitory regulation of DLPFC circuitry. Support Contributed By: MH43784 and MH45156

ALTERED VESICULAR GLUTAMATE TRANSPORTER EXPRESSION IN CORTICOTHALAMIC CIRCUITS IN SCHIZOPHRENIA

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While numerous studies have found alterations of postsynaptic molecules in schizophrenia, a growing body of evidence implicates presynaptic factors. Three vesicular glutamate transporters (VGLUT1-3) have been identified and are known to package glutamate into vesicles in the presynaptic terminal for subsequent release into the synaptic cleft. Recent studies have shown that VGLUTs regulate synaptic activity via the amount of glutamate released. Accordingly, we hypothesize that VGLUTs are altered in schizophrenia, possibly contributing to dysfunction of synaptic activity. Using in situ hybridization and Western blot analysis we investigated alterations in VGLUT1 and VGLUT2 transcript and protein expression in the anterior cingulate cortex (ACC), the dorsal lateral prefrontal cortex (DLPFC), and the dorsal thalamus in schizophrenia. To assess the effects of treatment with antipsychotic medications, we also measured VGLUT1 and VGLUT2 transcript and protein expression in rats treated with haloperidol (2 mg/kg/day) for 28 days. We found an increase in VGLUT1 transcript and a reduction in VGLUT1 protein expression in the ACC of schizophrenic subjects. We did not detect changes in VGLUT1 expression in the DLPFC, and we did not find any changes in VGLUT2 mRNA or protein in the ACC or DLPFC. We also found an increase in VGLUT2 mRNA expression in the thalamus. We did not find changes in VGLUT1-2 mRNA expression in the frontal cortex or in the thalamus of rats treated with haloperidol. Western blot analysis of VLGUT1-2 protein expression in the thalamus in schizophrenia and in rats treated with haloperidol will also be presented. In summary, we found increased VGLUT1 mRNA and decreased VGLUT1 protein expression in the ACC, and increased VGLUT2 mRNA in the thalamus in schizophrenia, suggesting an abnormality of presynaptic function in these regions. Our findings suggest that schizophrenia may be associated with decreased innervation of the ACC as well as other thalamic efferent targets and suggest that the functional roles of VGLUTs and other presynaptic molecules may be important pharmacological targets for the diagnosis and treatment of schizophrenia.

SUBCELLULAR AND MOLECULAR ABNORMALITIES OF THE GLUTAMATE SYNAPSE IN SCHIZOPHRENIA

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The glutamate, dopamine, and developmental hypotheses of schizophrenia all suggest impairment of molecular processes that underlie myriad neurological functions, such as filtering of sensory input, learning, and executive decision making. The diverse and variable symptom profile observed in schizophrenia, as well as these seemingly divergent hypotheses, may be reconciled if schizophrenia is reconceptualized as a disorder of neuroplasticity. Recent advances have identified a number of molecular correlates of neuroplasticity, including long-term potentiation (LTP) and long-term depression (LTD), which are cell-level electrophysiological phenomena postulated to be, in part, the basis of learning and memory. The postsynaptic density (PSD) is a critical element of the molecular machinery that facilitates LTP and LTD. The PSD contains receptors, structural molecules, chaperones, and signaling molecules that coordinate the highly regulated responses to presynaptic neurotransmitter release. These and other molecules facilitate the synthesis, post-translational modification, and trafficking of PSD molecules within the cell. In schizophrenia, we hypothesize that the family of molecules responsible for trafficking, insertion, regulation, recycling and degradation of glutamate receptors are abnormally expressed, leading to impairment of PSD assembly and function. To test this hypothesis, we have measured the expression of NMDA and AMPA receptor interacting proteins in the prefrontal and cingulate cortex as well as thalamus of subjects with schizophrenia. We have found significant changes in the expression of molecules that facilitate NMDA and AMPA receptor function, including SAP102, PSD95, stargazin, and GRIP. We have also found changes in AMPA and NMDA receptor subunit phosphorylation, suggesting altered glutamate receptor trafficking. These data suggest that the expression of the family of molecules that interacts with and regulates ionotropic glutamate receptors is abnormal in schizophrenia. Given the central role of these regulatory molecules in synaptic plasticity, our data support a hypothesis of abnormal neuroplasticity in schizophrenia, and indicates that these molecules and the underlying biological functions that they facilitate are high yield targets for pharmacological intervention in this devastating illness.

SOMATOSTATIN RECEPTOR SUBTYPES 1 AND 2 MRNA EXPRESSION IN THE DORSAL LATERAL PREFRONTAL CORTEX OF INDIVIDUALS WITH SCHIZOPHRENIA

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We have previously demonstrated that expression of the mRNA for the neuropeptide, somatostatin (SST) is reduced in the dorsal lateral prefrontal cortex (DLPFC) of subjects with schizophrenia. Somatostatin is localized to a subset of GABA interneurons in the human DLPFC and acts through a family of 5 seven-transmembrane G protein-coupled receptor subtypes (SSTR1-5) to produce putative inhibitory effects on neuronal firing. In mice, SSTR1 and SSTR2 are the most abundant SSTR subtypes in the cortex. SST knockout mice demonstrate a significant increase in the density of SSTR1 immunopositive neurons, without a change in the density of SSTR2 immunopositive neurons. Assuming that the reduction of SST mRNA in the DLPFC of individuals with schizophrenia is a component of the primary pathology of the illness, these mice studies suggest that a compensatory increase in the expression of SSTR1 mRNA is present in the DLPFC of subjects with schizophrenia, whereas the expression of SSTR2 mRNA would be predicted to be unchanged. To test these hypotheses, we are analyzing the expression of SSTR1 and SSTR2 mRNAs across cortical layers in DLPFC area 9 in 23 pairs of subjects with schizophrenia and control subjects matched for age, sex, and post-mortem interval. Expression levels of the mRNAs are being determined with in situ hybridization utilizing 35S-labeled riboprobes and autoradiographic film analysis. Several lines of evidence confirm the specificity of the SSTR1 and SSTR2 riboprobes. First, sense riboprobes for SSTR1 and SSTR2 mRNAs did not produce signals above background. Second, the distinctive laminar distributions of SSTR1 and SSTR2 mRNAs are similar to

previously reported distributions in the human PFC. The mRNA expression of SSTR1 is highest in layers 2 and superficial 3, moderate in deep layers 3 through superficial 6, and low in layers 1 and deep 6. The mRNA expression of SSTR2 is low in layers 1 through 4 and high in layers 5 and 6. Determination of the expression levels of SSTR1 and SSTR2 mRNAs and quantitative comparisons across matched pairs of subjects by cortical layer are currently being conducted in a blinded fashion. Results from this study will provide insight into specific SSTR subtypes that could serve as novel targets for the treatment of schizophrenia. Support Contributed by: NIH MH043784 and MH045156

INFLUENCE OF SERT L/S AND BDNF VAL66MET POLYMORPHISMS ON CANDIDATE GENE EXPRESSION LEVELS IN THE HIPPOCAMPUS IN SCHIZOPHRENIA

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The anterior hippocampus (AH) has been implicated in the pathophysiology of schizophrenia by several convergent lines of evidence. The anterior and posterior hippocampi have different connectivity patterns that may have functional implications. We have found that mRNA for brain-derived neurotrophic factor exon 5 (BDNF), NR1 subunit of the NMDA receptor and glutamatic acid decarboxylase 67 (GAD67) are differentially expressed along the rostrocaudal axis of the hippocampus in schizophrenia. In this study, we investigated the influence of schizophrenia risk gene polymorphisms, BDNF val66met and the 44 base pair repeat (long/short) of the serotonin transporter (SERT) polymorphism on expression of these candidate markers. We hypothesize that BDNF val66met and SERT L/S polymorphisms would influence BDNF and NR1 expression in the AH but not PH of the hippocampus in schizophrenia. In situ hybridization studies were conducted with probes for BDNF exon 5, NR1 and GAD 67 mRNA in serial sections of the AH and PH obtained from matched post mortem tissue in 22 individuals with schizophrenia (SCH) and 22 normal controls (NC). We performed quantitative densitometric analysis in the whole hippocampus and by layer within the CA1, CA3 and the dentate gyrus (DG). Genotyping was performed using PCR, restriction enzyme digestion (for BDNF val66met) followed by gel electrophoresis. The effect of BDNF val66met and SERT genotype on NR1, GAD67 and BDNF was determined using non-parametric statistical tests. The BDNF val66met polymorphism did not influence expression of BDNF exon 5, NR1 or GAD67 mRNA levels in AH or PH in controls or cases of schizophrenia. SERT L/L cases have significantly lower BDNF exon 5 mRNA in the AH compared to the S carriers in cases of schizophrenia but not controls. There was no effect on NR1 or GAD 67 expression in either control or schizophrenia cases. Secondary analyses identify the CA3 subfield of the AH as an important region where the SERT polymorphism exerts its effect on BDNF. Conclusions: The BDNF val66met polymorphism does not influence expression of BDNF exon 5, NR1 or GAD67 mRNA levels in the hippocampus. The SERT L/S polymorphism influences BDNF exon 5 expression in the anterior hippocampus in cases of schizophrenia but not controls. These data suggest that the SERT polymorphism has a regionally-specific effect in the CA3 of the AH that could be related to alterations of hippocampal synaptic function and plasticity in schizophrenia.

MEMBRANES PHOSPHOLIPID RATIO IN PATIENTS WITH SCHIZOPHRENIA: A COMPARISON BETWEEN PATIENTS WITH AND WITHOUT ABNORMAL MEMBRANE LIPID DISTRIBUTION

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Background: Modification of the overall phospholipid ratios and polyunsaturated fatty acids composition is a replicated biological finding in red blood cell (RBC) membranes from patients with schizophrenia compared to healthy subjects. Substantial decrease of phosphatidylethanolamine (PE) in RBC membranes (also observed in platelets, fibroblasts, and brain tissue membranes) and a parallel increase of sphingomyelin are the two main findings in this patients' population. A significant increase of the percentage of external leaflet PE was recently found to account for these lipid modifications. Significant external PE percentage increase was found in 2/3 of the studied schizophrenia population (n=65). Age, sex and antipsychotic treatment were not associated with this PE abnormality. In the hypothesis of a PE ratio decrease in the population with abnormal PE distribution (aPE SCZ), a compensatory phospholipid substitution is likely to occur in order to maintain membrane biochemical and biophysical properties. RBC membrane phospholipid ratios were examined. Comparison was made between patients with (aPE SCZ) and without (nPE SCZ) external PE abnormal distribution. Method: RBC membranes from schizophrenia patients (n=65) were isolated after blood puncture. Membrane phospholipids were extracted by the method of Bligh and Dyer. Liquid chromatography mass spectrometry (LC-MS/MS using the Q-Trap) was performed to analyse membrane phospholipids. Results: PE ratio was decreased in the RBC membrane of the aPE SCZ population. In the same population, phosphatidylcholine and sphingomyelin ratio were concomitantly increased. Several mechanisms can account for these results. Limitation of these findings is related to the small number of patients in the nPE SCZ population.

EVIDENCE FOR THE INVOLVEMENT OF THE SEPTIN FAMILY IN SCHIZOPHRENIA AND BIPOLAR DISORDER: A PROTEOMIC INVESTIGATION OF THE DORSOLATERAL PREFRONTAL CORTEX

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There is much evidence for both overlap and distinction in the presentation and molecular characterisation of schizophrenia and bipolar disorder. In both, abnormalities in size and activity are well-documented in the dorso-lateral prefrontal cortex (dlPFC) and thus this cortical brain region is an ideal candidate to explore in order to reveal differential and similar abnormal cellular processes present in these disorders. In this study, 2D gel electrophoresis was used to evaluate changes in protein expression in post-mortem brain samples comprising of 35 controls, schizophrenics and bipolar disorder patients obtained from the Stanley

Foundation Brain Consortium. In schizophrenia 32, and in bipolar disorder 81, separate protein spots were found to be significantly differentially expressed ($p<0.01$) in comparison to controls. Thus far, subsequent identification of 12 of the schizophrenia associated proteins and 39 of the bipolar proteins has been carried out using mass spectrometry. Together these proteins indicate abnormalities in synaptic function, cellular metabolism, the cytoskeleton and neuronal growth and development. Interestingly, five protein spots were found to be isoforms of proteins from the septin family (5, 6 or 11), which were significantly ($p<0.01$) up-regulated in the disease condition in comparison to controls. A further two forms of Septin 5 were found to be significantly up-regulated at $p<0.05$, which collectively represented the largest change in one family of proteins revealed by this study. Functionally, Septin 5 and 6 have previously been localised to synaptic vesicles with the former present predominately in inhibitory pre-synaptic terminals. Additional proteins of interest found to have significant increases in expression include Dynamin I, a presynaptic protein involved in neurotransmitter release altered in schizophrenia in comparison to controls, and three forms of T-complex I, a potential susceptibility gene in schizophrenia, altered in either bipolar disorder or both psychiatric disorders in comparison with controls. This work supports previous findings of GABAergic and pre-synaptic dysfunction in schizophrenia through using a non-hypothesis driven approach. In addition, as this is the first time the septin protein family has been implicated in psychiatric disorders; it is important that further work is now carried out to elucidate their interactions with other candidate proteins involved in this disorder in order to reveal their underlying involvement in schizophrenia and bipolar disorder.

DECREASED EXPRESSION OF TYROSINE HYDROXYLASE IN THE SUBSTANTIA NIGRA OF SCHIZOPHRENIA BRAINS

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Tyrosine hydroxylase (TH) is the rate enzyme for the synthesis of the neurotransmitter dopamine in the mammalian brain. Dopamine levels are known to be altered in some psychiatric diseases, such as schizophrenia. Some reports have shown a reduction in the immunoreactivity for TH in the prefrontal cortex of schizophrenic brains, but little is known about the protein expression levels of this enzyme in the substantia nigra of subjects affected by this disease. Alterations on TH expression have also been reported in the basal ganglia of rodents treated with antipsychotic drugs, but some of the results are conflicting. The present study was designed to assess the expression of TH in the substantia nigra of schizophrenic brains compared to control brains by means of Western-blot techniques. Protein samples (25µg of total protein) representative of the rostrocaudal extension of the substantia nigra from schizophrenic (n=6, one with bipolar-schizophrenia mixed symptoms) and matching [for age, gender and post-mortem interval (PMI)] control brains (n=6) [schizophrenia mean age 45.33±14.73 and PMI 18.83±4.96; controls mean age 54.8±9.28 and PMI 18.00±1.41] from the Maryland Brain Collection (Baltimore, MD) were loaded onto polyacrylamide gels. Proteins were resolved using SDS-PAGE and transferred onto PVDF membranes. TH was detected using a monoclonal antibody (Sigma) diluted 1:10000, and bands were visualized using a chemiluminescent system (Biorad), followed by quantization of optical density (OD). The membranes were reincubated with an antibody against actin (Chemicon) diluted 1:40000 as an internal control. Using OD as an indirect measurement of TH expression, we found a statistically significant decrease (t-test, $p<0.04$) in the amount of TH in protein samples from schizophrenic brains (mean OD=-13.63±46.87) when compared to matching control samples (mean OD=38.61±5.58). These differences were not due to sample loading error as assessed by analysis of actin expression (mean schizophrenia OD=73.93±2.24 versus mean controls OD=73.60±2.46). Our results also show that the variability from the mean value (standard deviation) in OD for TH within the schizophrenic group was 8-fold higher than in the control group. These results show that the reduction of TH is not dependent on certain parameters such as age, gender or PMI and also suggest that further analysis of the effect of the antipsychotic medication and schizophrenia subtypes is needed. Supported by NIMH66123

INCREASED LEVEL OF THE ASTROCYTE GLUTAMATE TRANSPORTERS IN THE ANTERIOR HIPPOCAMPUS IN SCHIZOPHRENIA

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Schizophrenia is a psychotic disease affecting roughly 1% of the world population. It manifests itself by positive symptoms (delusions, hallucinations, and thought disorder), negative symptoms (apathy, withdrawal, anhedonia) and cognitive deficits (impairments in attention, working memory and executive functions). Despite extensive research, the molecular mechanisms underlying the disease remain unknown. One of the current hypotheses of schizophrenia states that NMDA-mediated glutamatergic transmission is reduced at critical brain synapses. NMDA-mediated neural transmission is influenced by the presynaptic neuron, by the postsynaptic neuron and by astrocytic function. After binding to the specific receptors, clearance of the synaptic glutamate is carried out mainly by two excitatory aminoacid glial transporters: EAAT1 and EAAT2. The two excitatory aminoacid transporters clear approximately 80% of the synaptic glutamate, hence indirectly but powerfully influence glutamatergic transmission. Many human postmortem studies and imaging studies report hippocampal alterations in schizophrenia. Our previous rCBF data implicate dysfunction at rest in the anterior region of hippocampus/medial temporal lobe (MTL). We are therefore pursuing the hypothesis that this functional alteration represents a change in NMDA mediated glutamate signaling in anterior MTL. We compared EAAT 1 levels in a cohort of cases with schizophrenia (N=14) and matched normal controls (N=14) whose tissue quality was good (RIN >7; pH >6.5). EAAT1 was quantified using Western Blot technique. We found a significant increase in EAAT1 level in the anterior hippocampus of the schizophrenia cases (SCZ: EAAT1 = 2.5 ± 1.5 relative units (r.u.); NL: EAAT1 = 1.7 ± 0.9 r.u.; p-value = 0.05), but not in the posterior hippocampus (SCZ: EAAT1 = 2.3 ± 0.9; NL: EAAT1 = 1.9 ± 1.1 r.u.; p-value = 0.12). We intend to confirm this finding in a new cohort, as well as to investigate the protein levels of EAAT2 and the message levels of both proteins. These data are consistent with the hypothesis that synaptic glutamate levels are low in the anterior hippocampus in schizophrenia due to an increased uptake of glutamate at the EAAT1 site.

MEMBRANE PHOSPHOLIPID BIDIRECTIONAL MOVEMENT IN RED BLOOD CELL FROM PATIENTS WITH SCHIZOPHRENIA

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Background: A significant increase of the percentage of external leaflet PE was recently found to account for the membrane lipid modifications described in patient with schizophrenia. Significant external PE percentage increase was found in 2/3 of the studied schizophrenia population (n=65) inducing a decrease of the PE asymmetrical distribution in RBC membranes. Patients with and without abnormal PE distribution are respectively denoted aPE SCZ and nPE SCZ. Age, sex and antipsychotic treatment were not associated with this PE abnormality. The phospholipidic asymmetrical distribution in membranes is a important biological phenomenon involved in crucial biophysical and biochemical cells processes. The creation and maintenance of this phenomenon are due to the concomitant activity of membrane transporters either increasing the phospholipid ratio in the inner leaflet (internalization) or in the outer leaflet (externalization). A mechanism is proposed to account for this result. It implies that the external PE over representation is associated with PE replacement from the internal PE pool. Modification of PE inner and outer movements across the bilayer membrane is thus hypothesised. PE internalization and externalization depend on specific transporters (respectively flippase and floppase) which can be independently activated. We used 2 specific techniques to assess flippase and floppase activities. Method: RBC from schizophrenic patients and healthy controls were isolated after blood puncture in the aPE SCZ group (n=3), nPE SCZ group (n=3), and control group (n=3). Decrease in labelled PE signal in buffer measured by electron spin resonance methods allows Internalisation rate calculation. Externalisation rate was assessed by measurement of external PE labelling with trinitro benzylsulfonic acid after calcium induced floppase activation by ionophore addition. Results: Unexpectedly, flippase activity was identical in the 3 subgroups. A slight but not significant increase flippase activity was paradoxically observed in the aPE SCZ group. Floppase activity was quantitatively similar between the 3 groups but differ in the externalised PE and PS fatty acids composition from the aPE SCZ group.

DETECTION AND EXPRESSION OF MULTIPLE CATECHOL-O-METHYLTRANSFERASE MRNA VARIANTS IN HUMAN BRAIN

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The catechol-o-methyltransferase (COMT) enzyme is important for regulating levels of dopamine in the prefrontal cortex (PFC). The human COMT gene contains a polymorphism (Val158Met), which alters the activity of the enzyme and is associated with PFC function. In addition, COMT may be genetically associated with schizophrenia. There are two confirmed COMT protein isoforms translated from the COMT gene: membrane-bound (MB-) and soluble (S-) COMT. In addition, we have recently described a novel protein variant of COMT, the relative immunoreactivity of which is altered in the PFC of patients with schizophrenia and bipolar disorder, compared with controls. We have investigated splicing of COMT mRNA in human brain, as part of our investigations to identify and characterise the novel protein variant. Two strategies were employed to investigate COMT mRNA variants by RT-PCR in human brain. Firstly, we investigated the expression in brain of potential COMT mRNA variants identified from the NCBI ACEview database. In addition, the presence of novel mRNA variants was investigated using sets of intron-spanning primers to target fragments of the known COMT mRNA. This approach has identified several COMT splice variants, resulting from novel exons and deletions within the known COMT mRNA transcript. Several of these variants potentially result in modified peptide sequence, whilst other variants alter non-coding regions. The expression of these variants will be described in various brain regions (frontal lobe, temporal lobe, hippocampus, caudate, cerebellum) as well as in foetal brain and adult liver. The functional characterisation of these novel variants is ongoing. These data add an additional level of complexity to the biology of COMT in the human brain. It will be important to investigate the functional impact of these mRNA variants and to investigate whether any of them result in the novel protein variant which we have described. This work is of potential therapeutic importance, since variant forms of COMT may be relevant to its involvement in schizophrenia and bipolar disorder, and to the use of COMT inhibitors in ameliorating their cognitive deficits.

ROLE OF N-TERMINUS PHOSPHORYLATION ON SYNTAXIN-1 ACTIVITY: IMPLICATIONS FOR NEUROTRANSMITTER RELEASE

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In spite of over a hundred years of research, schizophrenia, the most chronic and disabling of the severe mental disorders, remains without cure. While some aspects of the disease (mainly the psychosis) are amenable to treatment, its most chronic and disabling aspects (i.e., negative and cognitive symptoms) are not. Among the various aspects of brain function that are probably aberrant in schizophrenia, neurotransmitter release, an obligatory event in synaptic activity, is a promising target of research. In fact, several of the molecules involved in this process have been associated with schizophrenia. That is the case of the pre-synaptic protein syntaxin-1 (Stx-1); a member of the tSNARE family of proteins that mediate exocytosis. While it is clear that Stx-1 plays an essential role in neurotransmitter release, how exactly it does this, and how its activity is regulated is poorly understood. Post mortem studies have detected increased syntaxin immunoreactivity in the cingulate cortex of schizophrenic brains, higher syntaxin mRNA levels in the temporal cortex of young schizophrenia patients, and a recent study has shown a genetic association between the syntaxin-1A gene and schizophrenia. Our working hypothesis was, on the one hand, that synaptic transmission is abnormal in the schizophrenic brain, and that this is due (at least in part) to aberrant neurotransmitter release. On the other hand, we hypothesized that Stx-1 may be one of the malfunctioning synaptic components. Since previous research has shown that Stx-1 is phosphorylated in vivo, and phosphorylation is such a universal means of regulating a protein's function, we proposed that Stx-1 phosphorylation may be altered and contribute to the aberrant brain function characteristic of schizophrenia. To test this hypothesis, we have developed a phospho-specific antibody that detects the previously characterized phosphorylation site on Stx-1 (Ser14), and used it to assess levels of phospho-Stx-1 in post mortem human brain tissue. In the present study we validate our phospho-Ser14-specific antibody and provide preliminary evidence that Stx-1 phosphorylation may in deed be altered in the schizophrenic brain.

GLUTATHIONE REDOX COUPLING AND REACTIVE NITROGEN SPECIES IN SCHIZOPHRENIA

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Biological systems have evolved complex protective strategies against free radical toxicity. Under physiological conditions the potential for free radical-mediated damage is kept in check by the antioxidant defense system (AODS), comprising a series of enzymatic and non-enzymatic components including superoxide dismutase, catalase, glutathione peroxidase (GSH-Px), and glutathione reductase (GR). These enzymes act cooperatively at different sites in the metabolic pathway of free radicals. Recently, we have observed that a dynamic state is kept in check during the redox coupling under normal conditions. By contrast, lack of such correlations in brains with schizophrenia (SZ) point to a disturbance of redox coupling mechanisms in the AODS, possibly resulting from a decreased level of glutathione (GSH) as well as age-related decreases of oxidized GSH and GR activities. Taken together, our previous results showing altered membrane dynamics and AODS enzyme activities in SZ, and findings from other investigators are consistent with the notion of free radical-mediated neurotoxicity in SZ. There are multiple pathways to excess free radical generation and subsequent oxidative stress. One such pathway is the formation of peroxynitrite by a reaction of nitric oxide (NO) and superoxide radical. NO is formed from L-arginine by NO synthase (NOS). A constitutive cytosolic isoform, neuronal NOS, appears to be fairly stable in the postmortem brain tissues. In human brain, NO is metabolized primarily in the form of nitrate. A significantly increased level of NO was found in brains with SZ than those of normal and non-schizophrenic psychiatric controls. These findings were independent of age, brain weight, postmortem interval, sample storage time, alcohol use or cigarette smoking. Under physiologic conditions, NO and its metabolites react with a variety of thiol compounds to form dissociable complexes, thereby regulating its inhibitory function. Because the reaction of NO with free thiols competes with the same substrate such as GSH for decomposition of hydrogen peroxide by GPx, the excessive NO formation may further lead to significant depletion of GSH in schizophrenia. In conclusion, free radicals are involved in membrane pathology, and may play a role in SZ. (Supported by the Dept. of Veterans Affairs, Merit Review Grant and NIH grant, NIMH 58141)

6. Neuropathology, Histology

DOPAMINE TRANSPORTER ABNORMALITIES IN THE AMYGDALA OF SUBJECTS DIAGNOSED WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

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Growing evidence supports a pivotal role for the amygdala in the pathogenesis of schizophrenia (SZ) and bipolar disorder (BD). The amygdala receives substantial dopaminergic innervation, raising the possibility that this region may be vulnerable to abnormalities relative to dopaminergic transmission, as suggested by postmortem investigations and association of these diseases with dopamine-related gene polymorphisms (Reynolds, 1983; Greenwood et al., 2006; Tunbridge et al., 2006). To test this hypothesis, we measured densities of dopamine transporter-immunoreactive (DAT-IR) terminals in the lateral (LN), basal (BN), accessory basal (ABN), cortical (CO) nuclei of the amygdala of 12 normal control subjects, 14 BD and 10 SZ subjects. Serial sections (1.04 mm interval) through the whole amygdala were obtained using systematic random sampling criteria and processed for immunocytochemistry using an antibody raised against DAT. Densities of DAT-IR terminals were measured with computer-aided light microscopy using stereology-based sampling methods. Differences between groups were analyzed using a stepwise linear regression process. In SZ, significant decreases of DAT-IR terminals were detected in the LN (t= -4.6; p= 0.0002), BN (t= -2.63; p= 0.017), ABN (t= -3.51; p=0.0025), and CO (t= -5.05; p= 0.0001). Exposure to antipsychotics significantly affected the outcome measure (DAT-IR terminals) and was positively correlated with densities of DAT-IR terminals in these regions. In BD, a subtle increase of DAT-IR terminals densities was detected only in the BN (t= 2.12; p= 0.046). Differences between SZ and BD were found to be statistically significant in LN (p= 0.0057), BN (p= 0.05), ABN (p= 0.015) and CO (p= 0.002). These results point to abnormalities of the dopaminergic system in the amygdala of SZ, and suggest that antipsychotic drugs may increase densities of DAT-IR terminals, thus correcting for reductions associated with this disease. The present results raise the possibility that a defect of dopaminergic transmission in SZ may contribute to a disruption of the functional activity of the amygdala and, perhaps, to the clinical manifestations of this disease. These results also point to a poignant difference between the pathophysiology of SZ and BD, one that may account for pharmacological and clinical dissimilarities. Funded by NIH MH066955 and MH066280.

PRESENCE OF HERPES SIMPLEX HOMINIS TYPE I VIRUS IN THE REGIONS OF INTEREST [ROIS] OF THE BRAIN OF SCHIZOPHRENIC PATIENTS

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Summary. In agreement with previous reports the advances obtained in understanding central nervous system (CNS) viral infections make viruses attractive etiological candidates for schizophrenia. Among these candidates is Herpes Simplex Hominis type I Virus (HSV-1) due its capacity to remain latent with periodic reactivation, its affinity for the limbic system, the part of the brain involved in schizophrenia, its reactivation by endocrine changes, stress and immune alterations and for its relation to genetic predisposition that makes some individuals more susceptible to chronic viral infections for HSV-1. Presumptive evidence for viral etiology requires the demonstration of a virus, antigen or viral antibody. Neuropathological examination from post-mortem studies of the brain has provided definite diagnosis in many slow viral infections of the Central Nervous System and the technology used at cellular level appears to be an adequate tool for future research in schizophrenia. Electron microscopic techniques due to their higher resolution power are among those techniques that might be used in future research workup since the macroscopic examination of the brain through the current imaginologic techniques as positron emission tomography and magnetic resonance imaging are inappropriate for study at cellular and molecular level the structures that have been implicated in the physiopathology of schizoprenia: amygdala, hippocampus and auditory cortex. An electron microscopic analysis of these structures (the unique in the medical literature) was done in a post-mortem study of 16 schizophrenic patients and 10 controls. The findings of intranuclear inclusion bodies were suggestive of viral etiology in our first observations together with the presence of viral like particles which reacted in a positive form with anti-herpes viral antibody. The presence of a virus does not always mean that it is etiologically related to the disease under study specially related to HSV-1 as many normal persons carry this virus in their brain, but the observation of similar neuropathological findings in the brain of fetuses from schizophrenic mothers and in experimental animals inoculated with cerebrospinal fluid [CSF] from schizophrenic mothers made us to consider this virus as an etiological agent since Koch postulates had been partially fulfilled.

DECREASED MRNA EXPRESSION OF NETRIN-G1 AND NETRIN-G2 IN THE TEMPORAL LOBE IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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The membrane bound axon guidance molecules Netrin-G1 (NTNG1) and netrin-G2 (NTNG2) play a role in the formation/maintenance of glutamatergic synapses. Both genes have been reported to be associated with schizophrenia. The single nucleotide polymorphisms (SNPs) associated with schizophrenia are either intronic and/or within untranslated regions, suggesting that they may confer disease susceptibility by altering some facet of their expression. The aim of our study was to determine if NTNG1 and NTNG2 mRNA expression is altered in schizophrenia or bipolar disorder. NTNG1 and NTNG2 mRNA expression was analyzed in the temporal lobe (hippocampal formation, and perirhinal and inferior temporal gyri) of samples from the Stanley Medical Research Institute Array collection (35 schizophrenics, 34 bipolar disorder patients and 35 control subjects). Four NTNG1 mRNAs were detected and quantified by RT-PCR using an Agilent 2100 analyzer. For NTNG2 mRNA, total expression was quantified using in situ hybridization histochemistry (ISHH) and image analysis. For NTNG1, a significant effect of diagnostic group on the G1c isoform was found, being significantly reduced in bipolar subjects as compared to controls, and with a similar trend in schizophrenia. Preliminary ISHH studies suggest that decreased NTNG1c mRNA expression is most likely to originate from perirhinal and inferior temporal cortex. No other changes in expression of other NTNG1 isoforms (G1d, G1e and G1m) were found. For NTNG2 mRNA, significant effects of diagnostic group

were detected in CA4 and CA3, with a trend towards significance in the perirhinal cortex, but no alteration in dentate gyrus or inferior temporal cortex. In both schizophrenia and bipolar disorder, NTNG2 mRNA was reduced in CA3, with significant reductions also found in CA4 and perirhinal cortex in bipolar disorder. In summary, the expression of NTNG1 and NTNG2 mRNA is reduced in the temporal lobe in bipolar disorder and schizophrenia. Given their role in glutamatergic synapse formation/maintenance, decreased NTNG1 and NTNG2 mRNA expression provides an additional marker of glutamatergic synapse involvement reported in this brain region in both diseases. Whether the reported disease associated SNPs effect mRNA expression is being investigated. Study funded by the Medical Research Council and the Stanley Medical Research Institute.

HIPPOCAMPAL VOLUME AND NEURON NUMBER IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Reduced hippocampal volume is a common finding in schizophrenia and bipolar disorder. However, it remains unclear whether this is due to a loss of neurons. Thus, we studied hippocampal volume and cell number in schizophrenia and bipolar disorder. Methods: Complete hippocampi from 14 schizophrenia and 14 bipolar disorder subjects were matched with hippocampi from healthy control subjects. Each hippocampus was cut coronally into 2.5 mm thick slabs and one 100 µm thick section was taken from the top of each slab, mounted, and stained for Nissl-substance. We used the Cavalieri principle to estimate hippocampal volumes and the optical fractionator method to obtain an unbiased estimate of neuron number in three sectors of the pyramidal cell layer (cornu Ammonis 1, 2-3, and 4). Neuron size was estimated using the nucleator probe. Results: The three groups did not differ in the volume of total hippocampal, pyramidal cell layer, or non-pyramidal cell layer volumes. The schizophrenia group had significantly fewer neurons in sector CA4 compared with control subjects. The bipolar disorder group did not differ significantly from either the control or schizophrenia group in the number of neurons. We observed a general trend of decreased neuron size in schizophrenia and bipolar disorder, reaching significance in the CA2-3 sector of bipolar disorder subjects. Conclusion: We found a significantly decreased number of CA4 neurons in schizophrenia. We found no significant volume change and no loss of neurons in the hippocampus of bipolar disorder subjects. Our finding indicates that cell loss in the hippocampus occurs in schizophrenia but not bipolar disorder.

EXPRESSION OF CB_1 CANNABINOID RECEPTOR IN THE ANTERIOR CINGULATE CORTEX IN SCHIZOPHRENIA, BIPOLAR DISORDER, AND MAJOR DEPRESSION

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The human endogenous cannabinoid system is an appealing target in the investigation of psychiatric disorders in general and schizophrenia in particular. Clinical studies support the association between cannabis use and schizophrenia; and prolonged abuse of cannabis may trigger relapse of psychotic symptoms and is thought to induce manic symptoms in bipolar disorder. While little research has been done in bipolar disorder, several lines of evidence suggest a role for endocannabinoids and their receptors in the pathology of schizophrenia. Elevated levels of anandamide have been determined in cerebrospinal fluid (CSF) of schizophrenic patients. An increased binding of [3H]CP-55940 to CB_1 cannabinoid receptors in the dorsolateral prefrontal cortex of schizophrenic patients was reported that was independent of cannabis ingestion. A study using radioligand binding of [3H]SR141716A found an increase of specific binding to CB_1 cannabinoid receptors in schizophrenia in anterior cingulate cortex (ACC). As the ACC plays an important role in cognition, particularly in relation to motivation and attention, we analyzed the expression of the CB_1 cannabinoid receptors at the protein level using immunohistochemistry. To make the distinction between mental disorders with schizophrenia and those without, patients with bipolar disorder and major depression were included in a quantitative post-mortem study and data were compared to a control group (each n=15). Densities of neurons and glial cells immunopositive for CB_1 cannabinoid receptors were evaluated using a stereological counting approach. In this study of post-mortem ACC, we found no evidence of increased or decreased density of CB_1 cannabinoid receptors in schizophrenia or bipolar disorder. Counter to former assumption it is likely that different medications do have an impact on the expression of CB_1 receptors. While in schizophrenia no change was observed, in bipolar patients a decrease of CB_1 receptor-immunoreactive-negative glial cells following antipsychotic medication of the first generation was seen. Further we found an even stronger reduced numerical density of CB_1-immunoreactive-negative neurons after intake of SSRI in major depression. In major depression, supplementing existing studies, which show reduced numbers of glial cells, we could further demonstrate a decreased CB_1 receptor expression on glial cells, indicating that the human endogenous cannabinoid system might also be involved in mood disorders.

FRONTAL MYELIN HISTOLOGY AND COGNITIVE FUNCTION IN SCHIZOPHRENIA

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Cognitive impairment is present early in the course of schizophrenia and probably antedates psychotic symptoms. In chronically institutionalized patients with schizophrenia, cognitive impairment is progressive, and dementia is usually present by the end of life. Since myelin is essential to neuronal connectivity and becomes compromised with age, we sought to determine the relationship of cognitive impairment to myelin integrity in elderly, chronically institutionalized patients with schizophrenia. Cognitive and myelin evaluations were completed on 81 subjects (age 79±12, 50% F), none of whom had undergone frontal lobotomy. Most had been extensively treated with antipsychotic drugs but had become ill before the introduction of these drugs in the 1950's. Myelin was evaluated in ~200 randomly chosen microscopic fields from Verhoeff stains of the dorsal prefrontal region, yielding an average myelin rating for each case. Cognitive function was evaluated with the Scales of Cognitive Impairment Rated from Institutional Records (Schizophrenia Res 35(1999)131), in which several cognitive scales are applied to the subject's performance as reported in hospital records from the onset

of illness, the final 2 years, and each 10-year intervening interval. Subjects were divided by a median split of myelin ratings. CDR total (sum of scores for the 6 items of the Clinical Dementia Rating) at the onset of illness and in the final years of life were significantly greater (p=0.02) in the group with lower myelin ratings, but the change in CDR total over the course of illness did not differ significantly (p>0.3). Angiopathy, infarction, AD, and age were all associated with greater final CDR totals and greater increases in CDR totals. However, despite the association of these conditions with lower myelin ratings, they were not associated with differences in initial CDR totals. Onset by age 25 was associated with greater initial and final CDR totals than in cases with later onset, but there was no significant effect of age of onset on myelin rating. Since age-adjusted myelin ratings did not differ from nonpsychiatric subjects, these results suggest that normal variability in myelination (or in a precursor that eventually influences myelination), present by the age of onset of schizophrenia, has a clinically relevant effect on cognitive function throughout the course of the illness. *Support: MH60877, MH64168, NARSAD, Lieber Center for Schizophrenia Research*

EXPRESSION OF NEUREGULIN 1 AND, ITS RECEPTOR, ERBB4, IN THE OLFACTORY BULB IN SCHIZOPHRENIA

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The olfactory bulb (OB) is a unique part of the CNS in which to examine synaptic development and plasticity in schizophrenia because it undergoes continuous neurogenesis and re-innervation throughout life. The importance of investigating the OB is further underscored by the presence of olfactory deficits and OB dendritic abnormalities in schizophrenia. Genetic association studies suggest that the gene for neuregulin 1 (NRG1) is a candidate gene for schizophrenia. Furthermore, abnormalities in NRG1 expression and activity have been suggested to play a role in the etiology of schizophrenia. NRG1 is a growth and differentiation factor that regulates neuronal migration and survival. NRG1 and ErbB4 are both expressed in the olfactory bulb. The aim of this study was to compare the expression of NRG1 and one of its receptors, ErbB4, in the OB of control and schizophrenia subjects. Formalin-fixed OBs from 17 normal controls and 15 individuals with schizophrenia were provided by the Harvard Brain Tissue Resource Center and the Stanley Medical Research Institute. 20μm paraffin-embedded OB sections were labeled with antibodies raised against NRG1 and ErbB4 using an avidin-biotin peroxidase detection kit with DAB. The OB consists of concentric layers: olfactory nerve layer, glomerular layer, plexiform layer, mitral cell layer and granule cell layer. NRG1 protein is expressed in the olfactory nerve and glomerular layers of the OB, while ErbB4 is expressed in the olfactory nerve, glomeruli, mitral cells, and occasional cells of the granular layer. NRG1 and ErbB4 expression in the glomerular layer of the OB was analyzed by determining the optical density of the DAB reaction. No significant change in the expression of both proteins was observed in schizophrenia (Mann-Whitney U-test, p>0.05). These results are consistent with similar studies of the hippocampus and frontal cortex in schizophrenia. It also supports other evidence that NRG1 variants may not affect its expression between control and schizophrenia brains. Supported by NIH grant RO3 MH072875 and NARSAD Young Investigator Award to LR.

SYNAPTIC ORGANIZATION IN POSTMORTEM STRIATUM IN SUBJECTS WITH SCHIZOPHRENIA: TREATMENT RESPONDERS VS. NONRESPONDERS

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The patch and matrix compartments of the striatum, which process limbic and cognitive information, respectively, are differentially affected in subjects with schizophrenia (SZ). Our previous studies have shown an increased density of synapses characteristic of corticostriatal inputs in the caudate matrix and putamen patch in a heterogeneous group of SZ. The purpose of this study was to determine if the synaptic organization in subgroups of schizophrenia (SZ) was differentially affected in good responders (GR) vs. poor responders (PR). Our hypothesis is that psychotic SZ (either PR or off drug subjects) would have more dramatic differences in synaptic density than GR, and that these changes would be selective to the patches. Postmortem striatal tissue was obtained from the Maryland Brain Collection from 8 normal controls (NC), 6 GR, and 6 PR or off drug SZ cases. The mean ages and PMIs were NC, 43yrs and 5.0 hrs; GR, 53yrs and 4.5 hrs; PR, 44yrs and 5.7 hrs. Tissue was prepared for calbindin immunocytochemistry to identify patch matrix compartments, prepared for electron microscopy and analyzed using stereological methods. Data are presented as the mean, SD synaptic density per 10um3 Data were analyzed with ANOVA and FLSD. In the caudate, synapses characteristic of corticostriatal inputs were significantly higher in density in PR (2.5,0.7) than in either GR (1.8,0.2) or NCs (2.0,0.4). The same results were found in the putamen: PR (2.5,0.6) vs. GR (1.95,0.4) and NCs (1.8,0.5). In the caudate, synapses characteristic of thalmo-striatal inputs were similar in density between the NCs (0.22,0.1) and PR (0.21,0.12), while the GR showed an elevated synaptic density (0.36,0.07). The same results were found in the putamen: NCs (0.22,0.13) and PR (0.23,0.12), vs. GR (0.35,0.11). These increases in synaptic density were confined to the patches, which process limbic information. These data suggest that corticostriatal inputs are abnormally dense in areas of the striatum which process limbic information in PR. The failure to normalize this abnormality may play a role in treatment resistance and contribute to psychosis. These data also suggest that thalamostriatal inputs are normal in PR, but are abnormally high in GR. The increase may be compensatory and could play a role in treatment response. Supported by MH60744 (to RCR).

POST MORTEM STUDIES OF DENDRITIC ABNORMALITIES IN SCHIZOPHRENIA AND MOOD DISORDERS

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The most pronounced abnormalities reported in post mortems brains from subjects with schizophrenia have involved the dendrites of pyramidal neurons in the neocortex and hippocampal formation. These abnormalities include diminished spine density, arborization, MAP2 immunoreactivity, and spinophilin mRNA. To determine the sensitivity and specificity of these findings requires large samples, extensive

clinical characterization, and reliable methodology. Particular difficulties include the inconsistency of Golgi stains, which are used to visualize dendrites and their spines, and the absence of accepted methods for quantifying immunohistochemical stains, which tend to localize antigens consistently but to suffer from variability in darkness and dynamic range. To address these difficulties, we modified handling of tissue in the Macedonian/New York State Psychiatric Institute Brain Collection, beginning at the autopsy table, to optimize Golgi impregnation and immunoreactivity. We developed a new Golgi method, "NeoGolgi," which has yielded consistent, uniform impregnation in all autopsy cases, comparable in quality to that obtained in experimental animals. We have also developed a procedure for linear densitometry to compare immunoreactivity of subregions of the hippocampal formation, normalized for intensity and dynamic range of staining. This procedure provides highly reproducible analysis of stained sections and does not require automated or operator-adjusted thresholding. Preliminary results indicate a significant loss of dendritic spines on the apical and basilar dendrites of subicular pyramidal cells in schizophprenia. A significant loss of MAP2 immunoreactivity appears to be present in the medial half of the subicular pyramidal cell layer in schizophrenia, while we see no such decrease in mood disorders. These results suggest that by combining different modalities, it may be possible to associate specific dendritic abnormalities with specific psychiatric disorders. *Support: MH64168, NARSAD, Liber Center for Schizophrenia Research, American Foundation for Suicide Prevention*

AUDITORY CORTEX WIDTH, HEMISPHERIC ASYMMETRY AND SCHIZOPHRENIA

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Auditory areas of cortex are thought to have anatomical hemispheric asymmetry, and there is evidence that this asymmetry is altered in schizophrenia. We assessed asymmetry using measurements of cortical width, and the width of upper layers (I-III) and lower layers (IV-VI) in 10 schizophrenia and 11 control male postmortem brains. This was done with software that we developed to measure widths semi-automatically and display them as color-coded flat maps of the entire cortical region. Measurements were made on 1 mm-spaced Nissl stained sections through the rostral-to-caudal extent of the planum temporale and Heschl's gyrus. In primary auditory cortex (A1) we found a striking left>right asymmetry of the thickness of the upper cortical layers, and this asymmetry was similar in schizophrenia and control brains. In contrast to the upper layers, the lower layers showed little evidence of asymmetry. In the planum temporale, control brains also had left>right asymmetry of the upper cortical layers, but schizophrenia brains showed a loss of this asymmetry, mainly due to comparative thinning of the upper layers in the left hemisphere. As in A1, the lower layers showed little evidence of asymmetry in controls, or alteration in schizophrenia. In addition to hemispheric differences, width measurements also provide a quantitative tool to differentiate cortical areas. For example, the upper layers of A1 were consistently thinner compared to the planum temporale, although this difference was substantially less in the schizophrenia left hemisphere. The lower layers, in contrast, were thicker in A1 compared to other areas. The findings demonstrate a clear hemispheric asymmetry in human auditory cortex in the thickness of upper cortical layers. To our knowledge this asymmetry has not been previously reported. The findings also provide evidence for altered asymmetry in schizophrenia, in the upper cortical layers of the planum temporale but not A1. Our previous measurements of cortical volumes in these brains did not reveal alterations in schizophrenia, and it is possible that measuring laminar thickness is a more sensitive method. Semi-automated mapping of cortical widths is a novel tool that permits efficient exploration for pathological changes localized to cortical subregions. Supported by the Stanley Medical Foundation, MH067138, MH64168 and MH60877.

ELEVATED MICROGLIAL DENSITY IN SCHIZOPHRENIA AND DEPRESSION IS ASSOCIATED WITH SUICIDE

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Suicide has a high prevalence in patients with schizophrenia and affective disorder. A recent own postmortem study [Steiner et al., Acta Neuropathol, 2006] revealed increased microglial densities in two schizophrenic patients who had committed suicide. Therefore, the hypothesis of microglial activation during acute psychosis was proposed. Alternatively, "suicide" would be a diagnosis-independent factor leading to microgliosis. To clarify this question, microglial HLA-DR-expression was analyzed by immunohistochemistry in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), mediodorsal thalamus (MD) and hippocampus of 16 schizophrenics, 14 depressed patients with affective disorder and 10 matched controls. A subgroup of 6 schizophrenics and 7 patients with affective disorder who committed suicide was included. Statistical analysis (ANOVA) revealed no influence of diagnosis on microglial density (DLPFC: P=0.469; ACC: P=0.349; MD: P=0.569; hippocampus: P=0.497). However, significant microgliosis was observed in the DLPFC (P=0.004), ACC (P=0.012) and MD (P=0.004) of suicide patients. A similar trend was seen in the hippocampus (P=0.057). In conclusion, immune aspects may play a hitherto underestimated role in suicide. One might speculate on a role of interleukin-1β, interleukin-2 or nitric oxide, which are released from activated microglia. These substances are known to modulate noradrenergic or serotonergic neurotransmission and may be associated with suicidality.

THE ROLE OF OLIGODENDROCYTE PATHOLOGY IN SCHIZOPHRENIA

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Neuroimaging and microarray studies provide evidence for myelin and oligodendrocyte (Ol) abnormalities in schizophrenia (SZ). Previously we found a deficit of Ol in the prefrontal cortex (PFC) and in adjacent white matter, lower number of Ol satellites of pyramidal neurons and a loss of pericapillar Ol in the PFC in SZ compared to normal controls. Electron microscopy demonstrated prominent dystrophy, apoptosis, necrosis of Ol and close apposition of microglial cells to damaged Ol in SZ brain. We hypothesized that microglial reactivity is associated with degen-

eration of Ol leading to altered Ol-neuron interactions. Electron microscopic morphometric study of microglial cells and of myelinated fibers was performed in the PFC (area 10, layer V) in 40 chronic SZ cases and 40 normal controls matched for age, gender and postmortem delay. There were no significant differences in cell size and volume density (Vv) of microglial cells in SZ group as compared to the control group. However, Vv and proportion of microglial cells closely apposed degenerating Ol perikarya differed significantly in the subgroups of SZ with predominantly negative and predominantly positive symptoms (SPNS and SPPS subgroups) from the control group (Kruskal-Wallis test, $p<0.001$, Mann-Whitney U-test, $p<0.01$, Table). The proportion of myelinated fibers (MF) with atrophy of axon and swelling of periaxonal Ol processes in SPNS and SPPS subgroups significantly differed from the control group (Kruskal-Wallis test, $p<0.0001$, Mann-Whitney U-test, $p<0.001$, Table). These data suggest that microglial cells contribute to Ol degeneration in SZ brain. Altered interactions of Ol with axons, neuronal somata and capillaries found in SZ brain suggest a key role of damage and loss of Ol in alteration of neuronal connectivity and in atrophy of neurons in SZ. Supported by the Stanley Medical Research Institute.

Table. Median values of the parameters measured.

Parameters	Controls (n=40)	SPPS (n=18)	SPNS (n=20)
Vv Mg-degenerating Ol	0	0.01	0.03
% Mg-degenerating Ol	0	3.5	11
% altered MF	0.03	2.16	2.43

DECREASE IN BDNF AND TRKB MRNA LEVELS ACROSS MULTIPLE CORTICAL AREAS IN SCHIZOPHRENIA, BIPOLAR DISORDER AND DEPRESSION

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The signaling mediated by BDNF through the trkB receptor may lead to alterations in the GABA neurons in schizophrenia. Previous studies have described a decrease in BDNF and trkB mRNA in the frontal cortex in schizophrenia. This decrease is correlated with a decrease in GAD-67 mRNA levels. We investigated whether the BDNF and trkB reductions and the correlations with GAD-67 levels extended to other areas, including the orbital, cingulate, superior temporal (STG) and inferior temporal (ITG) cortices. Using in-situ hybridization we examined BDNF, trk-B and GAD-67 mRNA levels in four diagnostic groups: schizophrenia, bipolar disorder (BP), depression and controls (N=15/group). In the orbital cortex there was a significant effect of diagnosis on trkB in layer VI with all three diagnostic groups significantly lower than controls ($F=4.43$, $p=0.008$). TrkB and GAD-67 levels were significantly correlated across all cortical layers. In contrast, BDNF mRNA levels were not significantly different in any layer and there was no correlation between BDNF and GAD-67. In the cingulate cortex, there was a significant effect of diagnosis on BDNF in layers Vb and VI with all three diagnostic groups significantly lower than controls ($F=3.15$, $p=0.03$; $F=5.6$, $p=0.002$ respectively). TrkB levels were not significantly different in any layer but were somewhat reduced in all groups compared to controls. BDNF was correlated with GAD-67 in layers V and VI while trkB and GAD-67 levels were significantly correlated across all cortical layers. In STG there was a significant effect of diagnosis on BDNF and trkB in layer VI with all three diagnostic groups significantly lower than controls ($F=5.1$, $p=0.004$; $F=3.0$, $p=0.04$ respectively). There was also a significant effect of diagnosis on BDNF levels in layer II ($F=3.1$; $p=0.03$) with reductions in schizophrenia and BP. BDNF and trkB levels were both correlated with GAD-67. In ITG, there was a significant effect of diagnosis on BDNF and trkB in layer VIa with all three diagnostic groups significantly lower than controls ($F=4.9$, $p=0.005$; $F=3.6$, $p=0.02$ respectively). BDNF and trkB were significantly correlated with GAD-67. Thus BDNF and trkB are generally reduced in the deeper layers of cortex in schizophrenia as well as in BP and depression. Moreover, GAD-67 mRNA levels correlate with both BDNF and trkB levels in multiple cortical regions suggesting that the relationship between BDNF/trkB signaling and the GABAergic interneurons may be widespread.

DIFFERENTIAL ALTERATIONS OF KAINATE RECEPTOR SUBUNITS IN GABA INTERNEURONS IN THE ANTERIOR CINGULATE CORTEX IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Glutamatergic inputs exert both feedback and feedforward modulation on γ-aminobutyric acid (GABA)ergic neural circuits; together these modulatory mechanisms regulate the flow of information within the cerebral cortex by adjusting the spatial and temporal architecture of GABA neurotransmission. To explore whether disturbances of GABA interneurons in the anterior cingulate cortex (Brodmann's area 24) in schizophrenia and bipolar disorder involve perturbations of glutamatergic modulation of these neurons via the kainate subclass of glutamate receptor, we used double in situ hybridization to examine the expression of the mRNA for the GluR5 and GluR6 kainate subunits, labeled with [35S], in glutamic acid decarboxylase (GAD)67 mRNA-containing neurons, labeled with digoxigenin, in the anterior cingulate cortex in 20 triplets of schizophrenic, bipolar, and normal control subjects matched for age, postmortem interval, and whenever possible, sex, hemispheric laterality, and pH. Quantitative analyses revealed that the density of the GABA interneurons that expressed GluR5 mRNA was significantly decreased by 43% and 40% in layer 2 in schizophrenia and bipolar disorder, respectively. In contrast, the density of the GABA cells that expressed GluR6 mRNA was unaltered in either condition. The amount of GluR5 or GluR6 mRNA expressed by GABA cells that contained a detectable level of these transcripts was also unchanged. Finally, the density of cells that did not contain GAD67 mRNA (largely pyramidal cells), but expressed the mRNA for the GluR5 or GluR6 subunit did not show any alterations. Thus, glutamatergic modulation of GABA, but not pyramidal neurons, via kainate receptors containing the GluR5 subunit appears to be selectively altered in the anterior cingulate cortex in schizophrenia and bipolar disorder. These data may shed light on how modulation of glutamatergic activity on GABA cells via subtype specific kainate receptors may help influence information processing deficits in the cerebral cortex in these disorders.

PARVALBUMIN-CONTAINING NEURONS, GAMMA OSCILLATIONS, AND THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

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Disturbances of GABA (γ-aminobutyric acid) neurons in the cerebral cortex play a crucial role in the pathophysiology of schizophrenia. Furthermore, increasing evidence suggests that, among the subclasses of GABA neurons, the fast-spiking basket and chandelier cells that contain the calcium-binding protein parvalbumin (PV), which exert perisomatic and axo-axonic inhibition, respectively, on pyramidal cells, may be preferentially affected. In order to gain deeper insight into how disturbances of GABA neurons may compromise information processing in the cortex, it is important to understand how the pre- and post-synaptic elements of these neurons may be altered. Toward this end, we have found that the density of GABA cells that express the mRNA for the NR2A subunit of the N-methyl-D-aspartate (NMDA) receptor complex is significantly decreased in postmortem brains from subjects with schizophrenia. Quantification of gene expression in laser-captured cells further indicates that the amount of NR2A mRNA is significantly reduced in neurons that are immunoreactive for PV. Together these findings suggest that glutamatergic transmission via NMDA receptors on GABA neurons, perhaps preferentially those that contain PV, appear to be reduced in schizophrenia. Furthermore, we have found that the amount of the mRNA for the alpha 1 and alpha 2 subunits of the GABAA receptor in laser-captured pyramidal cells is decreased and increased, respectively, in schizophrenia. Because the alpha 2 subunit is selectively localized to synapses formed by chandelier cells whereas the alpha 1 subunit is heavily localized to those formed by basket neurons, these findings are consistent with the idea that the innervation of pyramidal cells by PV-containing GABA neurons may be altered in schizophrenia. These findings will be discussed in the context of how gamma oscillations may be disturbed as a result and how such disturbances may contribute to the pathophysiology and the onset and progression of schizophrenia.

NORMAL OLIGODENDROCYTE CELL NUMBERS IN ANTERIOR THALAMUS IN SCHIZOPHRENIA

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Reduced numbers of oligodendrocytes (OL) and neurons have been reported in the anterior thalamus of elderly schizophrenic subjects (Young et al., 2000, Biol Psychiatry; Byne et al., 2006, Schizophrenia Research). To determine whether OL deficits occur in this region in schizophrenia in subjects who died at a less advanced age, we estimated OL cell numbers in the anteroventral/anteromedial (AV/AM) thalamus and OL cell density in the adjacent anterior horn of the interior capsule (IC) in subjects of the Stanley Foundation Brain Collection. Subjects with schizophrenia, bipolar disorder, and major depression were compared to normal controls, using ANCOVA to investigate clinical and post-mortem factors potentially influencing OL populations. OLs were identified by either morphological (Nissl) or immunohistochemical (CNPase) criteria and counted with stereology-based techniques. We observed no evidence for an alteration in AV/AM or IC OL cell density or total OL cell number in any of the four diagnostic categories. However, in Nissl counts, ANCOVA provided evidence that prior treatment with mood stabilizers, female gender and sampling from the left hemisphere was associated with reduced density of OL cells in the AV/AM of psychiatric subjects. We also observed that a trend for homozygosity at the ”short” allele of the 5HTTLPR variation of the serotonin transporter was associated with reduced density of AV/AM OLs. The association of mood disorder treatment with increased OLs was particularly robust in the AV/AM; comprising a 63% increase in OL density and a 40% increase in total OL cell number. There was also a trend for OL density to be increased in the IC (25%) with mood stabilizer treatment. The data provide the first evidence that mood stabilizers affect brain function by altering OL proliferation, maturation or survival. In contrast to data suggesting reduced numbers of neurons and oligodendrocytes in AV/AM in older schizophrenic subjects, data from the younger schizophrenic subjects of the Stanley Foundation do not suggest a specific deficit in OL cell number or neuron number (Young et al., 2004, Am J Psychiatry) in this portion of the limbic thalamus.

7. Genetics, Clinical

PHARMACOGENETICS OF TARDIVE DYSKINESIA IN AFRO-CARIBBEAN INPATIENTS ON NEUROLEPTIC TREATMENT

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Tardive dyskinesia (TD) is a potentially irreversible motor side-effect occuring in about 30% in patients chronically exposed to neuroleptics. Age, gender and genetic polymorphisms of dopamine D3 (DRD3), serotonin 2a (HTR2A) and 2c (HTR2C) receptors affect the risk for TD. There are no pharmacogenetic studies of TD in Afro-Caribbeans. Our aim was to investigate the association between TD and the polymorphisms Ser9Gly (DRD3), 102T>C (HTR2A) and Cys23Ser (HTR2C) in 109 Afro-Caribbean subjects (88 males and 21 females [Schizophr Res 1996;19:195]) treated with neuroleptics. Relationships between the genotypes and orofaciolingual dyskinesia (TDof; AIMS items 1-4), limb-truncal dyskinesia (TDlt; AIMS items 5-7), and the sum of the first 7 items of the AIMS (TDtotal) were analyzed with a covariance model using genotypes as classes and age as a continuous variable. The relation between age and TDof, TDlt, and TDtotal scores are shown in the table. The numbers represent shifts + standard error of the relation. The 0-values represent the reference genotype. In males, only the effects of Ser9Gly are shown, since the other 2 polymorphisms did not show statistically significant (P<0.05) effects. After correction for age, males and females with Ser9/Gly9 genotype exhibited higher TDof-values compared to those with Gly9/Gly9. Ser9/Gly9 polymorphism was significantly associated with higher TDlt-values in males but with lower values in females, implying gender-dependency. In females, but not males, 102T/102T was significantly associated with higher TDof and TDlt values. We conclude that in our population the genetic vulnerability for TD may differ between TDof and TDlt and is probably gender-dependent.

Genotypes (patients)	TDof values	TDlt values	TDtotal values
MALES			
Gly9/Gly9 (n=34)	0	0	0
Ser9/Gly9 (n=52)	**1.59±0.70(P=0.03)**	**0.52±0.26(P=0.04)**	**2.11±0.88(P=0.02)**
Ser9/Ser9 (n=2)	-1.16±2.30(P=0.62)	-0.45±0.84(P=0.60)	-1.60±2.91(P=0.58)
FEMALES			
Gly9/Gly9 (n=8)	0	0	0
Ser9/Gly9 (n=12)	**3.29±1.05(P=0.006)**	**-1.15±0.51(P=0.04)**	2.14±1.32(P=0.12)
Ser9/Ser9 (n=1)	2.70±2.45(P=0.29)	1.73±1.19(P=0.16)	4.43±3.05(P=0.17)
102C/102C (n=7)	0	0	0
102C/102T (n=13)	0.23±1.11(P=0.84)	0.15±0.33(P=0.65)	0.38±1.13(P=0.74)
102T/102T (n=1)	**5.23±2.36(P=0.04)**	**4.83±0.69(P<0.0001)**	**10.06±2.41(P=0.0008)**
Cys23/Cys23 (n=7)	0	0	0
Cys23/Ser23 (n=10)	1.82±1.04(P=0.10)	1.08±0.52(P=0.06)	**2.90±1.28(P=0.04)**
Ser23/Ser23 (n=4)	-1.08±1.28(P=0.41)	0.62±0.64(P=0.35)	-0.46±1.57(P=0.77)

GENETICS OF SCHIZOPHRENIA: SEGREGATION ANALYSIS OF ENDOPHENOTYPES

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Background: Endophenotyping is a promising strategy for genetic research on complex psychiatric disorders as endophenotypes improve power of a study while they may reduce genetic architecture. In the present study, we investigated heritability and genetic transmission patterns of several endophenotypes including verbal memory, set shifting and fine motor functioning in Dutch families with schizophrenia. Methods: Thirty high-risk families including 138 subjects (15 probands and 123 of their relatives) were administered the CVLT delayed recall task, the Trailmaking task and the Purdue pegboard task. A segregation analysis was performed on the age and sex adjusted levels using the SEGREG module of S.A.G.E. Results: We found significant evidence of oligogenic inheritance of the three studied endophenotypes. We found no evidence for a Mendelian mode of transmission. The segregation analysis showed a homogeneous and a heterogeneous general model of transmission best fitted the data of respectively the verbal memory and the fine motor functioning task. When compared with a model with no genetic effect, the Akaike's Information Criteria (AIC's) were significantly lower for verbal memory (525.28 versus 531.72; p=.04) and fine motor functioning (698.88 versus 700.50; p=.05). For set shifting the environmental model could not be rejected. Conclusions: Our findings suggest an underlying genetic transmission for verbal memory and fine motor functioning. Further analysis on heritability and familial risk estimation for the Endophenotypes will be presented.

WORKING MEMORY AND PSYCHIATRIC SYMPTOMS IN FAMILIAL SCHIZOPHRENIA

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Working memory deficits have been proposed as an endophenotype of familial schizophrenia, present in both affected and unaffected family members. The Identical Pairs version of the Continuous Performance Test (CPT-IP) has been successful in detecting working memory deficits in unaffected relatives of patients with schizophrenia, and has been found to be heritable and stable over time, making it suitable as an endophenotype. In affected (SZ) patients and their unaffected (UA) siblings from 11 Canadian families where a familial form of schizophrenia is linked to chromosome 1q22, we investigated performance on the CPT-IP. Using a case-control design, we assessed working memory using the CPT-IP, Digit Span and Letter-Number Sequencing (LNS) subtests of the WAIS-III, and Trails B tests; and negative and positive psychiatric symptoms of schizophrenia using the five-factor model of the PANSS. Two-tailed T-tests were performed on the discrimination variable of the CPT-IP (d'), and correlations between d' and other neurocognitive and psychiatric symptom variables were assessed using Pearson's r. We found significantly poorer working memory skills in the SZ group on the fast and slow 4-digit sessions of the CPT-IP (p = 0.022 and p = 0.006 respectively), tasks involving verbal working memory. However, both the SZ and UA groups performed at the same impaired level on the CPT-IP shapes task (p = 0.091), which is indicative of similarly poor spatial working memory function. On correlational analyses, CPT-IP results correlated significantly with

the LNS. There were no significant correlations between the CPT-IP and positive or negative PANSS scores. Study results suggest that a 1q22-linked SZ cognitive endophenotype is associated with working memory deficits, and possibly more closely with spatial working memory than verbal working memory. Working memory deficits appear to be independent of positive and negative symptoms, further supporting them as an endophenotype in this familial form of schizophrenia.

GENETIC VARIATION OF BDNF IS ASSOCIATED WITH ANTIPSYCHOTIC-INDUCED WEIGHT GAIN SYNDROME IN SCHIZOPHRENIA

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A large body of evidence indicates that BDNF is important for food intake regulation. Furthermore, a polymorphism in the gene encoding BDNF 66val/met has been associated with obesity, anorexia nervosa, and schizophrenia. The metabolic syndrome has been identified as a group of changes in weight-related measures including triglycerides, HDL-cholesterol, fasting blood sugar and blood pressure with a greater prevalence (estimated to be 37 % and 60%) in schizophrenic patients. Predisposing factors include genetic variation, inactivity, poor diet, and dysregulation of the hypothalamic-pituitary-adrenal axis (HPA). Because previous studies have indicated that BDNF 66val/met is associated with both schizophrenia and metabolic abnormalities related to weight, we tested for a genetic association between BDNF 66 val/met and metabolic measures in schizophrenia. 109 patients, (18 – 64 yrs), meeting DSM-IV criteria for schizophrenia, schizoaffective disorder or bipolar disorder, were recruited from six different sites for a study of the effect of olanzapine and risperidone on metabolic measures. Patients treated with olanzapine, risperidone or clozapine within one month prior the study entry were excluded from the trial. All patients provided written informed consent for participation in this study. Patients were also assessed for psychopathology using Brief Psychiatric Rating Scale. Our results show that subjects with BDNF 66met/met homozygous genotype had a significantly greater BMI (n=8, 33.7+/- 2.5) compared to that of patients with all other genotypes (n=101, 28.4 +/-.7) (F=4.25, p=0.04). No other fasting metabolic measures, including triglycerides, total-, LDL- or HDL-cholesterol, blood glucose and hemoglobin A1C were associated with a genetic variation in BDNF. There was also no relationship between baseline psychopathology and BDNF 66val/met alleles or genotype. This is the first report of association between genetic variation of BDNF and antipsychotic-induced weight gain. In conclusion, our results show that genetic variation in BDNF could increase vulnerability for elevated BMI in schizophrenia.

NDEL1 INFLUENCES RISK FOR SCHIZOPHRENIA AND IMPACTS COGNITIVE FUNCTION

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Evidence suggests that the DISC1 gene may represent a connecting node within a network of multiple proteins that acts to influence multiple clinical phenotypes. DISC1 confers a risk for developing a range of psychiatric illnesses and it has been linked with several clinical phenotypes of major psychiatric disease, including cognition, brain morphology, and positive symptoms. These broad-ranging effects suggest that its action may be mediated by multiple loci within the gene via differential effects on expression, in addition to complex interactions among DISC1 and its multiple confirmed binding partners. The enzyme activity of a protein, nuclear distribution element-like (NUDEL), is inhibited by DISC1. This interaction may be related to DISC1's role in schizophrenia (SZ), as intact function of NUDEL is necessary for several neurodevelopmental processes that are believed to be abnormal in SZ. Despite evidence of the functional importance of these proteins, systematic investigation into the effects of genetic variation within the genes that regulate the binding partners of DISC1 is still required. We conducted a case control study in 294 Caucasian SZ patients [31.3% female; mean age=38.4] and 225 Caucasian controls [59.6% female; mean age=47.6] to test for an association between the gene that codes for NUDEL (Ndel1) and SZ. We also tested for Ndel1's effects on cognition. We genotyped 6 SNPs: rs12601035, rs1391768, rs1391766, rs931672, rs2012190, and hCV1239811 and haplotypes were generated using PHASE. Haplotype analyses revealed a single haplotype block, including 2 major (yin/yang) haplotypes (GCCT and ATTC). 2 SNPs were excluded: rs2012190, which was very rare and rs12601035, which was not in LD with the others. Ndel1 ATTC was significantly over-represented in SZ (66% carriers) as compared with healthy controls (57% carriers) (Chi2=3.7; p=0.05; OR=1.22). The ATTC haplotype had a significant effect on WAIS-R digit span performance (F=8.9; df=1,258; p=0.003) with carriers (Mean= 14.1 +/- 4.7) performing worse than non-carriers (Mean= 15.8 +/- 4.8). These data suggest that the DISC1 binding partner, Ndel1, modestly influences the risk for SZ. In addition, Ndel1 genetic variation affects performance on a measure of attention and working memory and is consistent with our previous report of DISC1's effects upon the same cognitive measure. Future large-scale studies are needed to adequately assess the interaction effects of these genes.

PROJECT AMONG AFRICAN AMERICANS TO EXPLORE RISKS FOR SCHIZOPHRENIA (PAARTNERS): NEUROCOGNITIVE FUNCTIONING IN PROBANDS AND THEIR BIOLOGICAL RELATIVES

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The Project among African-Americans to Explore Risks for Schizophrenia (PAARTNERS) is a multi-site collaboration that aims to identify genes underlying liability to schizophrenia and schizoaffective disorder (see Aliyu et al., Schizophrenia Research, in press). PAARTNERS is distinguished among genetic studies of schizophrenia in its study population and inclusion of a standardized, computerized neurocognitive battery (CNB). We expect this battery to be a useful tool to understand the neurocognitive basis of schizophrenia and related disorders. The Penn CNB uses 14 tasks to assess 10 neurocognitive domains: abstraction and flexibility (ABF), attention (ATT), working memory (WM), verbal memory (VMEM), face memory (FMEM), spa-

tial memory (SMEM), language (LAN), spatial processing (SPA), sensori-motor dexterity (S-M), and emotion processing (EMO). The computerized format provides for separate evaluations of accuracy and response time (speed). Schizophrenia and schizoaffective disorder probands and their unaffected biological relatives fulfilling family structure inclusion criteria complete the CNB, a standardized and comprehensive diagnostic evaluation, and a blood draw for DNA. As of August 2006, across eight data collection sites, the CNB had been completed by 1,623 participants (schizophrenia/schizoaffective patients: n=668, M:F=407:627, mean age=39.8, SD=11.6; biological relatives: n=955, M:F=310:645, mean age=45.6, SD=15.8). Current evidence indicates that relatives unaffected with psychopathology and patients differ significantly, but not substantially (by Cohen criteria), in their accuracy on most neurocognitive measures. VMEM, however, shows a more substantial difference. Similar results in response time were obtained for all domains, except ATT, for which patients show more substantial response times. Estimating heritability of the traits by modeling a mean effect of diagnostic status, age, sex and education reveals substantial and significant heritability for accuracy of many of the domains, and some significant heritabilities for response times. These results, in total, support the utility of neurocognitive abilities as quantitative endophenotypes of schizophrenia and related disorders. Supported by NIMH R01's: MH66006, MH66278, MH066049, MH66181-03, MH66121, MH066005, MH66050, MH66263, MH66004.

THE AUSTRALIAN SCHIZOPHRENIA RESEARCH BANK (ASRB)

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Schizophrenia represents one of the most perplexing and challenging problems confronting both researchers and health-care providers today. With a prevalence of 4:1,000 (Saha et al, 2005), significant advances in schizophrenia research have been limited by the difficulty in achieving sufficiently large samples that are well characterised in terms of clinical, cognitive and neuroanatomical evaluations, in order to study the causal role of multiple small-effect genetic factors. To overcome this limitation, a coalition of researchers has established the Australian Schizophrenia Research Bank (ASRB), building on four existing, successful Australian schizophrenia research facilities, namely the NISAD Schizophrenia Research Register, Hunter DNA Bank, Virtual Brain Bank, and the WA Family Study of Schizophrenia (WAFSS). The ASRB aims to expand, enrich and link existing programs of infrastructure as a resource to support a wide spectrum of schizophrenia research studies. The ASRB will consist of comprehensive, cross-referenced data from a large sample of people with schizophrenia (N=2,000) and healthy non-psychiatric controls (N=2,000) of comparable age and gender profile. Data will also be collected from family members where more than one person is affected by schizophrenia. Participants complete a comprehensive standardised clinical assessment battery to confirm (or screen for) diagnosis, and to collect additional clinical, neuropsychological (including current and premorbid IQ, RBANS, working memory, executive functioning and inhibition) and social function data. A medical history, drug and alcohol use, and neurological soft sign assessment are also completed. Amongst healthy controls and relatives, psychosis proneness (SPQ) and criteria for schizotaxia are assessed. Blood samples and MRI brain scans will also be collected. The ASRB will be a unique facility providing the foundation for advancing the understanding of schizophrenia by linking genetic, neuroanatomical, cognitive and clinical information in a large cohort. The size of the cohort will provide sufficient statistical power to allow researchers to address a range of important questions in relation to schizophrenia using the new technologies available to neuroscience. Such approaches have the potential to lead to a parsing of the schizophrenia phenotype and the identification of aetiologically significant subtypes of the disorder together with their genetic underpinnings.

VOLUMETRIC MRI BRAIN MEASURES IN FAMILIAL SCHIZOPHRENIA

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Background: Common brain findings in general population schizophrenia when compared to healthy controls include ventricular enlargement and volume reduction in cortical gray matter and subcortical structures. Schizophrenia is a neurodevelopmental disorder that likely involve genetic causal factors. We have previously identified a form of familial schizophrenia (FS) associated with significant genome-wide linkage to chromosome 1q22 (Brzustowicz et al., 2000), and it would be important to delineate the clinical phenotype of this form of FS. Objective: To assess brain volumes in members affected by schizophrenia (SZ) and their unaffected relatives (UA) in 1q22-linked FS families using magnetic resonance imaging (MRI). Method: 14 family members with SZ (mean age=50.6 y, SD=8,2; 5 male, 9 female), and 20 first degree UA family members (mean age=48.1 y, SD=10.6; 9 male, 11 female) had MRI scans of the brain according to a research protocol. Scans were analysed quantitatively using a semi-automatic procedure to derive ventricular, whole brain, lobar, and subcortical structure gray matter(GM), white matter (WM), and cerebrospinal fluid (CSF) volumes. Results: The two groups did not differ in sex or age, but subjects with SZ had a significantly lower WAIS-III full-scaled IQ (90.1 SD=18.3 vs 110.3 SD=11.4; t=3.98, df=32, p=0.0004). The groups, however, differed significantly ($p<0.05$) in left frontal lobe, bilateral insula, and bilateral globus pallidum grey matter volumes, and left lateral ventricular volume. After controlling for IQ, between group significant differences in volumes were found in right temporal lobe grey matter, left insula grey matter, bilateral globus pallidum and putamen grey matter, and left temporal lobe white matter. Conclusion: The differences in brain volumes on MRI in FS members with and without schizophrenia share some similarities with reported differences between patients with schizophrenia and healthy controls in the general population.

ALTERNATIVE STRATEGIES FOR GENE-GENE INTERACTION ANALYSIS: APPLICATION TO THE HTR2A/HTR3A INTERACTION IN CLINICAL RESPOPNSE TO ANTIPSYCHOTICS

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Serotonin receptors blockade is the major basis for the antipsychotic action of atypical antipsychotic drugs (AP). Genetic factors affecting the density and/or function of serotonergic receptors, transporters

and enzymes may therefore affect AP response. This exploratory study investigates the effect of the interaction of C102T in HTR2A and C178T in HTR3A genes on antipsychotics response in a sample of 168 patients with diagnoses of schizophrenia. Patients were prospectively assessed using the Brief Psychiatric Rating Scale (BPRS) at baseline and following the antipsychotic treatment. The patients were categorized as responder and non-responder defined as 20% reduction of BPRS score. In this report, we applied different analysis methods to detect the effect of the HTR2A/HTR3A interaction on the clinical response. When we compared the global p-value calculated with the chi-sq and with Helix Tree, we found a value of 0.019 and 0.003 respectively. This report suggests that different software yields different p-values, thus threshold p-values should be always rejected given the opportunity of false positive by using different programs.

MISPERCEPTION IN FIRST-EPISODE PATIENTS WITH SCHIZOPHRENIA AND THEIR HEALTHY YOUNG SIBLINGS AND THE RELATIONSHIP WITH THE COMT-GENE

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Background: Communication Deviance (CD) is a measure of subclinical thought disorder expressed in speech. In patients with schizophrenia it was found to be associated with a family history of schizophrenia spectrum disorders among patient's parents and siblings. Therefore CD has been suggested to be a genetic vulnerability factor for schizophrenia. An important factor of CD is misperception. We hypothesized misperception to be present in first-episode patients with schizophrenia as well as their healthy young siblings. Methods: We included fifty-two patients who met DSM-IV criteria for schizophrenia, twenty-seven of their healthy unaffected siblings, and thirty-four non-psychiatric healthy controls of similar ages and educational level. Misperception was measured using the communication deviance protocol for the Thematic Apperception Test. Results: The presence of misperception was a robust finding in patients with schizophrenia and their healthy siblings when compared to healthy controls ($p = 0.001$). Preliminary analysis shows an association between misperception and the COMT-gene. Conclusions: The results suggest that misperception can be a valuable endophenotype for schizophrenia and could be used as such in future genetic association studies. Preliminary analysis shows an association between misperception and the COMT-gene.

COORDINATED DYSMORPHIC DEVIATIONS WITHIN AN EMBRYOLOGICALLY-DERIVED ENDOPHENOTYPE: THE CRANIOFACIAL FRONTONASAL-MAXILLARY ANLAGEN INTERFACE IN SCHIZOPHRENIC PROBANDS AND THEIR UNAFFECTED FIRST-DEGREE RELATIVES

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This study evaluates specific developmental models of schizophrenia based on quantitative measures of craniofacial dysmorphology. These dysmorphic phenotypes have the advantages of being objectively diagnosed and biologically interpretable; owing to the close embryologic linkage of brain and face, dysmorphic phenotypes also have the potential to reveal insights into the neurodevelopmental bases of this disorder. This is because both brain and craniofacial structures derive from common embryological origins and are molded simultaneously by shared forces. Therefore, it is plausible that genetic deviations or environmental insults during development could manifest themselves both in brain pathology and craniofacial anomalies. We have found that anomalies and lateral asymmetries delineated by the interface of the frontonasal and maxillary anlagen (embryonic primordia) are statistically overrepresented among both schizophrenic probands and their clinically unaffected first-degree relatives. Moreover, we have reported that there is a significant relationship between brain and craniofacial dysmorphology within subjects. In the present study, we tested whether lateral asymmetries along the frontonasal-maxillary interface were either randomly assorted (as predicted by a "fluctuating asymmetry" model) or significantly correlated (supporting a model of coordinated alteration). Our results strongly point to the latter, with substantial within-subject correlations, e.g., between quantitative orbital and maxillary interface deviations. These relationships appear among schizophrenic probands and particularly among the subset of dysmorphic cases. Remarkably, these associations also appear among the first-degree relatives of the schizophrenic probands —- even those who are psychiatrically normal. These findings further underscore the potential utility of this endophenotype to increase the power of genetic linkage studies of schizophrenia.

REDOX DYSREGULATION AND OXIDATIVE STRESS IN SCHIZOPHRENIA: GENETIC AND FUNCTIONAL ANOMALIES IN GLUTATHIONE SYNTHESIS

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Converging evidence speak in favor of an abnormal susceptibility to oxidative stress in schizophrenia. It is however unclear if this is a primary cause, due to a defect of the redox regulation system, or a secondary effect due to unknown processes including excessive production of reactive oxygen species. We previously reported in schizophrenia patients a decreased level of glutathione (GSH), the principal non-protein antioxidant and redox regulator, both in cerebrospinal-fluid and prefrontal cortex. To identify possible genetic causation, we studied genes involved in GSH metabolism. Case-control association study of single nucleotide polymorphisms (SNP) from the GSH key synthesizing enzyme glutamate-cysteine-ligase (GCL) modifier subunit (GCLM) was performed in two populations: Swiss (patients/ controls: 40/31) and Danish (349/348)(Tosic&al AmJHumGen06). We found a strong association of SNP rs2301022 in the 5' region of GCLM gene (Danish: $c2 = 13.2$, $p=0.023$ after correction for multiple testing). Evidence for GCLM as a risk factor was confirmed in linkage study of NIMH families. Moreover, we observed a decrease in GCLM mRNA levels in patient fibroblasts and they showed a significant correlation with the associated SNP. Interestingly, Dalton and al reported in GCLM knock-out mice an increased feedback inhibition of GCL activity, resulting in 60% decrease of brain [GSH], a situation analogous to patients. These mice exhibited an increased sensitivity to oxidative stress. Similar-

ly, under oxidative stress conditions, GCL enzymatic activity was also decreased in patient fibroblasts. In an animal model with GSH deficit we observed a decreased number of dendritic spines in pyramidal cells and an abnormal development of parvalbumine immunoreactive GABA neurons in prefrontal cortex similar to those reported in patient. In addition, GSH depletion in hippocampal slices impairs long term potentiation and as such may be implied in cognitive disturbances. These results on the genetic and functional anomalies in GSH synthesis, combined with observations that GSH deficient models reveal morphological (GABA interneurones), electrophysiological (NMDA hypofunction), and behavioral (cognitive functions) anomalies analogous to those observed in patients, suggest that GCLM allelic variant is a vulnerability factor for schizophrenia. This may represent, among other factors, one primary, causal mechanism leading to redox dysregulation and oxidative stress in schizophrenia.

VIOLENT BEHAVIOR ASSOCIATED WITH HYPOCHOLESTEROLEMIA DUE TO A NOVEL APOB GENE MUTATION

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A 26-year-old male, the index patient, presented with persecutory delusions and suicidal behavior. He had ten paternal male relatives in two prior generations. Five of these died by violent suicide and one, of the five, also committed a double homicide. The index patient was found to be hypocholesterolemic due to being heterozygous for a novel mutation of apolipoprotein B (apoB-29.4). His mother and paternal grandmother were normocholesterolemic, whereas a surviving paternal uncle was hypocholesterolemic and heterozygous for the apoB-29.4 mutation. This indicated that the index patient's father and paternal grandfather, who both died by violent suicide, were obligate heterozygotes for the apoB-29.4 mutation and that the index patient inherited the mutation from his paternal grandfather. The odds ratio for the association between hypocholesterolemia and violent behavior in this family, where cholesterol status was known, was 16.9 (95% confidence interval 1.1 to 239.3). Therefore, our results support an inheritable relationship between violent behavior and hypocholesterolemia. Violent Behavior Associated with Hypocholesterolemia Due to a Novel APOB Gene Mutation.

A POLYMORPHISM IN THE 3' UNTRANSLATED REGION OF THE DOPAMINE TRANSPORTER IS ASSOCIATED WITH BRAIN MORPHOLOGY VARIATION IN SCHIZOPHRENIA

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Although the dopamine system is a critical pathway in schizophrenia, little is known about variants in dopamine pathway genes that may have an influence on the disorder. In this study, a polymorphism in the 3' untranslated region of the dopamine transporter (DAT1) was genotyped in a set of subjects with schizophrenia spectrum disorders and a set of psychiatrically normal controls. The polymorphism consists of a 40 base pair repeat sequence, with ten or nine repeats of the sequence being the most common. This polymorphism has effects on the level of expression of the transporter, with evidence that 10-repeat alleles have higher DAT1 expression than 9-repeat alleles. The ten repeat allele of this variant was found to occur at a higher but non-significant frequency in affected subjects compared to controls. Tests for association with brain morphology measures were also performed in two independent sets of subjects with schizophrenia and normal controls. Brain volume measurements were obtained by automated measurement of structures from brain MRI scans. Set 1 has 129 affected subjects and 34 controls, while Set 2 has 115 affecteds and 63 controls. In all subjects from both sets regardless of affectation status, 10-repeat homozygotes have increased total gray matter volume, as well as decreased total and frontal white matter volume. Schizophrenia 10-repeat homozygotes from both sets were found to have larger cerebral volume, but smaller cerebellar volumes compared to 9-repeat carriers. Analysis of covariance (ANCOVA) was performed separately on each group of affected and control subjects in the 2 sets, with brain volume measurement the dependent variable, genotype the independent variable (10-repeat homozygotes vs. 9-repeat carriers), and age, gender, and total intracranial volume as covariates. Both total and frontal white matter was found to be significantly associated with DAT1 genotype by ANCOVA in Set 1 schizophrenia subjects, but not in controls. In Set 2 schizophrenia subjects, a significant association between total cerebral and cerebellar volumes with DAT1 genotype was identified. These results indicate that a polymorphism in the dopamine transporter may contribute to brain morphology differences in subjects with schizophrenia.

GENE EXPRESSION BIOMARKERS OF PSYCHOSIS

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Purpose: For diseases like diabetes and hypothyroidism, a simple blood test is routinely used to achieve optimal doses of medication. The goal of this study is to identify a genetic fingerprint from blood capable of discriminating between patients during a state of psychosis and patients once they are stable on medication using gene expression microarrays. The fingerprint was from changes in levels of gene expression that relate to the patient's improvement. Methods: RNA was isolated from paired blood samples collected from 5 patients with schizophrenia when they are first admitted to the hospital and again once the patient the patient recovered. Results: Preliminary pair wise analysis using Gene Chip Operating Software (GCOS) of whole blood from 5 paired samples (2 female, 3 males) and 1 paired lymphocyte sample (male) suggests there are 340 genes that are differentially expressed in 4 out of 6 samples during the state of psychosis. Linkage: Twenty-two genes map within 7 regions linked to schizophrenia. Fourteen of the 22 genes are expressed in multiple regions of brain, brain expression was not detected for 2 genes and 6 genes have not been tested for brain expression. Biological candidates: Sixteen differentially expressed candidate genes not found in linkage regions have been implicated in schizophrenia by other methods. Pathways: Biological processes were identified for 59% of the differentially expressed genes using the Gene Ontology Mining Tool. A significant proportion of genes involved in toxin metabolism(P=1.4 x10-34), humoral immune response (P=6.6x10-10), angiogenesis (P=1.9x10-9), drug transport (P=1.7x10-8), reproductive behavior(P=4.0 x10-8) and secondary metabolism (P=4.1x10-4) were some pathways implicated. Conclusions: Once verified a genetic fingerprint of psychosis can then be used as an indicator of treatment success or ineffectiveness and lead to the ability to further optimize treatment of schizophrenia that takes into account a person's genetic response to medication.

ADJUDICATING NEUROCOGNITIVE ENDOPHENOTYPES FOR SCHIZOPHRENIA

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Objective. Although genetic influences on schizophrenia are well established, localization of the genes responsible for this illness has proven extremely difficult. Given evidence that genes predisposing to schizophrenia may be transmitted without expression of the clinical phenotype, efforts have focused on developing endophenotypes. While several neuropsychological measures have been proposed to be endophenotypes, few studies have systematically assessed batteries of neurocognitive tests to determine which tests are most sensitive to liability for the illness. Methods. 269 Latino individuals were administered a standard neuropsychological battery. 214 of these were members of families with at least two siblings diagnosed with schizophrenia or schizoaffective disorder. The remaining were community controls without history of major psychiatric illness. Neurocognitive measures found to be heritable were entered into analyses designed to determine which tests covary with the degree of genetic relationship to affected individuals. Results. Although five measures were found to uniquely model genetic liability for schizophrenia, digit symbol coding was the most sensitive. To assess the specificity of these endophenotypes, performance on these measures were compared to family members with bipolar and unipolar affective disorders. These markers clearly distinguished between individuals with psychotic illnesses and those with major depression. Conclusions: As measures contributed uniquely to discriminate individuals at varying risk for schizophrenia, our findings imply multiple independently inherited elements to the liability for the illness. We present a practical model for adjudicating endophenotypes and determining which measures are best suited for use in linkage analyses.

ASSOCIATIONS BETWEEN THE COMT POLYMORPHISM AND SYMPTOM DIMENSIONS IN SCHIZOPHRENIA

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COMT Val158Met likely influences prefrontal dopamine activity and is thought to confer vulnerability for schizophrenia. The Val allele has been associated with decreased performance and prefrontal activity during working memory tasks; whereas, the Met allele has been associated with better executive functioning. The goal of the present study was to investigate the relationship between COMT polymorphism and symptom dimensions of psychotic and bipolar affective disorders. The Operational Criteria Checklist for Psychiatric Illness (OPCRIT), which allows assessment of clinical features over the course of the illness, was used to derive symptom dimensions, encapsulating positive, negative, and mood features of the disorders. Preliminary analyses suggest that the Val allele is associated with greater vulnerability for delusions, particularly in psychotic disorders. In addition, the COMT genotype was associated with overall symptom severity in schizophrenia patients, but not in bipolar affective disorder patients. The present analysis suggests COMT polymorphism may confer both general and specific risk for clinical features in schizophrenia. We will present further analyses of the COMT polymorphism and symptom dimensions to detail the clinical phenotype associated with a likely vulnerability gene in schizophrenia.

HERITABILITY OF ENDOPHENOTYPIC MEASURES FOR SCHIZOPHRENIA: THE CONSORTIUM ON THE GENETICS OF SCHIZOPHRENIA (COGS)

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Understanding the genetic architecture of endophenotypes is becoming a prominent strategy for exploring complex disorders. A major advantage of the use of quantitative endophenotypes is that they are likely to be more correlated with the genetic and neural substrate abnormalities than is the "fuzzy", qualitative DSM-IV diagnosis of schizophrenia itself. The Consortium on the Genetics of Schizophrenia (COGS) has undertaken a multi-site investigation in order to assess the genetic architecture of important endophenotypes that show deficits in schizophrenia patients and their clinically unaffected relatives. 176 probands with schizophrenia and their 797 family members have been assessed for the following endophenotypes: Prepulse Inhibition (PPI) of the startle response, P50 Suppression, the Antisaccade Task, the Degraded Stimulus Continuous Performance Test (DS-CPT), the California Verbal Learning Task, Second Edition (CVLT-II), the Letter-Number Span (LNS) test, and several domains of the University of Pennsylvania Computerized Neuropsychological Battery. Variance component models were used to assess heritability, as well as the environmental and genetic correlations among the endophenotypes, in the first data release of over 100 families. All of the endophenotypes listed above, with the exception of one domain from the Penn Battery, were found to be significantly heritable ($p<0.05$), with heritabilities ranging from 21 to 53% in our initial analyses. Evidence for pleiotropy was demonstrated by significant environmental and genetic correlations between many of the endophenotypic measures. In addition, it is clear from this and related studies that many of the endophenotypes are at least partially "normalized" by the use of atypical, or "second-generation", antipsychotic medication in schizophrenia patients. This normalization obligates us to adopt novel strategies for making accurate heritability analyses. The COGS is the first large-scale and multi-site family-based heritability study of a large collection of endophenotypes for schizophrenia families and suggests that endophenotypes will be important measures to consider in characterizing the genetic basis of schizophrenia.

A NEUREGULIN 1 VARIANT ASSOCIATED WITH ABNORMAL CORTICAL FUNCTION AND PSYCHOTIC SYMPTOMS

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The present study investigated the effect of a variant in the Neuregulin 1(NRG1) promoter region on brain function as assessed by fMRI, symptom development and cognitive function in subjects at

high risk of schizophrenia. Subjects were recruited as part of the Edinburgh High Risk Study, a prospective cohort study of individuals aged between 16 and 25 from families with at least two individuals affected by schizophrenia. All participants were investigated with a combination of fMRI, sMRI and detailed clinical and neuropsychological assessment and were followed up regularly for up to 10 years. Genetic information was available for 79 high risk subjects and the risk-associated variant was strongly associated with the development of psychotic symptoms in this cohort (P=0.001). Subjects with the risk variant showed decreased medial frontal and middle temporal gyrus activation in fMRI whilst performing a sentence completion task (P<0.001 and P<0.05 corrected respectively). This effect could not be accounted for by medication as no subjects were receiving treatment at the time of scanning. No effect of the risk variant on grey matter density was observed, as assessed by voxel-based morphometry. Subjects with the risk variant also had a significantly lower pre-morbid IQ, as measured by the NART (P<0.05). These findings suggest that variation in the NRG1 promoter region contributes to the development of abnormalities in brain function, psychotic symptoms and cognitive abnormalities typical of schizophrenia, and provide evidence for the view that variants affecting gene expression can contribute to the pathogenesis of schizophrenia. Furthermore they provide evidence of a pathological mechanism, namely disturbance of fronto-temporal function, through which NRG1 may contribute to the development of psychotic symptoms. This work was funded by the Dr Mortimer and Theresa Sackler Institute Foundation, the UK Medical Research Council and The Stanley Medical Research Institute.

COGNITIVE CHARACTERISTICS OF SCHIZOPHRENIA PATIENTS AND THEIR UNAFFECTED SIBLINGS

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Impairments of multiple cognitive domains have been observed in various clinical phases of schizophrenic illness including prodromal phase. Numerous studies suggest that relatives of schizophrenia patients also exhibit some of those cognitive deficits which have a potential to serve as an endophenotype of the illness. We examined cognitive characteristics of schizophrenia patients and their healthy siblings to identify cognitive endophenotype of particular promise for use in molecular genetic studies of schizophrenia. Comprehensive neuropsychological tests were administered to three groups of subjects: 88 clinically stable schizophrenia patients, 42 healthy siblings of the patients, and 97 normal controls. Patients group showed significant impairments in wide-range of cognitive domains including attention and vigilance, verbal and visual working memory, verbal and visual memory and learning, speed of information processing, verbal fluency, and fine motor functioning. Compared to the normal control group, siblings group displayed significantly lower scores on Rey Auditory Verbal Learning Test, digit span backward, and verbal fluency tests (both category and letter) after controlling for the levels of education and general intelligence. Multi-variate analyses suggested that all of those measures were effective to discriminate siblings of patients from control participants. Impairments of verbal fluency, learning, and working memory found in patients with schizophrenia were also found in their healthy siblings. This finding suggests that those deficiencies are associated with genetic risk of schizophrenia and might be putative endophenotype of the disease.

COMPARISON OF NEUROPHYSIOLOGICAL AND COGNITIVE ENDOPHENOTYPES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Introduction: Schizophrenia (SZ) and Bipolar Disorder (BD) display clinical similarities, such as the presence of psychotic and mood symptoms, as well as similar responses to treatment. There is a growing body of research evidence suggesting that SZ and BD have overlapping genetic predisposition and share some pathogenetic mechanisms, particularly in the domain of psychosis. The primary goal of this research is to characterize the degree of overlap between SZ and BD by studying neurophysiological and neurocognitive endophenotypes in patients and their affected/unaffected relatives. Methods: Thus far 43 SZ probands (SZP) and 26 of their 1st degree relatives (SZR); 22 Bipolar I Disorder probands (BDP) and 24 of their 1st degree relatives (BDR) have entered the study. Ocular-motor measures were conducted using the Eyelink II camera system with high sampling rate (500 hz), and low noise (< 0.025 deg). Sensory gating endophenotype was evaluated based on Prepulse Inhibition (PPI) and P50 ERP. A broad battery of neuropsychological testing was also performed. Results: Socio-demographic characteristics (age, race, gender, education) were comparable between study groups. SZP had higher psychosis and total scores on the BPRS relative to the other groups. BD, Schizoaffective Disorder and ADD/ADHD lifetime diagnoses were more prevalent in BDR, whereas MDD and OCD were predominant among SZR. Regarding Axis II diagnoses, 46% of SZR had Cluster A (Schizophrenia spectrum) personality disorders/prominent personality traits; whereas Cluster B personality disorders were predominant in BDR (24%). So far, the study groups do not significantly differ in neropsychological performance on measures of executive function, working and declarative memory, and attention. There is a trend in IQ differences with higher levels found in BDP compared to SZP (effect size = 0.58). Neither SZ or BD probands groups, nor relatives groups differ in neurophysiological measures: on eye tracking tasks (smooth pursuit eye movements, anti-saccade task and memory-guided saccade task), PPI (at 120 msec inter-stimulus interval) and P50 ERP. To further characterize BP endophenotypic markers, BDP will be divided into two subgroups contingent upon the presence or absence of lifetime psychosis. Conclusions: Although the sample size is small, the results suggest that SZ and BD may have some shared neurocognitive and neurophysiological endophenotypes which possibly indicate vulnerability for psychosis.

USING THE FINDINGS OF THE EDINBURGH HIGH RISK STUDY TO PREDICT SCHIZOPHRENIA AND TO EXPLORE THE UNDERLYING MECHANISMS OF THE DISORDER

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The Edinburgh High Risk Study examined 163 young people at enhanced risk of schizophrenia for familial reasons over a 10 year

period covering the age of maximum risk of the disorder. Twenty-one developed schizophrenia and the remainder did not, although transient and partial psychotic symptoms which did not translate into formal illness occurred in 40% of the sample. Significant predictors of schizophrenia in terms of clinical, structural imaging and functional imaging variables were derived years before the psychosis developed. Progressive imaging changes were found and molecular genetic studies conducted at the end of the programme have shown highly significant relationships between genetic findings and a) clinical change in terms of the development of schizophrenia b) structural and functioning imaging change. These findings illustrate the value of longitudinal investigations in which serial imaging is combined with relevant genetic studies. References: Johnstone et al (2002) Br J Psych 186: 18-25 Owens et al (2005) Br J Psych 186: 386-393 Job et al (2005) NeuroImage 25: 1023-1030 Whalley et al (2004) Brain 127: 478-490 Whalley et al (2005) Brain 128: 2097-2198 McIntosh et al (2006) Biol Psych – in press

COGNITIVE PHENOTYPES IN PRODROMAL STUDIES

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The profile of cognitive deficits found in non-symptomatic individuals at genetic risk for schizophrenia who later develop the illness can inform genetic studies about the relative importance of various cognitive phenotypes. Clinically defined prodromal diagnostic criteria identify at-risk individuals with a 35-40% likelihood of developing a psychotic disorder within a year. The time course and predictive value of cognitive deficits in the development of psychosis has not been established. It is possible that deficits in specific cognitive domains or on specific cognitive measures may have a greater ability to predict the risk of psychosis and can serve as phenotypes in genetic studies. In two separate studies completed at three university medical centers, a comprehensive neurocognitive battery and clinical assessments were administered to subjects meeting Criteria of Prodromal States (COPS) criteria for being at risk for psychosis. Two comparison groups were also administered cognitive assessments: 59 first episode and 47 healthy subjects. Subjects were also evaluated at six-month and one-year follow-up periods. Primary analyses used a neurocognitive composite score and individual neurocognitive measures of vigilance, verbal memory, working memory, and processing speed. Results from one of the two studies suggested that at-risk subjects performed more poorly than healthy subjects (t=2.93, P=0.01), but better than first episode subjects (t= 4.72, p <.0001). At-risk subjects were particularly impaired on measures of vigilance and processing speed. Cognitive composite scores were significantly lower in at-risk subjects who progressed to psychosis (N=11; z=-1.2), while those at-risk subjects who did not progress to psychosis (N=17) performed better (z=-0.5), and not significantly different from controls. With regard to individual measures, poor CPT performance combined with better WAIS-R digit symbol performance predicted progression to psychosis. Severity of neurocognitive deficits was not related to duration of prodrome or to time to development of psychosis and neurocognitive function improved in all subjects except those who progressed to psychosis. These data suggest that neurocognitive impairment emerges early in the course of psychotic illness. Performance on specific tests of neurocognition may prove to be early risk predictors for subsequent development of psychotic disorders.

THE ASSOCIATION STUDY OF DRD3, DRD4 AND HTR2A WITH RISPERIDONE TREATMENT RESPONSE

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Objectives: Dopamine and serotonin receptor genes are promising candidates for pharmacogenetic study on atypical antipsychotics. The aim of this study was to identify the association of dopamine D3 receptor (DRD3) Ser9Gly, D4 receptor (DRD4) 12bp tandem repeat, and serotonin 2A receptor (HTR2A) T102C polymorphisms with non-response to risperidone in schizophrenia patients. Methods: A total of 84 schizophrenia patients were assessed for assessing risperidone treatment response. All the patients were in admission and showed acute psychotic symptoms with severity, CGI-S score more than 4. We collect the information through medical records, and psychiatrists who were in charge of each patient. The period that we assessed risperidone treatment response was 4 weeks after administering with risperidone. A Risperidone non-risponder group was defined by CGI-I score less than 4. We collected the sample for identifying the genotyping after informed consent. Results: Of 84 patients, 12 patients showed that risperidone non-response at 4 weeks. Two groups were not different in terms of duration of illness (6.8±7.1 vs. 5.8±5.4, p=0.57), age of onset (29.0±10.2 vs. 25.9±8.8,p=0.28), age(34.8±13.0 vs. 30.7±8.7, p=0.31), and proportion of male patients(58% vs. 50%, p=0.6). Non-responder group showed that high frequency Gly/Gly polymorphism in DRD3 but it did not reach to statistical significance (60.9% vs. 33.3%, p=0.076). The frequency of C/C genotype in HTA2A were lower in non-responder (58.3%) than in responder (80.6%), but it was not also statistically significant (p=0.088). The number of 12bp tandem repeat in DRD4 was not different between two groups. Conclusions: Several studies have reported that DRD3, DRD4 and HTR2A genes were related with risperidone treatment response. We wanted to replicate the previous report using schizophrenia with non-response to risperidone which represented the more extreme phenotype. Nevertheless we could not obtain statistically significant results; this study showed the suggestive evidence of association of DRD3 and HTR2A with risperidone treatment response.

CONCORDANCE OF THE DEFICIT/NONDEFICIT CATEGORIZATION IN AFFECTED SIBLINGS

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Introduction: Deficit and nondeficit schizophrenia differ relative to signs and symptoms, course of illness, pathophysiological correlates, treatment response, and association with risk factors, including differences in family history. These differences cannot be attributed to more severe positive psychotic symptoms or a greater duration of illness in the deficit group, and findings suggest the deficit group has a distinctive pathophysiology rather than a more severe form of the same pathophysiology. A previous study found a significant concordance (OR = 4.85) for deficit/nondeficit categorization in affected sib pairs. Hypothesis: We hypothesized that a deficit syndrome phenotype would have significant concordance in siblings. Methods: In a family history study, probands with schizophrenia or schizoaffective disorder and their relatives were administered the Oxford/Stony Brook Lifetime Symptom Check List. Sub-

jects with a history of a positive psychotic symptom were categorized into deficit (N=181) or nondeficit (N=385) groups using a form of the Proxy for the Deficit Syndrome. The deficit group had poorer premorbid function and greater negative symptoms, which could not be attributed to a greater severity of psychotic symptom, depressive symptoms, or chronicity. The deficit/nondeficit categorization had a concordance rate of 74% (concordant in 210/283 sib pairs; CI = 68.6% - 79.1%), compared to an expected rate of 56.4% (OR = 6.3). Conclusions: These findings replicate the familial concordance of deficit vs. nondeficit concordance within schizophrenia. These results, plus the other family and risk factor studies, suggest deficit and nondeficit schizophrenia differ in their etiopathophysiology. The deficit group may be an appropriate phenotype for genetic studies.

INDIVIDUAL SCHIZOPHRENIA ENDOPHENOTYPES ARE NOT SIGNIFICANTLY INTERCORRELATED: IMPLICATIONS FOR LINKAGE STUDIES

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Endophenotypes have proven to be valuable in genetic studies of schizophrenia, since they can potentially help to identify non-penetrant gene carriers, i.e. relatives of schizophrenia patients who do not exhibit schizophrenic symptomatology. In an attempt to increase the power of linkage studies, it is important to determine whether individual endophenotypes represent discrete neurobiological markers (each of which is associated with a separate schizophrenia susceptibility gene) or, alternatively, whether several endophenotypes are pleiotropic manifestations of the same gene. A number of endophenotypes have been proposed for schizophrenia. In this study, we examine three of them – smooth pursuit eye movements, thought disorder, and an embryologically derived measure of dysmorphology. We find that each of these endophenotypes is significantly correlated with schizophrenia and aggregates in clinically unaffected first-degree relatives at a higher rate than in our normal control group. Furthermore, these traits are observed far more often than schizophrenia itself in the relatives. Importantly, the proposed traits are not significantly intercorrelated. These findings suggest that (1) smooth pursuit eye movements, thought disorder, and the dysmorphology measure are potential endophenotyes for schizophrenia, and (2) each may be mediated by distinct neurobiological mechanisms, which in turn may be influenced by different gene(s). A linkage analytic approach that discriminates among phenotypes may be more powerful than one that combines the endophenotypes into a multivariate endophenotype.

TAILORING THE DEFINITION OF THE CLINICAL SCHIZOPHRENIA PHENOTYPE IN LINKAGE STUDIES

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The delineation of schizophrenia-related symptomatology is critical to phenotyping in linkage studies. A minority of first-degree relatives of schizophrenics (RelSZ) qualifies for a clinical diagnosis in the schizophrenia spectrum. In our sample, 7.1% (19/266) of RelSZ meet criteria for a diagnosis of schizophrenia and 8.6% (23/266) meet criteria for a schizophrenia spectrum personality disorder. Thus, at most ~15% of RelSZ would formally be classified as "affected" in a conventional linkage study of a clinical phenotype. The criteria for schizotypal personality disorder (SPD) were not developed with the purpose of identifying RelSZ. Rather, these signs and symptoms are based on the criteria used by Kety and colleagues to diagnose borderline schizophrenia in the Danish Adoption Study of Schizophrenia. Moreover, the requirement that five of the nine criteria for SPD be present to a clinically significant degree excludes many individuals with substantial but subthreshold levels of symptomatology. In this study we identified the combination of clinical signs and symptoms that maximized the discrimination between RelSZ (n=205) and nonpsychiatric controls (n=141) who did not qualify for a formal diagnosis within the schizophrenia spectrum. Logistic regression analysis showed that RelSZ and controls could best be distinguished on the basis of six characteristics related to interpersonal aversiveness: the absence of close friends or confidants other than family members, social anxiety, social avoidance, social isolation, introversion, and reserved emotions. We also evaluated the magnitude of the increase in sensitivity of this expanded definition of the clinical phenotype. Logistic regression scores greater than two standard deviations above the mean logistic score of the controls identified 11.2% (23/205) of RelSZ compared with 5.7% (8/141) of controls (Fisher's Exact: p=0.057). Adding the subgroup identified by this cluster of symptoms to the group of RelSZ who met formal diagnostic criteria for a schizophrenia spectrum disorder accounts for ~24% of first-degree relatives, almost doubling the proportion of relatives who could be considered "clinically affected." Since misclassification of gene carriers as non-gene carriers in linkage analyses increases the false negative risk dramatically, it may be advantageous to tailor the definition of the clinical phenotype to aspects of interpersonal aversiveness that optimize the identification of RelSZ.

PRELIMINARY MOLECULAR GENETIC INVESTIGATION IN A HIGH RISK COHORT STUDY

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Background: Prospective studies involving offspring of parents who developed psychoses have been important to investigate the influence of genetic vulnerability and environmental factors on child behavior etc. Objective: Identify the polymorphisms of the genes DAT1/VNTR (SLC6A3); dopamine receptor (D3), serotonin receptor (SLC6A4) and BDNF among offspring of functional psychoses women (schizophrenic and bipolar disorder) and offspring of women without any mental health disorders. Are there differences between these polymorphisms in women with functional psychoses more than healthy women? Are there differences in these polymorphisms in the functional psychoses' offspring more than healthy women's offspring? Methods: 212 mothers and her offspring were evaluated. Divided by mental disorder in three groups (60 with schizophrenia, 54 with bipolar disorder and 64 controls) of mother + 1 offspring randomically chosen (6-18-year old). Trained interviewers applied instruments to assess maternal psychopathology (Structured Clinical Interview for DSM-IV). Results: There were no statistically significant differences between the three groups of children regarding gender, age and mother's age, but the

schizophrenic group was poorer and showed low scores in the GAF than others groups. The control group had more African descendent than others. The first analyze of schizophrenics, bipolar and control groups (mothers + children) haven't showed significant differences in the allelic and genotypes frequencies in the polymorphisms of the genes dopamine receptor (D3), serotonin receptor (SLC6A4) and BDNF. Significant difference in homozygous carriers of the DAT1 9-repeat allele (9/9) than among heterozygous (9/10) and 10-repeat allele (10/10) in the control and bipolar group was observed. Genotype analyses: BDNF X2=2.012, p≤1; D4 X2=2.33, p≤1; 5HTT X2=4.68, p≤1; DAT1 VNTR X2=10,44, p≤0,05. Allelic analyses: BDNF X2=0, 34, p≤1; D4 X2=0, 26, p≤1; 5HTT X2=4,82, p≤1; DAT1 VNTR X2=2.17, p≤1. Conclusion: These preliminary results suggest that the DAT1 9-repeat allele (9/9) is associated with the group bipolar and controls group, but not with the schizophrenic group. The results demonstrated the controversies of the results in the genotype analyses founded in the literature.

ASSOCIATION BETWEEN SCHIZOPHRENIA AND BDNF-LINKED COMPLEX POLYMORPHIC REGION (BDNF-LCPR)

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Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophic factor family and promotes the development, regeneration, survival and maintenance of function of neurons. Several studies reported that a microsatellite polymorphism located approximately 1.0 kb upstream of the translation initiation site of BDNF was associated with psychiatric disorders such as schizophrenia and bipolar disorder. Recently, we found that this polymorphism is not a simple dinucleotide repeat, but it is highly polymorphic with a complex structure containing three types of dinucleotide repeats of 5'(CG)del/4/5, (CA)9-15, and (GA)2/3 (Okada et al, 2006). We obtained evidence for an association between this polymorphic region (BDNF-linked complex polymorphic region: BDNF-LCPR) and bipolar disorder; furthermore, a luciferase reporter gene assay in rat primary cultured neurons suggest that the risk allele is associated with a lower transcription activity, compared to the other alleles. In this study, we performed an association study between the BDNF-LCPR and schizophrenia. Subjects were 390 patients with schizophrenia (DSM-IV) and 388 controls. Genotyping of BDNF-LCPR was done by pyrosequencing. We found that homozygosity for the 5'(CG)del allele was more common in patients with schizophrenia than in controls (odds ratio 6.1, 95% CI: 1.8-21.0; p=0.001). The haplotype-based analysis also provided evidence for a significant association. In addition, we found that blood concentration of BDNF protein was significantly reduced with those healthy individuals who carried the 5'(CG)del allele. These results together with our previous findings suggest that the BDNF-LCPR is involved in the pathophysiology of schizophrenia as well as bipolar disorder via its effect on transcriptional activity.

DOPAMINE D2 RECEPTOR (DRD2 TAQ1 A) GENOTYPES IN PREDICTING BETTER TREATMENT RESPONSE TO ARIPIRAZOLE IN PATIENTS WITH SCHIZOPHERENIA

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OBJECTIVE: To evaluate the use of polymorphism in dopamine D2 receptor (DRD2 Taq1 A) genotypes in predicting treatment response to aripiprazole in patients with schizophrenia. METHODS: Ninety four schizophrenic patients were genotyped by DRD2 Taq1 A1 and A2 polymorphism and were grouped into A1/A1 alleles (n=14) and both A1/A2 and A2/A2 alleles (n= 74). They were treated with aripiprazole (10-30mg) only for 26 weeks and their clinical symptoms were evaluated with PANSS on each 0, 1, 2, 3, 4, 6, 8, 12, 16, 26 week. RESULTS: Until 6 weeks of aripiprazole treatment, there was no significant difference of PANSS scores between two groups. However, on 8 week of aripirazole treatment, patients with A1/A1 genetype showed better improvement of clinical symptoms than patients with A1/A2 or A2/A2 genotypes (0<0.001) and this difference was maintained to the end of treatment (26 week). In addition, patients with A1/A1 genotype showed better response rate to aripirazole treatment than other genotypes. There was no significant difference in aripiprazole dosages between groups CONCLUSIONS: Results of this study showed the possibility of tailored pharmacotherapy with aripiprazole, the dopamine D2 receptor partial agonist, for schizophrenic patients and genotype procedure before starting pharmacotherapy could be helpful for choosing proper antipsychotics for schizophrenic patient .

THE NRG1/ERBB4 SIGNALING PATHWAY IN SCHIZOPHRENIA. FROM UPSTREAM EFFECTORS TO DOWNSTREAM INTRACELLULAR SIGNALING NETWORKS

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The NRG1/ErbB4 pathway is known to be a critical regulator of neurodevelopment and adult brain function through its effects on migration, axonal guidance, synapse formation and neurotransmitter function. These events are mediated via intracellular signaling pathways, including the ERK/MAPK and PI3K and the downstream regulation of the actin cytoskeleton. Genetic association has recently identified the NRG1 receptor, ErbB4 as a susceptibility gene for schizophrenia. At present, the molecular mechanisms that underlie genetic risk at the ErbB4 locus are unclear, as is the specific nature of involvement of downstream signaling pathways in the disease. We have examined ErbB4 splice variant specific gene expression (JM-a, JM-b, CYT-1 and CYT-2) in the hippocampus and DLFPC in schizophrenia, utilizing qPCR in 84 controls and 48 patients and examined for effects of allelic variation in 4 reported genomic risk variants in the gene. In the DLPFC, mRNA for JM-a and CYT-1 containing ErbB4 isoforms are significantly increased in patients with schizophrenia. A main effect of genotype was observed in the DLPFC and hippocampus at a single risk SNP located in intron 12 (rs4673628) on JM-a containing isoforms. 3 intronic risk SNPs (rs7598440; rs707284; rs839523) and a core-risk haplotype were associated with elevated expression of CYT-1 containing ErbB4 splice variants.

ErbB4 receptors containing the CYT-1 exon are coupled to the PI3K intracellular signaling pathway. Our findings suggest that altered ErbB4 signaling in schizophrenia may represent a critical upstream regulator of specific intracellular pathways that impact on cellular events related to the disease. To this end, we examined a number of interacting signaling molecules that are downstream targets of ErbB4/CYT-1 activation and key regulators of the actin cytoskeleton, including, PI3K, Rac1, Cofilin, Slingshot and LIMK1 in the human brain in the disease, and at the level of clinical association. Our findings suggest that dysregulated splicing of the ErbB4 gene underlies the genetic association with schizophrenia and that the NRG1/ErbB4/PI3K pathway may be an important genetic network involved in the disease. Consequences for schizophrenia pathogenesis will be discussed in the context of a model postulating that genetic risk at the NRG1, ErbB4 loci impacts functionally on regulation of intracellular signaling cascades linked to the organization of the dynamic actin cytoskeleton.

WHOLE GENOME ASSOCIATION IN SCHIZOPHRENIA REVEALS NOVEL SUSCEPTIBILITY LOCUS

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Background: The development of whole genome association (WGA) technology provides an opportunity to rapidly identify novel susceptibility genes for complex phenotypes. We report converging results of a WGA study in a case-control schizophrenia (SZ) cohort, and a gene sequencing study in an independent case-control cohort. **Methods:** For the WGA study, patients (65F/113M) and controls (63F/81M) self-identified as Caucasian non-Hispanic; testing of 210 ancestry informative markers (AIMs) revealed no stratification. For the sequencing study, 71 clozapine-treated patients (28F/43M) and 31 controls (18F/13M), all at least 90% Caucasian based on 76 AIMs, were examined. For WGA, 500,568 single nucleotide polymorphisms (SNPs) were assayed (Affymetrix). Quality control procedures yielded mean call rates of 97%, reliability >99%, and 439,511 high-quality SNPs available for analysis. Likelihood ratios were analyzed for the best possible genotypic split (e.g., recessive or dominant models) for each SNP (excluding monomorphic and very rare SNPs), yielding 362,188 splits. Using Bayesian reasoning, the genomewide significance threshold was set to $p<4.2*10^{-7}$ (yielding an empirical false discovery rate q<.05). Sequencing was performed on exons and flanking regions for two genes neighboring the most significant SNP from the WGA study. Sequencing reactions were carried out in both directions using M13F and M13R primers using BigDyeTM Terminator Cycle Sequencing, and electrophoresis was run on the ABI Prism 3700 DNA Analyzer. **Results:** In the WGA study, one SNP demonstrated an association beyond the genomewide threshold ($p=3.7*10^{-7}$). Homozygosity for the common (C) allele was significantly associated with SZ; 59% of cases (105/178), but only 31% of controls (44/143, one not called) were C/C homozygotes (OR = 3.23; pop. attributable risk = 23.5%). In the sequencing study, we identified 8 novel, rare missense mutations. A total of 16 amino acid substitutions were detected in cases, with only 1 detected in controls (p=0.031). Additionally, common SNPs (MAF≥.10) were examined and 3 haplotype blocks were identified; two were significantly associated with SZ, as were 5 intronic SNPs within these 2 blocks. **Discussion:** While there is some prior cytogenetic and linkage support for this chromosomal region, neither gene examined in this study has been previously implicated in SZ. Results are consistent with prior biological and epidemiological data in SZ, as will be discussed.

BDNF: MOLECULAR DIFFERENTIATION OF SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Background - Recent population genetic studies suggest a partial overlap in genetic transmission of schizoaffective disorder and mood disorders. Allelic variaton in the gene encoding Brain Derived Neurotropic Factor (BDNF) has been associated with affective disorders in several reports, but studies examining association of BDNF polymorphisms to schizophrenia have provided mixed results. It is hypothesized that BDNF allelic variation is associated with the mood component of disorder, and that haplotype frequencies will be similar in patients with schizoaffective disorder and primary mood disorders, as distinct from patients with schizophrenia and healthy volunteers. Methods - We tested for an association between a 5-marker BDNF haplotype and SCID-based, consensus DSM-IV diagnosis, in 373 Caucasian patients and 220 Caucasian healthy comparison subjects. Primary diagnoses included schizophrenia (n=208), schizoaffective disorder (n=60), bipolar disorder (n=76), and major depressive disorder (n=29). Results - We detected a significant association between BDNF haplotypes and illness manifestation. The common haplotype (containing the valene variant of the Val66Met polymorphism) was overrepresented in patients with schizoaffective disorder and affective disorders compared to healthy volunteers. Moreover, the common haplotype showed significantly greater frequency in schizoaffective patients compared to patients with schizophrenia. Patients with schizophrenia did not significantly differ from healthy volunteers. Conclusions - To our knowledge, this is the first candidate gene study to differentiate schizoaffective disorder from schizophrenia. These data suggest that the effect of BDNF genetic variation may be associated with the clinical phenotype of affective dysregulation across several DSM-IV diagnostic categories, representing a step towards the molecular classification of psychiatric illness.

SELECTIVITY OF PLEIOTROPIC MAJOR GENE MODELS

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We have developed methods for estimating power to detect linkage to a bivariate phenotype (disease; endophenotype). These methods take into account the asymmetry of the ascertainment design used in family studies of psychiatric endophenotypes, in which probands are ascertained for having a disease and relatives are examined for recurrence on an endophenotype. We have previously applied this method

to data on schizophrenia and a thought disorder endophenotype associated with schizophrenia. We showed that the observed data on recurrence risks for both phenotypes fit a range of major gene models with pleiotropic effects. For thought disorder, the models tended to be dominant with very high penetrance, whereas for schizophrenia, the models tended to be partially recessive with much lower penetrance. Moreover, power to detect linkage was excellent in samples much smaller (100 nuclear families) than those typically thought to be necessary. We have now applied the same methods to bipolar disorder and a thought disorder endophenotype associated with that illness. The major gene models with pleiotropic effects that fit the observed data on recurrence risks for bipolar disorder and bipolar-related thought disorder are very different from those that fit the observed data on schizophrenia and schizophrenia-related thought disorder, but they too have excellent power to detect linkage. Those models tend to be dominant with moderate-high penetrance for both phenotypes. We next evaluated whether 1) the schizophrenia bivariate trait models fit the observed data on the bipolar disorder-related phenotypes, and 2) the bipolar disorder bivariate trait models fit the observed data on schizophrenia-related phenotypes. Models that fit recurrence risks for one bivariate trait do not fit recurrence risks for the other bivariate trait. The selectivity of the goodness of fit supports differences in the genetic transmission of schizophrenia and bipolar illness, although it does not rule out overlapping susceptibility loci.

RELATIONSHIP BETWEEN CLINICAL DSM DIAGNOSIS AND COGNITIVE DEFICITS IN THE OFFSPRING OF MULTIGENERATIONAL FAMILIES DENSELY AFFECTED BY MAJOR PSYCHOSIS

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Little is still known from the high-risk (HR) studies about the precursors and the specific risk mechanisms for schizophrenia (SZ) and bipolar (BP) disorder. The appearance of behavior problems or neurocognitive difficulties in childhood have been suggested as increasing the likelihood of developing major psychosis in HR studies. The aim was to investigate the relationship between non-psychotic DSM-IV disorders and cognitive deficits as precursors of SZ and BP in the offspring at high risk who descend from densely affected multigenerational families and to look for specific or shared patterns in HRSZ or HRBP. We gathered over a period of 15 years a sample of 46 multigenerational kindreds (N=1,200 family members, Maziade et al. 2005). The offspring were selected in the nuclear families (having one parent affected by SZ or by BP) descending from these pedigrees: from the fourth or the fifth generation, we selected 63 subjects in childhood or post-adolescence, at very HR of SZ (N=29 HRSZ) or BP (N=34 HRBP) (average age of 16.3 ± 4.3). Subjects were assessed in several cognitive domains: intelligence, attention, motor functions, memory and executive functions: WISC-III or WAIS-III after 16 years, Continuous Performance Test-II, Stroop test, Continuous Performance Test-II, Purdue Pegboard, Rey complex figure, California Learning Test. Episodic memory was assessed in visual and auditory modalities. Fifty-five percent of the HR offspring displayed a non psychotic DSM-IV diagnosis. Our preliminary findings revealed that HR when compared to matched controls presented significant under-functioning in global intelligence (mean IQ=96 in HR and IQ=107 in controls, P<0.0001), verbal memory (P=0.001), visual memory (P=0.001), executive function initiation and planification (P=0.004 and P=0.01 respectively) and working memory (P=0.02) domains. Some of the differences were shared by HRSZ and HRBP and a few were specific to each HR subgroup. The HR with and without a clinical diagnosis did not significantly differ in terms of neurocognitive function. In other terms, we observed little overlap between the behavior clinical diagnosis and the cognitive deficits. Our preliminary data suggest that these two potential precursors of SZ and BP (behavior disorders and cognitive deficits) might be independent in HR subjects and might represent two independent risk pathways that may explain heterogeneity in SZ and BP. Research supported by the CIHR (2005-2010) MOP 74430.

ASSOCIATION OF SCHIZOPHRENIA WITH THE PHENYLTHIOCARBAMIDE (PTC) TASTE RECEPTOR HAPLOTYPE ON CHROMOSOME 7Q

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Objective: Patients with schizophrenia exhibit a decreased ability to taste phenylthiocarbamide (PTC). PTC taste sensitivity is an inherited trait determined primarily by allelic variation of the taste-receptor gene TAS2R38 on chromosome 7q. The authors examined the TAS2R38 genotypes of schizophrenia patients, to determine if the increased prevalence of non-tasters in this patient population was indicative of a specific genetic association. Method: The genotypes of two non-synonymous coding SNPs in TAS2R38 were assayed for 176 schizophrenia patients and 229 healthy comparison subjects and the two-allele haplotypes were estimated. Results: There was an over-representation of the major PTC non-taster haplotype among patients of European descent, relative to comparison subjects of similar ancestry. Patients and comparison subjects of African ancestry did not differ. Conclusions: The PTC non-taster haplotype is a genetic marker that may be used to identify subsets of schizophrenia patients who potentially harbor vulnerability genes in this region of chromosome 7q.

INFLUENCE OF THE COMT VAL158MET POLYMORPHIM IN THE SEVERITY OF THE PSYCHOTIC SYMPTOMS AND IN THE RESPONSE TO THE NEUROLEPTIC TREATMENT IN A SAMPLE OF PATIENTS WITH SCHIZOPHRENIA

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Genetic variation in the Catechol-O-Methyltransferase (COMT) gene may influence the susceptibility to schizophrenia and the response to neuroleptic treatment. The authors aimed to test for an association between a COMT rs4680 (Val158Met) genotype and an eventual influence in the clinical outcome and in the response to treatment. The genotypes for SNP rs4680 were determined in 114 patients

with schizophrenia. The severity of psychotic symptoms was assessed by the PANSS scale, and the response to neuroleptic treatment after a period of observation of 6 months by the GAF scale. The relationship between the genotype and PANSS and GAF scores was done using Kruskal-Wallis test. Val/Val patients showed a higher severity of the psychotic symptoms both al baseline and after the period of treatment, that was significant in all PANSS-subscales and in PANSS-T. Val/Val patients showed a slightly worse response to the neuroleptic treatment than Val/Met and Met/Met patients (p=0.03). Our results show an influence of the Val158Met polymorphism on the severity of psychotic symptoms and on the response to neuroleptic treatment.

Relationship between the COMT Val158Met genotype and the severity of psychotic symptoms (PANSS scores) and the response to treatment (GAF score)

	PANSS-P-pre (p=0.042)	PANSS-P-post (p<0,001)
Val/Val	28	14
Val/Met	27	8
Met/Met	20	7
	PANSS-N-pre (p=0.039)	PANSS-N-post (p=0.044)
Val/Val	27	14
Val/Met	23	10
Met/Met	21	9
	PANSS-PG-pre (p=0.044)	PANSS-PG-post (p=0.022)
Val/Val	48	32
Val/Met	48	23
Met/Met	43	24
	PANSS-T-pre (p=0.009)	PANSS-T-post (p=0.002)
Val/Val	103	60
Val/Met	98	41
Met/Met	84	40
	Response to treatment (difference in GAF score) (p=0.03)	
Val/Val	30	
Val/Met	35	
Met/Met	35	

Significance comes from Kruskal-Wallis test.
In all genotype groups the median of the scores is expressed.

ABERRANT HOMOCYSTEINE METABOLISM AND THE RISK OF SCHIZOPHRENIA AND OTHER DISORDERS RELATED TO THE CENTRAL NERVOUS SYSTEM: DATA FROM ASSOCIATION AND FAMILY STUDIES

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Several lines of evidence support the theory of an association between methyl carbon metabolism, in which homocysteine is an intermediate metabolite, and schizophrenia. The methylenetetrahydrofolate reductase (MTHFR) gene, localized on chromosome 1.p36.3, harbours the most common genetic determinant of hyperhomocysteinemia, the 677C>T polymorphism. Studies investigating the association between aberrant homocysteine metabolism and schizophrenia are presented and discussed in different ways. Firstly, the contribution of elevated homocysteine concentrations and the MTHFR 677C>T polymorphism to the risk of developing schizophrenia is discussed using the results of a meta-analysis of genetic association studies. The association of the 677TT genotype and increased risk of schizophrenia (odds ratio=1.36 [95% CI: 1.07-1.72]) is suggestive for a causal relation between aberrant homocysteine metabolism and schizophrenia. Secondly, applying a family-based study design may circumvent confounding by population stratification as detected in case-control studies. Moreover, studying the prevalence of the MTHFR polymorphism may reveal a mother-child interaction in utero, if any, which has been demonstrated for neural tube defects. Results of a meta-analysis using data from three family-based studies, including our own data, are presented. We conclude that currently no evidence exists for an independent maternal genetic effect involving the MTHFR 677C>T polymorphism on schizophrenia risk. It is possible that mothers carrying the MTHFR polymorphism may be predisposed to increased risk of schizophrenia offspring when maternal folate status is low during pregnancy. Thirdly, the combined effect of genes encoding for enzymes of the methylation pathway may confer a significant susceptibility to schizophrenia. Genetic variants that modulate homocysteine or folate levels are genes of particular interest to study in relation to the risk of schizophrenia. Some combinations are discussed. Lastly, mild hyperhomocysteinemia and the common MTHFR variant are risk factors for various other disorders of the central nervous system, such as neural tube defects, Alzheimer's disease, and depressive disorder stressing the pivotal role of the homocysteine metabolism in humans. We discuss the involvement of the MTHFR variant and these central nervous system related disorders, including schizophrenia, and the related pathogenic mechanisms.

ASSOCIATION OF POLYMORPHISMS OF NEUREGULIN 1 GENE WITH COGNITIVE ENDOPHENOTYPES OF SCHIZOPHRENIA

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Previously the authors have investigated cognitive functioning of unaffected siblings of schizophrenia patients and identified possible endophenotype markers, i.e., deficits in verbal learning, working memory, and verbal fluency. Neuregulin 1 gene (NRG1) is identified as a positional and functional candidate gene of schizophrenia and known to be involved in the CNS development. One of the hypothetical roles of this gene in increasing the vulnerability of schizophrenia is the regulation of the cognitive processes. The present study investigated an association between the polymorphism of NRG1 and cognitive endophenotype markers in the Korean population. The subjects were sixty-one clinically stable schizophrenia patients and eighty-five normal controls. Four cognitive function tests (Rey Auditory Verbal Learning Test, digit backward test, category and letter fluency tests) that could effectively discriminate siblings of schizophrenia patents from normal controls in the previous study of the authors were administered. Three SNP markers (SNP8NRG221533, SNP8NRG241930, SNP8NRG243177) located at the 5' end of NRG1 were genotyped. For SNP8NRG22153 and SNP8NRG243177, association between genotype and cognitive functioning was not found both in patients and controls. For the control group, individuals having G allele of SNP8NRG241930, the risk allele of schizophrenia identified in the previous large-scale association study of the authors (Kim et al. 2006 Am J Med Genet) displayed lower scores in all of the cognitive measures. Significant association between genotype and cognitive functioning was observed for the Auditory Verbal Learning Test (p=0.033). A trend of association was also observed for the letter fluency test (p=0.060). These

associations were not found in the patients group. These results suggest that NRG1 is associated with deficits of verbal learning and verbal fluency and might contribute to the risk of schizophrenia through the effects on cognitive processes. For the patients group, the degree of cognitive decline appears to be under more complex genetic and environmental controls.

AGE OF ONSET AND DURATION OF UNTREATED PSYCHOSIS IN FIRST EPISODE PSYCHOSIS: INTERACTION EFFECTS BETWEEN CANNABIS AND COMT

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Age of onset and duration of untreated Psychosis (DUP) have been proposed as key factors in the prognosis of psychosis. Whereas gender differences in age of onset have been established and there is an emerging evidence of the association between cannabis use and an earlier age of onset, the role of other variables remains unclear. The Val158Met polymorphism of Catechol-O-Methyltransferase (COMT) has shown differences in clinical variables between genotypes and a possible association with an earlier age of onset. In addition, an interaction between COMT genotype and cannabis has been previously found in the modulation of risk of psychosis. The aim of this study was to examine the effects of COMT genotype, cannabis and their interaction in the age of onset and DUP in a representative group of first episode psychosis patients. Age of onset, DUP and cannabis consumption (regular vs. sporadic or non-users) were assessed in 169 caucasian drug-naïve patients with a first-episode of non-affective psychosis. COMT polymorphism was typed using PCR of the relevant region followed by digestion with NlaIII and electrophoresis. A multivariate ANCOVA was performed with DUP and Age of onset as dependent variables, cannabis and COMT genotype as fixed factors and gender as a covariate. The MANCOVA was significant for age of onset and DUP. Cannabis users had a significant earlier age of onset and shorter DUP. Age of onset was later in the Met homozygote group (non significant). The cannabis-COMT interaction showed a significant effect in both DUP and age of onset. Post hoc analyses showed that Val-Val and Val-Met groups had an earlier age of onset and longer DUPs, but only in the non-cannabis user group. Cannabis seems to modulate the age of onset and DUP independently of gender and to moderate the effect of COMT Val158Met polymorphism. Research Grants: Instituto de Salud Carlos III, FIS 00/3095, 01/3129, G0332, PI020499, Plan Nacional de Drogas SCO/3246/2004 and SENY Fundació Research Grant CI 2005-0308007.

	DUP		Age of Onset	
	F	p	F	p
Cannabis	1.793	0.182	16.887	<0.001
COMT	1.195	0.305	2.348	0.099
COMT-Cannabis Interaction	3.299	0.039	3.816	0.024
Gender	9.929	0.002	7.677	0.006

MANCOVA results. F values and level of significance in the between-subjects analysis for DUP and age of onset.

EFFECTS OF THE MTHFR C677T POLYMORPHISM ON NEGATIVE SYMPTOMS AND COGNITION IN SCHIZOPHRENIA

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Background: Altered serum folate and homocysteine levels may contribute to core deficits in schizophrenia, including negative symptoms and cognitive impairment. The C677T polymorphism of MTHFR, a key enzyme in the folate metabolic pathway, has been associated with overall schizophrenia risk in several studies, including a recent meta analysis (Lewis et al. 2005). Circulating folate, which largely reflects nutritional intake, supplies the substrate for the MTHFR reaction; thus, converging evidence implicates this biochemical pathway in schizophrenia. This investigation concerns specific contributions of the 677T allele to negative symptoms and cognitive impairment, and explores potential neural and biochemical mechanisms for these effects. Method: Outpatients with schizophrenia (present n=155) were genotyped for the MTHFR C677T polymorphism. Subjects underwent clinical characterization, including the Positive and Negative Syndrome Scale and an executive function battery, by raters blind to genotype. Subsets of individuals within this cohort also received serum folate and homocysteine assays (n=85), and underwent functional magnetic resonance imaging (fMRI) while performing an auditory source monitoring task (n=18). Results: Patients homozygous for the 677T allele (T/T) exhibited significantly worse negative symptoms than C/C or C/T subjects. T/T subjects also demonstrated impaired performance on two measures of executive function, the Verbal Fluency Test (total score) and Wisconsin Card Sort Test (ability to generate at least one category). Among T/T subjects, serum folate levels correlated significantly with negative symptoms (r=-.71) and verbal fluency (r=.81). fMRI analysis currently underway is examining whether MTHFR genotype influences activity in frontal regions related to semantic processing; these results will also be reported. Conclusions: The MTHFR 677T allele adversely affects negative symptoms, verbal fluency, and task switching. These symptoms have been linked by other schizophrenia investigators (e.g., Moore et al. 2006) and may collectively reflect a root dysfunction in frontal self-monitoring and semantic networks. The effects of MTHFR genotype on these symptoms, and on related frontal activity, may depend in part on serum folate concentrations. As such, T/T patients may express a schizophrenia subtype which is particularly amenable to folate supplementation. Supported by the APIRE/Lilly and Dupont Warren Fellowships.

ASSOCIATION STUDY OF NOVEL FUNCTIONAL POLYMORPHISMS OF THE D2DR GENE WITH SCHIZOPHRENIA

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We have identified a novel putative repressor element in the second intron of the human D2 receptor (D2DR) gene (D2-DRE), which has repressor activity in transcriptional assays (Rogaeva et al., 2006). We have identified the protein, called Freud-1 (Ou et

al., 2003; Albert and Lemonde, 2004) that mediates this repression, and have shown that it binds to and represses through the D2DRE. This protein is also expressed in dopamine neurons and likely to regulate D2 receptors in vivo. PCR and DNA sequencing revealed two novel polymorphisms proximal to D2-DRE, an A to G (8-bp proximal) and A to C base pair (60 bp proximal) that significantly reduced repressor activity of D2-DRE (Rogaeva et al. op.cit.). Derepression of the D2DR would lead to overexpression of D2 receptors, one factor thought to contribute to schizophrenia. We have initiated a study which will genotype a large cohort of schizophrenia patients and matched controls, for a novel dopamine-D2 haplotype consisting of three polymorphisms; the D2TaqIA and the novel D2-intron2 polymorphisms (A12740G and A12366C). Patients will be recruited from the Champlain District First Episode Psychosis Program (CDFEPP) at the Ottawa Hospital and the Schizophrenia Program at the Royal Ottawa Hospital (ROH). We hypothesize that one or more of these novel dopamine-D2 gene polymorphisms will associate with the diagnosis of schizophrenia. We will also seek to determine if there are associations between these polymorphisms and a family history of schizophrenia or major mental illness for the entire patient population, or with the age of onset of psychosis in the patient sample. The proposed study will be the first to examine the association of the novel functional D2-intron2 polymorphisms with schizophrenia. One of these D2 polymorphisms reduces binding and action of Freud-1, a repressor of the D2DR receptor gene, providing a potentially important new marker for D2DR gene expression. In a preliminary analysis of 12 patients and 13 matched controls within this data set, we found a trend for association of the Taq-T allele with schizophrenia sample $c2 = 2.520$, $df = 2$, $p = 0.2837$ (ns); allele: $p = 0.1319$ (ns). Genotype frequencies compared by c2 analysis with two-tailed p values; allele frequencies compared by Fisher's exact test with two-tailed p values. We will present our methods and results for a cohort of 40 schizophrenia and matched controls with the novel D2 intron 2 polymorphisms.

POLYMORPHISMS IN THE HOMEOBOX GENE OTX2 IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Recently, we investigated the possible involvement of OTX2, a homeobox gene crucial for forebrain development, in the pathogenesis of schizophrenia and bipolar disorder. The disruption of OTX2 in mice results in cortical malformations and causes serotonergic and dopaminergic cells in the midbrain to be expressed in aberrant locations. Our analysis found minor allele rs28757218 to be present in 30 out of 720 (4.2%) individuals with bipolar disorder but in only 6 out of 526 (1.1%) control individuals (odds ratio 3.5, 95% confidence interval 1.4-10.4, $p<0.003$.). On the other hand, the rs28757218 minor allele was found in 6 out of 458 (1.3%) individuals with schizophrenia. Currently, we are genotyping more samples to further verify our results. We are also trying to characterize the protein expression of OTX2 in postmortem brains to determine if this polymorphism is functional. Although, the minor allele rs28757218 does not appear to associate with schizophrenia, this polymorphism may be a risk factor for bipolar disorder.

VISUAL DYSFUNCTION IN CHILDHOOD IN A GROUP AT GENETIC RISK FOR SCHIZOPHRENIA

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Children with visual dysfunction have perinatal, neurological, visual-perceptual and cognitive abnormalities, which are similar to deviations found in patients with schizophrenia and their relatives. High-risk offspring of mothers with psychosis and control offspring of mothers with no history of psychosis were prospectively studied from birth to adulthood. We investigated whether (a) visual dysfunction is increased in early childhood in specific risk-groups, (b) visual dysfunction in early childhood predicts schizophrenia-spectrum disorders in adulthood, and (c) visual dysfunction in childhood is related to neurobehavioral dysfunction at different ages. The subjects were assessed with a standard test of vision at 4 yr of age. Neurological examinations were blindly performed in infancy and at 6 and 22 yr of age. DSM-III-R Axis I and II disorders were blindly assessed at the (93%-effective, n=166) follow-up at 22 yr of age. As compared with controls, only offspring of mothers with schizophrenia showed a significantly increased rate of visual dysfunction at 4 yr of age. In the total sample and among offspring of mothers with psychosis, both visual dysfunction at 4 yr of age, and its severity, were significantly associated with schizophrenia-spectrum disorders at 22 yr of age but no other psychiatric disorders. Visual dysfunction at 4 yr of age was significantly related to neurological abnormality at 6 yr of age, but not in infancy or at 22 yr of age. No association was found between visual dysfunction at 4 yr of age and neuropsychological impairment at 22 yr of age. Among offspring at genetic risk for schizophrenia, visual dysfunction in childhood may be an early marker of increased liability for schizophrenia, and even a selective predictor of schizophrenia-spectrum disorders in adulthood. The association between visual dysfunction and neurological abnormality at 6 yr of age may reflect disturbed neurological development, which changes manifest form by adulthood.

GENETIC AND CHILDHOOD TRAUMA INFLUENCES ON SCHIZOTYPAL FEATURES: A STUDY OF BIPOLAR AND SCHIZOPHRENIC RELATIVES

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Objective: Strong evidence exists for an association between childhood trauma and psychotic disorders. We investigated whether childhood trauma affected the phenotypic expression of schizotypyal dimensions in two populations of at-risk subjects i.e. unaffected first-degree relatives of either bipolar or schizophrenic probands. Method: A sample of 138 unaffected first-degree relatives was recruited (67 relatives of schizophrenic probands and 71 relatives of bipolar probands). The relationship between schizotypal features and childhood trauma scores was analyzed by partial correlations.Results: A positive correlation was found between childhood trauma scores and total schizotypal feature scores in first-degree relatives of schizophrenic subjects but not in first-degree relatives of bipolar probands. This positive correlation was primarily due to a strong association with the positive dimension of schizotypy. Conclusions: The fact that the effect of childhood trauma on risk for schizotypal features was strongest among subjects who were at high

genetic risk for schizophrenia suggests that only susceptibility genes for schizophrenia interacted with childhood trauma to predict the emergence of schizotypal features, mainly positive psychotic features.

PERSONALITY CHARACTERISTICS OF BIOLOGICAL RELATIVES OF SCHIZOPHRENIA PATIENTS ARE RELATED TO THEIR CATECHOL-O-METHYLTRANSFERASE GENOTYPE

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Quantitative dimensions that describe psychopathology may serve as sensitive measures of characteristics associated with genetic liability for psychotic disorders. Specifically, individuals with a higher than average genetic loading for psychotic disorders (i.e., first-degree biological relatives of affected individuals) may show aberrations in personality that are associated with genes found to be related to psychosis. We contrasted the personality pathology of first-degree relatives of people with schizophrenia and schizoaffective disorder (SZ-Rs), first-degree relatives of people with bipolar-I disorder (BPD-R), and controls using scale scores from the Dimensional Assessment of Personality Psychopathology (DAPP). We also characterized the Catechol-o-Methyltransferase (COMT) genotypes of the relatives. SZ-Rs scored lower than controls on stimulus seeking and higher than controls on social anxiety. Within SZ-Rs, individuals with the Met/Met COMT genotype had higher scores on narcissism and rejection of ideas than individuals with the Val/Val COMT genotype. Met homozygote SZ-Rs were similar to controls on narcissism and rejection of ideas. Val homozygote SZ-Rs were lower on narcissism and rejection of ideas than controls. BPD-Rs failed to show any difference in narcissism or rejection of ideas based on COMT genotype. Previous research has implicated the Val allele of the COMT gene in cognitive endophenotypes associated with schizophrenia. The present findings suggest that within SZ-Rs the Val allele may predispose low levels of narcissism and rejection of ideas. The dimensional assessment of personality pathology in individuals with genetic liability for psychosis appears to tap personality characteristics associated with specific genes that may contribute to psychosis.

AGE OF ONSET IN SCHIZOPHRENIA PROBANDS AS A MARKER FOR GENETIC LOADING IN SIBLINGS

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Prior research indicates that siblings of probands with schizophrenia have attenuated forms of psychopathology. The purpose of the present study was to determine whether age of onset of illness in probands with schizophrenia would be associated with the magnitude and pattern of psychopathology in their siblings. The subjects were participating in a study of psychopathology, cognition and neuromorphology in subjects with schizophrenia and their siblings at Washington University in St. Louis. The sample included 33 pairs of schizophrenia probands (28 male, 5 female) and their siblings (16 male, 17 female). Probands were recruited from local inpatient and outpatient treatment centers. Siblings were excluded (1) for a lifetime history of Axis I psychotic disorders (including bipolar disorder), (2) if they met DSM-IV criteria for substance dependence or moderate/severe substance abuse in the last 3 months, (3) had a severe medical disorder, (4) had a head injury with documented neurological sequelae, or (4) met DSM-IV criteria for mental retardation. Regression analyses were used to test the hypothesis that age of onset of the probands' psychiatric symptoms would account for a significant proportion of the variance of positive and negative symptoms reported by siblings. The siblings' gender, age at study participation, and education level were included in the model as covariates. Siblings were more likely to score higher on SIPS negative symptom scores, and SANS negative symptom scores, as well as individual SANS item ratings (anhedonia and avolition) when the probands' age of onset was 18 or younger (β=.47 to .36, p=.006 to .037). In contrast, there were no relationships between probands' age of onset and siblings' scores on measures of positive symptoms. The findings from this study support the hypothesis that negative symptoms are more prevalent in family members when the age of illness onset in probands is 18 years or younger. These results are consistent with the general hypotheses that negative symptoms, but not positive symptoms, are related to the genetic risk of developing schizophrenia, and that younger age of onset of schizophrenia is associated with greater genetic loading for the disorder. Supported by the Conte Center for the Neuroscience of Mental Disorders (P50 MH071616) and PHS grant R01 MH056584.

THE ASSOCIATION BETWEEN SCHIZOPHRENIA AND INTELLECTUAL IMPAIRMENT IS OF GENETIC ORIGIN

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We report the first study to quantify the extent to which the phenotypic correlation between schizophrenia and intellectual impairment is due to common genetic factors. Data from 162 twin pairs varying in their zygosity and affected status were used to 1) estimate the genetic and environmental contributions to the variability of intelligence and 2) decompose the covariance between intelligence and schizophrenia into parts due to genetic influences, shared family environment, and unique environment. A genetic model fitting approach was used, which employs the method of maximum likelihood to estimate model parameters from the observed data. As expected, intelligence was highly heritable (0.70), with no evidence of shared environmental contribution to family resemblance (0.008), but with substantial individual specific environmental influences (0.29). A significant phenotypic correlation was found between intelligence and schizophrenia (-0.61) with 92% of the covariance being explained by common genetic factors. This result was driven in the main by the association of schizophrenia and working memory (and to a lesser extent perceptual organization), two of the four domains of cognitive functioning that make up intelligence (the others being verbal comprehension and processing speed). Working memory was the most heritable (0.65) and its phenotypic correlation with schizophrenia was mainly due to genetic effects. To conclude, a substantial genetic overlap between intelligence and schizophrenia was found possibly mediated by common genes related to working memory.

EVIDENCE THAT THE COMT VAL158MET POLYMORPHISM MODERATES SENSITIVITY TO STRESS: AN EXPERIENCE-SAMPLING STUDY

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Preliminary evidence has been presented for a role of the Val158Met Catechol-O-Methyltransferase (COMT) polymorphism in the processing of emotional stimuli and the reactivity to stressful events. Guided by the tonic-phasic dopamine model, the proposed mechanism is that Met carriers display excessive cognitive stability that is adaptive in circumstances where holding information is demanded (eg working memory), but this cognitive stability could be dysfunctional in circumstances where rapid adjustments to changing external stimuli is required. The aim of the current study was to investigate the hypothesis that the Met allele would moderate affective and psychotic responses to stressful events in daily life, and that this would be more evident in groups with higher levels of risk for psychosis. Thirty-one patients with a clinical diagnosis of psychotic disorder according to DSM-IV criteria, 5 relatives of patients and 25 healthy controls were studied with the Experience Sampling Method (ESM), a structured diary technique assessing current context and psychopathology in daily life. Multilevel regression analyses revealed a significant gene-environment interaction between Val158Met COMT and momentary stress responses. Subjects with the Met/Met genotype had a greater increase in negative affect (NA: B=0.14, 95% CI 0.09-0.18, p<0.001) as well as a greater psychotic reaction (B=0.69, 95% CI 0.41-0.97, p<0.001) in reaction to stress than did subjects with the Val/Met or the Val/Val genotype. For the increase in NA in reaction to stress, this was true for both patients and controls (patients: $\chi 2$=5.9, p=0.05; controls: $\chi 2$=13.9, p=0.001), whereas for the psychotic response to stress, this phenomenon was only observed in patients ($\chi 2$=14.8, p<0.001). The current findings support the role of the Val158Met COMT polymorphism in the processing of emotional stimuli, and provide an attractive link between the Met allele and an increased emotional response to daily life stressors. The current findings also suggest that, rather than more strongly, Met-carriers with a pre-existing liability to psychosis react differently to daily life stressors than healthy Met-carriers, namely with an increase in psychotic as well as affective symptoms, whereas healthy Met-carriers only react with an increase in affective symptoms.

INHERITABILITY OF EXON EXPRESSION ALTERATIONS IN SCHIZOPHRENIA

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Gene expression is a quantitative trait with a strong heritable component as reported in recent yeast, mice, maize, and human studies. The study of transcriptome regulation of individual transcripts has previously focused on cis-regulatory effects. Loci with large trans-regulatory effects might be an important mechanism for transcript alteration in schizophrenia [1]. Here we present evidence of exon-specific expression alterations in schizophrenia using a screen of 1.4 million putative exons and a mapping of strong trans- and cis-regulatory loci for these exons. We studied lymphoblastic cell lines under two environmental conditions to measure the effects of stress on the exon expression in these cell lines of 4 families with schizophrenia matched for gender and age to unaffected members. We measured linkage to cis- and trans-regulatory loci of exon expression quantitative traits using a microsatellite marker scan and a previously described method [1]. We present evidence that: 1) specific exon expression alterations in schizophrenia are linked to cis- and trans- regulatory loci, 2) exons containing SNPs hybridize differentially to Affymetrix probes which suggests that allelic expression may be detected with the exon array platform, and 3) differential exon expression in schizophrenia occurs in the absence of overall transcript expression differences. Exon expression patterns present an interesting variant of an expression phenotype to study cis and trans regulatory loci in schizophrenia and other complex disorders.

[1] Vawter, MP et al. (2006). Genome scans and gene expression microarrays converge to identify gene regulatory loci relevant in schizophren

ASPM INFLUENCES CEREBELLAR AND CORTICAL VOLUMES IN TWO SAMPLES OF INDIVIDUALS WITH SCHIZOPHRENIA

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Background—*ASPM* influences whether neural progenitor cells remain pluri-potent or enter terminal differentiation. *ASPM* mutations can cause microcephaly, and common SNPs appear to have contributed to the evolutionary enlargement of the primate brain. We examined whether *ASPM* was associated with brain structure volumes in individuals with schizophrenia (SZ). **Methods**—We genotyped rs3762271, a C/A SNP central to the cortical evolution haplotype, in 268 SZ individuals and 90 controls who were imaged using one of two MRI protocols (PR1 and PR2): 135 SZ individuals with PR1, and 128 with PR2; 18 controls with PR1 and 72 with PR2. Also, 233 SZs and all controls were tested across 5 domains of cognitive functioning. All SZs were assessed for neurological, cerebellar, and soft sign abnormalities. ANCOVAs and chi-square tests assessed genotype effects on the trait measures. **Results**—rs3762271 was not associated with SZ. Significant genotype effects, however, were found in SZ individuals for volumes of: cerebral cortex, parietal lobe, parietal WM, cerebellum, and cerebellar GM. In ***both*** the PR1 and PR2 groups, AA < CA < CC for the cortical structures, and AA > CA > CC for the cerebellum. In combined analyses using protocol as a covariate, the effects became stronger: total cortex F=11.69, p=0.0007; parietal lobe F=24.41, p<0.0001; parietal WM F=15.21, p=0.0001; total cerebellum F=15.70, p<0.0001; and cerebellar GM F=17.92, p=<0.0001. Partial *r*2 values for the genoytpe effect ranged from 0.044-0.068. In the combined analyses, genotype also produced significant effects on cortical WM, frontal WM, and parietal GM. Linear genotype effects were also observed for problem solving (F=5.11, p=0.02) and language (F=8.37, p=0.004), with AA > CA > CC. SZs with cerebellar signs had a higher proportion of CC genotypes than those without cerebellar signs (X2=9.91, p=0.007). No similar effects were found in controls for either imaging or cognitive measures. **Discussion**—We find that rs3762271 is associated with brain structure volumes, cognitive abilities, and cerebellar neurological abnormalities in individuals with SZ. The SNP produced concordant effects across two samples, though in opposite directions in the cerebrum compared to the cerebellum. These strong but contrasting effects may be due to differing times of expression of *ASPM* in these structures and/or to the unique embryonic derivation of cerebellar tissues.

COMPLEX GENETICS IN HUMAN BRAIN: LESSONS FROM COMT AND SCHIZOPHRENIA

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Genetic risk for schizophrenia is complex, involving multiple genes that interact with each other and with the environment and that vary across populations. COMT illustrates many of these principles. Neuroimaging studies and studies of cognition have found consistent associations of a functional val158met polymorphism with aspects of cortical information processing and regulation of the brainstem DA reward system. However, association with psychiatric phenotypes, particularly schizophrenia, has been notably inconsistent and weak. We explored the effects of multiple functional loci in the gene as they might interact to effect COMT gene processing and enzyme activity. We have shown that a variant in the 5' regulatory domain of the gene (rs 2097603) effects enzyme activity and tested whether a variant (rs165599) in the long 3'UTR previously found to be part of a high risk schizophrenia haplotype including the val allele which changes the seed sequence for binding of miR-485-5p would effect COMT expression. The G allele at this locus was predicted to exaggerate the val effect on enzyme activity by obliterating miRNA binding. An effect of this SNP on expression of the long 3'UTR was confirmed in normal postmortem human brain ($p<.0001$). We tested whether combinations of alleles at these three loci would predict frontal lobe function with greater effect size than val met alone. The GvalG haplotype, predicted to translated into the greatest COMT enzyme activity, was associated with the most inefficient physiological response in PFC during working memory assayed with fMRI ($p<.0001$). Diplotypes homozygous for inefficient haplotypes showed significant association with schizophrenia in a case control dataset that was nonsignificant at any of the individual SNPs ($P=.05$). Finally, inefficient haplotypes showed significant epistatic interactions with risk SNPs in other genes that are individually negative in our datasets, including DAOA and RGS4. COMT thus illustrates an emerging principle in complex genetics that not only are phenotypic manifestations dependent on interactions with other genes and with environmental factors, but even within the gene itself, where there are multiple functional loci that combine to determine its biologic state and its resulting phenotype.

NOVEL SCHIZOPHRENIA SUSCEPTIBILITY GENES FROM BRAIN EXPRESSION PROFILES

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The molecular genetics of schizophrenia susceptibility genes appear to involve the regulation and splicing of transcripts or proteins. Thus, the gene expression profiles of patient tissue may provide clues to the identification of candidate risk genes. We selected 12 genes recently reported as differentially expressed in a large number of schizophrenia patients as determined by microarray and genotyped haplotype tagging SNPs in 170 Caucasian families with a schizophrenic offspring. Family-based association was assessed using FBAT and significant signals were observed in 5 of the 12 genes. In particular, SNPs located in a potassium channel gene demonstrated the highest linkage disequilibrium (LD) with the illness. Association to this gene was confirmed in a larger family dataset (290 families) and in three additional independent datasets of varying ancestry and ethnicity, including two family sets and a large case control sample. The associated SNPs are correlated with impaired IQ/Processing speed and episodic memory, inefficient activation of the HF measured with fMRI during the encoding phases of a memory based task, and reduced HF grey matter volumes even in healthy control risk allele carriers. We identified in human brain a novel isoform of this gene, with its transcription start site near the risk sequence variants, and which is highly expressed within the human brain, unique to primates, and different in structure from other known isoforms. Moreover, we found that this isoform is more abundantly expressed in brain tissue from schizophrenia patients than in controls and that risk genotypes are associated with increased expression specifically of this isoform in two independent cohorts of brains from healthy controls and also in two independent cohorts of patients with schizophrenia. This novel isoform is predicted to change K+ currents within the brain, specifically to modify repolarization efficiency and lead to desynchronization of interneuron assemblies, thought to be a critical aspect of cortical dysfunction in schizophrenia.

DOPAMINE TRANSPORTER GENE (DAT1) VARIABLE NUMBER TANDEM REPEATS POLYMORPHISM, EYE TRACKING, SENSORIMOTOR AND SENSORY GATING IN SCHIZOPHRENIA

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Application of endophenotypes in the genetic dissection of schizophrenia is crucial in reducing clinical and genetic heterogeneity. We have previously demonstrated association between COMT gene and predictive pursuit, a specific schizophrenia endophenotype. In this study, we examined association between the 40-bp variable number of tandem repeats (VNTR) polymorphism in the dopamine transporter (DAT1) gene and three established schizophrenia endophenotypes (eye tracking, prepulse inhibition of the startle reflex [PPI], and the P50 auditory-evoked potential). Previous studies suggest a functional effect of the DAT1 10-repeat (10/10 genotype) variant in modulating cortical dopamine and associated neurocognitive functions compared to non-10/10 genotypes. We hypothesized that DAT1 may affect eye tracking, PPI, and P50 measures. Maintenance pursuit (a global measure) and predictive pursuit gains were compared in 89 schizophrenia patients, 40 unaffected first-degree relatives, and 80 healthy controls, with DAT1 genotype; PPI and P50 were obtained in a subgroup (n=139). There was no genotype-by-diagnosis interaction on maintenance pursuit performance, PPI, and P50. Predictive pursuit gain was significantly different in cases compared to unaffected first-degree relatives and healthy controls ($p=0.008$). Examination of the effects of being DAT1 10/10 vs. non-10/10 genotype showed a significant diagnosis-by-genotype interaction ($p=0.02$): schizophrenia cases with the 10/10 genotype fared worse than non-10/10 cases in predictive pursuit ($p=0.02$). An opposite effect was observed in healthy controls and in relatives ($p>0.05$, ns). Subjects with 10/10 genotype were significantly different on predictive pursuit performance in patients, relatives, and controls ($p<0.001$). In all subjects, P50 potential by genotype was signifi-

cantly different (p=0.002). There was no genotype effect on PPI. Our data suggests that this functional DAT1 polymorphism affects performance on a specific smooth pursuit eye movement measure and on P50 sensory gating. Schizophrenia subjects with 10/10 genotype performed worse on predictive pursuit gain and healthy controls with DAT1 10/10 genotype performed the best with unaffected relatives falling in between. The DAT1 10/10 genotype was associated with P50 gating in all subjects, but no between-groups interaction was observed. This data provides evidence of complex interactions between DAT1 polymorphism and putative schizophrenia endophenotypes.

5-HT2C RECEPTOR AND LEPTIN POLYMORPHISMS, OBESITY AND METABOLIC SYNDROME IN SCHIZOPHRENIA

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Weight gain and consequent glucose dysregulation and dyslipidaemia are major side effects of long-term antipsychotic treatment. Abdominal obesity and its metabolic consequences constitute metabolic syndrome. The prevalence of metabolic syndrome in patients with schizophrenia treated with antipsychotics is 36%, is at least twice as high as the general population (De Hert et al., 2006). Although the mechanism of antipsychotic associated metabolic changes is not clearly understood, the substantial variation between individuals and races suggest that genetic factors may be important in the occurrence of antipsychotic-induced pathology. To evaluate the relative contribution of functional polymorphisms in the leptin and 5-HT2C receptor genes to metabolic changes in patients with schizophrenia or schizoaffective disorder we are conducting a cross-sectional study. Interim analysis has been undertaken on 130 subjects. Measurements taken included blood pressure, random blood glucose level, cholesterol, triglycerides, leptin plasma level; waist circumference, body mass index. Metabolic pathology was defined according to IDF criteria. Central obesity, defined as increased waist circumference was present in 74% of the patients; 60% of patients had increased triglycerides level, 41% exhibited raised blood pressure; metabolic syndrome was determined in 40% cases. All samples were genotyped for the 5-HT2C receptor -759C/T and leptin -2548A/G polymorphisms. There was no association between 5-HT2C polymorphism and presence of obesity and metabolic syndrome. However, leptin gene polymorphism showed that AA allele carriers exhibited significantly lower frequency of metabolic syndrome than carriers of G allele (p=0.035). Combined genotype analysis showed that 5HT2C/leptin gene polymorphisms interaction terms on the main measures of obesity (BMI and waist circumference) are highly significant ($p \leq 0.001$). In patients with the "high risk" 5-HT2C C/CC genotype, effect of the leptin genotype on obesity was highly significant ($p < 0.01$). Effect of leptin genotype on the frequency of metabolic syndrome within the 5-HT2C C/CC group was very strong (p=0.001). These findings present further evidence of association and interaction between 5-HT2C receptor -759C/T, and leptin -2548A/G polymorphisms in determining risk of both obesity and metabolic syndrome in patients with schizophrenia.

8. Genetics, Basic

EPIGENETIC DETERMINANTS OF GABAERGIC DYSFUNCTION IN SCHIZOPHRENIA

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A key enzyme for GABA synthesis, GAD1, is frequently dysregulated in brain of subjects diagnosed with schizophrenia or autism. To examine the role of epigenetic regulators of transcription, we profiled histone and DNA methylation at the GAD1 locus (2q31), and GAD1 mRNA levels, in fetal, child and adult prefrontal cortex, including 65 schizophrenia and autism cases with matched controls. Tri-methylation of histone H3 lysines 4 and 27 showed peak levels at the proximal GAD1 promoter, consistent with the previously reported concentration of these modifications around transcription start sites in dividing cell lines. The prefrontal deficit in GAD1 mRNA in a subset of cases diagnosed with schizophrenia or autism was associated with a selective loss of the open chromatin mark, H3K4me3, at the GAD1 promoter. In the affected cases, a set of GAD1 SNPs conferred a histone methylation shift towards the repressive chromatin mark, H3K27me3. DNA methylation levels at proximal GAD1 sequences, while higher in H3K27me3- than in H3K4me3-tagged nucleosomes, were not elevated in diseased cortex. Furthermore, GAD1-H3K4me3 and the corresponding mRNA were regulated during an extended period of prefrontal maturation, as reflected by progressive increases from prenatal to childhood to postpubertal ages. Likewise, in rodents, Gad1 H3K4me3 and mRNA levels were co-regulated in differentiating cells and during cortical development. There was a 3-fold increase in open chromatin, Gad1-H3K4me3, after chronic treatment with the atypical antipsychotic, clozapine. Together, these findings identify differential histone lysine methylation as a chromatin-remodeling mechanism linking cortical development to GABAergic dysfunction in schizophrenia and autism.

HETEROZYGOUS NEUREGULIN 1 MUTANT MICE ARE MORE SENSITIVE TO THE BEHAVIOURAL EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL

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Environmental stressors such as cannabis use may precipitate schizophrenia especially if the individual has a genetic vulnerability to the disease. Human and animal research indicates that neuregulin 1 (Nrg1) is a susceptibility gene for schizophrenia. The aim of this study was to investigate, whether dysfunction in the Nrg1 gene modulates the behavioural effects of delta-9-tetrahydrocannabinol (THC), the major psychotropic component of cannabis. Different sets of heterozygous Nrg1 transmembrane-domain mutant mice (Nrg1 TM HET) were treated with acute THC (0, 5 or 10 mg/kg i.p.) 30 min before being tested in the open field (OF), hole board (HB), light-dark (LD), elevated plus maze (EPM), social interaction (SI) and prepulse inhibition (PPI) tests. Nrg1 HET mice showed differences in baseline behaviour in regard to locomotor activity, exploration, and anxiety. More importantly, they were more sensitive to the locomotor suppressant actions of THC compared to wild type-like (WT) mice. In addition, Nrg1 TM HET mice expressed a greater THC-induced enhancement in % PPI than WT mice. The effects of THC on anxiety-related behaviour were task-dependent, with Nrg1 TM HET mice being more susceptible than WT mice to the anxiogenic effects of THC in LD, but not in the EPM, SI and OF tests. Nrg1 TM HET mice were more sensitive to the acute effects of THC in an array of different behaviours including those that model symptoms of schizophrenia. It appears that variation in the schizophrenia-related neuregulin 1 gene alters the sensitivity to the behavioural effects of cannabinoids.

INVESTIGATIONS OF A MOUSE LACKING D-AMINO ACID OXIDASE (DAO) ACTIVITY AND THE IMPLICATIONS FOR DAO AS A THERAPEUTIC TARGET FOR SCHIZOPHRENIA

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D-amino acid oxidase (DAO) degrades D-serine, a co-agonist at the NMDA receptor (NMDAR). Hypo-function of the NMDAR has been suggested to be a possible cause of schizophrenia. Intriguingly, DAO has been recently identified as a risk factor for schizophrenia through genetic association studies. A naturally occurring mouse strain (ddY/DAO -) has been previously identified which lacks DAO activity. We have further characterized this strain both behaviourally and biochemically to evaluate DAO as a target for schizophrenia. We have confirmed that this strain lacks DAO activity and shown for the first time it has increased occupancy of the NMDAR glycine site due to elevated extracellular D-serine levels and enhanced NMDAR function in vivo. Furthermore the ddY/DAO- strain displays behaviours which suggest that it will be a useful tool for evaluation of the clinical benefit of DAO inhibition in schizophrenia.

ARRAY CGH AND COPY NUMBER VARIATION IN SCHIZOPHRENIA

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Genomic copy number variations (CNVs) are known causes of genetic diseases, including cancers and mental retardation. We hypothesize that CNVs may also contribute to the genetic etiology in a subset of patients with common psychiatric disorders, including schizophrenia. Comparative genomic hybridization arrays (aCGH) have been successfully used to detect CNVs, including microinsertions and microdeletions that cannot be detected by conventional cytogenetic methods. This method has not yet been widely applied to schizophrenia. Therefore, we performed aCGH on genomic DNA derived from 33 probands with schizophrenia or schizoaffective disorder from multiplex families originally ascertained as part of a sib-pair study. The array, designed and constructed at the Roswell Park Cancer Institute, consisted of PCR representations of 6,116 BACs spanning the human genome at 0.5-1 MB intervals, spotted in triplicate. All test samples were compared to pooled genomic DNA from

10 normal controls. Application of three alternative statistical algorithms for detecting copy number variation yielded 39 chromosomal regions of interest. Nineteen of these regions have thus far been subjected to a second tier of analysis (qPCR and/ or FISH). These methods confirmed the presence of three deletions (4q12 in three probands, 5p15 in one proband, and 11q13 in seven probands). None of the three loci are known to be CNVs in the normal population. Systematic association studies and further characterization of these regions are in progress. These results demonstrate the feasibility of aCGH analysis of schizophrenia, the necessity for carefully confirmation of aCGH findings by alternative methods, and the possibility that CNV may be relevant to the etiology of schizophrenia.

IDENTIFICATION OF PTPRZ1 AS A SCHIZOPHRENIA SUSCEPTIBILITY GENE

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Neuregulin and the neuregulin receptor ERBB4 have been genetically implicated in schizophrenia. We made use of the yeast two-hybrid system to identify proteins that would interact with ERBB4, as a means of further dissecting molecular pathways that might contribute to schizophrenia susceptibility. In this screen, we identified MAGI-2 as an ERBB4-binding protein. As MAGI proteins were previously shown to interact with receptor phosphostyrosine phosphatase beta/zeta (PTPRZ1), binding of MAGI to ERBB4 could form a phosphotyrosine kinase/phosphotyrosine phosphatase complex. Studies in cultured cells confirmed a functional interaction between ERBB4, MAGI, and PTPRZ1. Given the evidence for a functioning complex of ERBB4, MAGI, and PTPRZ1, we then examined MAGI-2 and PTPRZ1 for genetic association with schizophrenia. PTPRZ1 showed significant association with schizophrenia in a large case-control sample. The data provide evidence for a role for PTPRZ1 signalling abnormalities in the etiology of schizophrenia and provide further support for an important role for neuregulin signalling abnormalities in the etiology of schizophrenia.

INVESTIGATION OF POST TRANSCRIPTIONAL GENE SILENCING IN SCHIZOPHRENIA

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In the neurodevelopmental model of schizophrenia, regulatory factors that control the appropriate spatial and temporal expression of critical molecules involved in neural processes such as cell division, migration, branching, connectivity and have special significance. In this study we are investigating the expression of small regulatory RNA molecules in this category, known as micro RNAs (miRNA). These non-coding RNA molecules negatively regulate the expression of target genes by specifically guiding cellular gene silencing machinery to their 3' untranslated regions (UTR), through a recently characterised mechanism described as post-transcriptional gene silencing (PTGS). High throughput analysis of mature miRNA expression in postmortem grey matter from the superior temporal gyrus and dorsolateral prefrontal cortex was facilitated by the establishment of a custom micro array platform. Preliminary analysis of miRNA expression profiles from a cohort of schizophrenia subjects and match controls reveals differential expression in a number of miRNAs. We are currently attempting to validate these changes in expression by northern blot and quantitative PCR. The implication of these findings are substantial, as each of these miRNAs are predicted to regulate many target genes with potential significance to the development of schizophrenia.

PROTEOME PROFILING OF THE PREFRONTAL CORTEX (PFC) AND HIPPOCAMPUS OF SCHIZOPHRENIA BRAINS

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Background: Structural and functional abnormalities have been identified in a number of brain regions, particularly the hippocampus and PFC (both grey and white matters) of schizophrenic subjects including volume reduction and cytoarchitectural irregularity. Abnormalities in the activities and/or volume of the PFC and hippocampus (both anterior and posterior regions) seem to be well correlated with a number of cognitive, negative and positive symptoms. The molecular mechanisms underlying the neuronal pathology in both regions are largely unknown. Hypothesis: We hypothesize that these mechanisms will be elucidated by applying a high-throughput proteomics approach to determine alterations in the protein expression profile between the schizophrenic and control brains. Method: Matched brain tissue samples between schizophrenic and control subjects were provided by the NSW Tissue Resource Centre (Sydney, Australia); BA46 grey matter (10 cases and 10 controls), BA46 white matter (10, 10), anterior (7, 7) and posterior (9, 9) hippocampus. Proteins were extracted and analysed by two dimensional gel electrophoresis (2DGE) in duplicates. Protein profiles were analysed using Nonlinear Phoretix 2D Expression software and proteins identified using MALDI-TOF mass spectrometry (MS). Results: We examined and compared the expression levels of over 600 and 1000 protein spots varying in intensity for the BA46 and hippocampus samples respectively. Differentially expressed proteins and their isoforms involved in a number of cellular processes were identified. Conclusion: 2DGE in combination with MS can be successfully applied to identifying molecular factors and mechanisms that may underlie neuropathology in schizophrenia brains.

TRANSGENIC MANIPULATIONS OF PUTATIVE SCHIZOPHRENIA SUSCEPTIBILITY GENES: A STRATEGY FOR CLARIFYING LINKAGE/ASSOCIATION SIGNALS AND MOLECULAR PATHWAYS

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Progress in identifying genes that contribute to susceptibility to schizophrenia and other psychiatric disorders has been hindered by a number of factors, including non-Mendelian transmission patterns, probable genetic heterogeneity, and an inability to detect premorbid and non-penetrant carriers of predisposing genes. In addition, recent evidence suggests that some susceptibility loci may be shared among conditions traditionally viewed as etiologically distinct. Our approach is based on the notion that schizophrenia and other complex diseases can best be conceptualized as sets of quantitative traits that reflect intermediate states between predisposing genes and

symptomatic expression (endophenotypes). We are pursuing a 'translational phenomics' strategy to specify the neuroendophenotypic effects of sequence variations in genes associated with schizophrenia and bipolar disorder across the cognitive, anatomical, physiologic, cellular and molecular levels of analysis and to determine the correspondences between these genotype-phenotype relationships across humans with and at risk for schizophrenia and bipolar illness and mice with experimentally induced alterations of these genes. We demonstrate the merits of this approach in relation to a series of experiments evaluating a transgenic mouse model of the Disrupted in Schizophrenia 1 gene (DISC1) for association with behavioral and neural phenotypes previously seen to be associated with schizophrenia-related haplotypes of DISC1 in humans. Multiple such correspondences have been observed in terms of neurocognition, neuronal morphology, and neuronal physiology. We also discuss how the use of multiple manipulations of the same gene and an inducible transgene platform may facilitate isolating critical regions of genes that will aid in the identification of functional polymorphisms in humans and in the determination of the temporal-developmental and regional-neuroanatomical specificity of these targeted mutations. While most of the examples to be presented pertain to DISC1, work in progress is extending this approach to other putative susceptibility loci, including dysbindin.

NEW GENETIC MOUSE MODELS OF SCHIZOPHRENIA: MIMICKING COGNITIVE DYSFUNCTION BY ALTERING SUSCEPTIBILITY GENE EXPRESSION

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Translation of human genetic mutations into genetic mouse models is an important strategy to study the pathogenesis of schizophrenia, identify potential drug targets and test new drugs for new antipsychotic treatments. Recent discoveries of susceptibility genes for schizophrenia offer opportunities to develop a new generation of genetic mouse models of schizophrenia based on the genetic susceptibility. Most of the susceptibility genes have been linked or associated with cognitive dysfunction, a symptom relatively resistant to current antipsychotic treatments and viewed as a core symptom for schizophrenia. Unlike hallucinations and delusions, some domains of cognitive function, such as working memory, can be directly tested in mouse models. To mimic cognitive dysfunction, we overexpressed human catechol-o-methyl transferase (COMT) –val transgene, the high risk allele of the COMT gene for schizophrenia, in inducible tissue-specific transgenic mice. The COMT-val transgenic mice were analyzed in a radial arm-maze test. Our results demonstrated that the working memory was impaired in the COMT-val transgenic mice with high level of COMT over-expression in pyramidal cells of frontal cortex. The transgenic mice showed normal locomotor activity, but slower response to the baited food rewards in the maze. The working memory deficit and slower response are typical cognitive symptoms in schizophrenia. Therefore, the COMT transgenic mouse model is a valid model for cognitive dysfunction resulted from high activity of COMT in frontal cortex and the results suggest that a COMT inhibitor might be an effective drug for the treatment of cognitive dysfunction in schizophrenia. For other susceptibility genes, knocking out the gene by homologous recombination or knocking down the gene by siRNA silencing should be used if the lower activity allele is the risk allele. The new generation of the genetic mouse models could shed light on the etiology of schizophrenia and lead us to new hypotheses, novel diagnostic tools, and a more effective therapy.

IDENTIFYING SUBTYPES IN PSYCHOSIS USING GENE EXPRESSION MICROARRAY STUDIES

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Defining psychiatric phenotypes is primarily the result of clinical consensus rather than empirical research. Phenotypic variability and extensive genetic heterogeneity have been confounding factors in genetic linkage and association studies in schizophrenia and bipolar disorder. Most researchers consider schizophrenia and bipolar disorder different psychiatric disorders. However, the data from the Stanley brain collection indicates there is considerable overlap in abnormal findings between the two disorders, e.g., 15 out of 23 neurochemical abnormalities overlapped in one meta-analysis. These findings have contributed to an ongoing re-evaluation of the traditional dichotomy. Bipolar disorder with psychotic features may be closely related to schizophrenia suggesting psychotic features may be a useful categorical factor to distinguish psychiatric patients. In the present study, we have categorized psychiatric patients into two groups based on psychotic features. We have analyzed the gene expression microarray data of the patients that is available in the Stanley Medical Research Institute (SMRI) online genomics database (www.stanleygenomics.org). The SMRI online genomics database contains 12 microarray studies and is derived from two sets of brain samples, the Stanley Array collection (105 subjects) and the Stanley Consortium collection (60 subjects). Using microarray data analysis software, we have conducted a variety of analysis such as class comparison, class discovery and class prediction between psychosis and non-psychosis groups. We have identified subtypes of patients in the psychosis group based on cluster analysis and principal component analysis. Detailed demographic factors were analyzed by analysis of covariance and quantitative trait analysis in order to examine confounding effects. Biological pathways that were most significantly altered in the psychosis group included growth factor, energy metabolism and metallothionein-related pathways. Analysis of biological pathways and gene expression profile between different subtypes of psychosis were also conducted. In conclusion, using psychotic features as a categorical factor increases the power of analysis and by identifying subtypes in psychosis we may identify novel pathways and genes that are involved in psychosis. These findings may contribute to our understanding of the etiology of psychosis and to the development of novel targets for drug discovery in the future.

NEUREGULIN-ERBB SIGNALING IN DEVELOPMENT AND PLASTICITY: MODELING SCHIZOPHRENIA NEUROPATHOLOGY

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Schizophrenia is a devastating psychiatric disease that affects 0.5-1% of the world's adult population. The hypothesis that this disease is a developmental disorder of the nervous system with late onset of its characteristic symptoms has been gaining acceptance in past years. However, the anatomical, cellular and molecular bases of schizophrenia remain unclear. Numerous studies point to alterations

in different aspects of brain development as possible causes of schizophrenia, including defects in neuronal migration, neurotransmitter receptor expression, and myelination. Recently, the Neuregulin-1 (NRG1) gene has been identified as a potential susceptibility gene for schizophrenia, and defects in the expression of erbB3, one of the NRG1 receptors, have been shown to occur in the prefrontal cortex of schizophrenic patients, suggesting that NRG1-erbB signaling is involved in the pathogenesis of schizophrenia. These findings open new possibilities to think about the molecular and cellular basis of schizophrenia in more mechanistic terms.

T CELL RESPONSES IN SCHIZOPHRENIA: STIMULATION WITH ANTI-CD3 LEADS TO LOWER PROLIFERATIVE RESPONSES IN PATIENTS, WITH CHANGES IN GENE AND PROTEIN EXPRESSION PROFILES

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Functional cellular responses in schizophrenia were investigated using peripheral blood T cells with a view to establishing whether physiological differences between patients and controls existed in peripheral tissue and to use this system to investigate underlying pathophysiology. T cells provide a good model in which to investigate cellular function as they are easy to isolate with high purity and can be obtained in a minimally invasive fashion. T cells stimulation can be carried out in vitro by mimicking T cell receptor signals via cross linking of cell surface CD3. This results in proliferation and cytokine secretion, involving signalling, protein synthesis and trafficking and gene transcription. Any global abnormalities in these physiological processes which may underlie the pathophysiology of schizophrenia may be traced using this system. T cells from both treated (n=39) and untreated (n=11) schizophrenia patients were found to have significantly lower proliferative responses to stimulation, compared to healthy controls (n=32). Gene expression analysis in freshly isolated T cells from six minimally treated patients and six controls was carried out using whole-genome CodeLink microarrays to identify genes potentially involved in the abnormal proliferative responses. Pathway analysis showed prominent transcript changes in categories pertaining to cell cycle machinery, intracellular signalling, oxidative stress and metabolism. Intriguingly, chromosomal location analysis of genes significantly altered between schizophrenia and controls revealed clusters at 1p36, 1q42 and 6p22, which have previously been identified as strong susceptibility loci for schizophrenia. Our results suggest that physiological differences between schizophrenia patients and controls can be detected in peripheral tissues. This work is supported by the Stanley Medical Research Institute and NARSAD

ROLES OF DISC1 IN ADULT HIPPOCAMPAL NEUROGENESIS

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Schizophrenia has been proposed as a disorder of neurodevelopment with onset in adulthood. Little is known about the specific roles of schizophrenia susceptibility genes in the adult brain. Disrupted-in-schizophrenia-1 (DISC1), a gene implicated in familial schizophrenia, is highly expressed in the dentate gyrus of the hippocampus throughout hippocampal development and in adulthood. Previous studies have shown that depletion of endogenous DISC1 impairs neurite outgrowth in vitro and proper development of the cerebral cortex in vivo. In the dentate gyrus of the adult hippocampus, new granule neurons are continuously generated from adult neural stem cells throughout life in all mammals examined, including humans. We have recently characterized the neuronal developmental process of newborn granule neurons in the adult mouse hippocampus, from neuronal fate specification of adult neural stem cells to migration, dendritic development and synaptic integration of their neuronal progeny. Interestingly, while adult neurogenesis recapitulates neuronal developmental process in a mature central nervous system environment, the neuronal integration process for adult born neurons is significantly prolonged compared to those during fetal development. This offers a unique opportunity to examine in detail the sequential events involved in neuronal development. We have also developed retrovirus-based strategies for "loss-of-function" and "gain-of-function" in vivo analysis of genes of interest in individual newborn neuron by morphological and functional analysis. We are currently examining the role of DISC1 in the neuronal morphogenesis, migration and synaptogenesis of new neurons in the adult mouse brain in vivo. Our study may reveal biological functions of DISC1 in adult neurogenesis and the etiology of schizophrenia and related psychiatric disorders.

LOCOMOTION, EXPLORATION, ANXIETY AND SENSORIMOTOR GATING IN THE EGF-LIKE DOMAIN NEUREGULIN 1 MUTANT MOUSE

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The association between Neuregulin 1 (NRG1) and schizophrenia has been well replicated, and its involvement in neural development is consistent with a role in susceptibility to this devastating illness. Alternative splicing of NRG1 can produce at least 15 different isoforms each containing an EGF-like domain, which alone is sufficient to activate ErbB receptor tyrosine-kinases. Nrg1 mutation affecting this EGF-like domain alters neural development and leads to a hyperactive phenotype in adult mice. However, these mutant mice have not been examined extensively for behavioural domains such as anxiety, exploration and sensorimotor gating. We applied a comprehensive behavioural phenotyping strategy for the domains motor activity, exploration, anxiety, and sensorimotor gating in a heterozygous EGF-like domain Nrg1 mutant animal model (Nrg1 EGF HET). Wild type-like and Nrg1 hypomorphic mice of 4-6 months of age were tested in paradigms such as the open field, the Light-Dark test, the elevated plus maze, the hole board task, and baseline and drug-induced (saline, amphetamine, and MK801 treatment) prepulse inhibition (PPI). As anticipated, Nrg1 EGF HET mice were hyperactive, showing increased locomotion across various tests. However, this increased activity did not extend to exploration-like behaviours, as the total number of head dips in the hole board task and rearing frequency in different paradigms was similar for Nrg1 EGF HETs and their wild type-like littermates. A trend towards decreased anxiety levels in Nrg1 EGF HET mice did not reach significance. Baseline sensorimotor gating of Nrg1 hypomorphs was wild type-like but treatment with amphetamine resulted in subtle impairments in prepulse inhibition. Nrg1 EGF HET mice are hyperactive compared to

wild type-like littermates but do not show major differences in exploration or anxiety. Nevertheless, sensorimotor gating of Nrg1 mutants was impaired after treatment with amphetamine. Further research has to investigate if the Nrg1 EFG HET model is a valid tool for schizophrenia research – especially compared to various animal models for several other Nrg1 isoforms.

PRENATAL INFLUENZA INFECTION AND ABNORMAL BRAIN DEVELOPMENT: A DNA MICROARRAY STUDY IN MOUSE

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Maternal viral infection is known to increase the risk for schizophrenia and autism in the offspring (Patterson, 2002). A recent microarray-based study in our laboratory showed involvement of a number of brain genes at day 0 (birth) in offspring of mothers infected at E9 of pregnancy (Fatemi et al, 2005). We sought to pursue the effects of E9 infection on brain genes, at postnatal days 35 or 56, in virally-exposed (N=3) or sham-infected controls (N=3) offspring. Brains were homogenized and subjected to DNA microarray, SDS-PAGE and western blotting. Microarray analysis of virally-exposed mouse brains showed significant ($p<0.05$) two-fold upregulation of 104 genes and downregulation of 103 genes in cerebellum and upregulation of 52 genes and downregulation of 21 genes in neocortex vs. controls in day 35 mice. At day 56, microarray analysis showed significant ($p<0.05$) two-fold upregulation of 27 genes and downregulation of 23 genes in cerebellum and upregulation of 13 genes and downregulation of 11 genes in neocortex vs. controls. Protein analysis showed significant ($p<0.05$) changes in levels of several important proteins such as aquaporin 4, nucleolin, connexin 43 and microcephalin in brains of exposed mice. These results implicate long-term effects of viral infection in utero on brain development in the mouse progeny. The generous support by the Jonty Foundation, Kunin Fund of St. Paul Foundation and the National Institute for Child Health and Human Development (5-R01-HD046589-02) to S.H.F. is greatly appreciated. References: 1. Patterson PH, 2002, Curr. Opin. Neurobiol. 12(1):115-118. 2. Fatemi SH, et. al., 2005, Synapse 57(2):91-99.

SP4 GENE IN HIPPOCAMPAL DEVELOPMENT AND ITS RELEVANCE TO HUMAN PSYCHIATRIC DISORDERS

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The hippocampus plays central roles in the formation of contextual memory and sensorimotor gating, a putative endophenotype for schizophrenia and other related psychiatric disorders. Reduced hippocampal volume has recently been identified as an important susceptibility factor for schizophrenia, bipolar disorder, and major depression. Nevertheless, the underlying molecular pathways that link hippocampal abnormalities with sensorimotor gating deficits remain unclear. Hypomorphic Sp4 mice, in which the Sp4 gene expression is partially reduced, display deficits in memory and sensorimotor gating associated with hippocampal vacuolization. The sensorimotor gating deficits are evidenced by consistent reductions in prepulse inhibition of startle. The expression of neurotrophin-3, which has been found to be critical for both adult neurogenesis and spatial memory, is down-regulated in Sp4 dentate granule cells. On the other hand, the Sp4 null mutant adult mice displayed fewer dentate granule cells, and the reduced number of dentate granule cells appeared to result from the disorganized proliferative zone during postnatal development of the dentate granule layer. The hippocampal vacuolization observed in the hypomorphic Sp4 mice was also verified in the Sp4 null mutant mice. Therefore, the Sp4 mediated genetic pathway is critical for the functional integrity of the adult hippocampus. Our human association studies on triad families (NIMH Genetics Initiative for Bipolar Disorder first, second, third, and fourth-wave pedigree collections) suggested a significant association of human SP4 gene with bipolar disorder. To expand our studies in different ethnic population, we examined the same group of SNPs in Chinese schizophrenia triad families. A significant association of SP4 gene with Chinese schizophrenia was also found at the same single SNP, but a different allele. Therefore, the studies of Sp4 transgenic mouse could provide novel insights for our understanding of hippocampal development, sensorimotor gating, and human psychiatric disorders. Supported by MH073991.

GENOTYPIC EFFECTS ON EPISODIC MEMORY: EXPERIENCE FROM BDNF, G72, AND GRM3

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Cognitive genomics is an important tool for parsing cognitive processes. In this presentation I will outline the effects of three genes on the neurobiology of episodic memory: BDNF, G72, and GRM3. it For BDNF data will be presented in large groups of normal controls, schizophrenic patients, and siblings of schizophrenic patients that show that a BDNF polymorphism 1.) affects intracellular trafficking of BDNF; and 2.) affects verbal episodic memory in behavioral testing. In sum, these results represent a mechanistic account of a role for BDNF in human memory and hippocampal function, and suggest that the val/met polymorphism produces these effects by altering intracellular trafficking and secretion of BDNF. A recently discovered gene, G72, was found to be associated with schizophrenia and with bipolar disorder, possibly because of an indirect effect on NMDA neurotransmission. In principle, if G72 increases risk for psychosis by this mechanism, it should also impact on cortically based cognitive and neurophysiological functions associated with NMDA signaling. Diagnosis by genotype interaction effects for G72 "SNP 10" were significant for cognitive variables assessing working memory, attention, and episodic memory, such that in the schizophrenia group an exaggerated allele load effect in the predicted directions was observed (i.e., epistasis was present). These data provide evidence that select SNP variations in the G72 gene region increase risk of cognitive impairment in schizophrenia. The nature of this impairment is broadly consistent with findings from a variety of studies of NMDA-based signaling cascades in excitatory neurotransmission. GRM3, a metabotropic glutamate receptor modulating synaptic glutamate, is a promising schizophrenia candidate gene: the A allele of SNP 4 was over transmitted to probands. This allele was associated with poorer performance on cognitive intermediate phenotypes involving verbal fluency and free recall in a list learning task. This pattern of results suggest retrieval failure that might be based on "prefrontal" processes. This allele also predicted lower prefrontal NAA, an in vivo MRI measure of tissue glutamate. These convergent data suggest GRM3 variants have an impact on prefrontal contributions to episodic memory function.

THE GENETICS AND PHARMACOGENETICS OF NEUROCOGNITION IN PATIENTS WITH SCHIZOPHRENIA

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Here we report an analysis of the effect of the atypical antipsychotic drugs olanzapine, quetiapine, risperidone, and ziprasidone, and the typical antipsychotic perphenazine. As part of the CATIE trial of antipsychotic effectiveness the patients were randomly assigned to one of the five drugs and measurements were taken at baseline and then at regular time points during an 18-month study period (over which the drug may be changed up to three times). We are using neurocognitive measurements taken at baseline and after two months of treatment with the first assigned drug. The candidate genes were selected based on drug modes of action and suspected determinants and modifiers of adverse reactions and cognitive deficits. The 3072 selected SNPs include both putative functional variants and tags, and have been genotyped with Golden Gate assays for approximately 750 CATIE samples. The neurocognitive battery comprised 10 tests that covered aspects of verbal fluency, working memory, verbal learning and memory, social cognition, motor function, attention, and executive function. Here, primary genetic discovery is carried out on new variables that emerge from a principal component analysis. All variants that show association with leading principal component analysis axes are then assessed for association with individual tests scores to ease replication in other cohorts, and to elucidate their molecular cognitive role. The results of the CATIE trial are compared to those observed in a separate cohort of 500 patients with a detailed neurocognitive battery in an effort to identify gene variants with consistent effects on both the improvement of neurocognition in response to treatment and to baseline neurocognitive deficits.

CHALLENGES IN CONSTRUCTING AND PHENOTYPING MUTANTS RELEVANT TO PSYCHIATRIC DISORDERS

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Defining how we harness the power of animal models in investigative strategies designed to understand and manipulate candidate causal factors for mental illness remains a critical challenge. The fact that mental illnesses are uniquely human disorders does not negate the feasibility of developing and using relevant animal models, but only defines the challenge and sets the limitation of an animal model. The generation of bona fide mouse models for most psychiatric disorders is highly unlikely due to constraints imposed by the complex plygenic nature of human psychiatric disorders, the magnitude and pattern of change during hominid brain evolution and by bthe limitations of the clinical diagnosis. The impossibility of developing an animal model that captures the totality of any given complex psychiatric phenotype argues for a more piecemeal recreation of components of the disorder. In this context, mouse models of "susceptibility genes" identified through forward genetic studies in humans hold tremendous promise in understanding the function of a gene in the context of simple cellular pathways, or even at the level of simple neural circuits and behavior. However, there are several important factors that need to be considered for the generation of such models and for the design and interpretation of their analysis. For example, one important consideration in developing genetic mouse models of psychiatric disorders has to do with the nature of the susceptibility allele. At present, given our restricted knowledge about the functional impact of human genetic variation, relatively accurate mouse models of risk alleles are feasible for only a small number of susceptibility genes. Traditionally, animal models of susceptibility genes are analyzed through behavioral assays. Indeed, much of the skepticism toward animal models of psychiatric disorders arises from the unfounded expectation that such animals should convincingly model hallmark features of the human psychiatric disorders such as grandiosity, delusions, hallucinations, or depression. Mechanistic insights into the nature of contribution of susceptibility genes cannot be gleamed by behavioral observation alone, but rather obtained from a combined approach that begins at the molecular and cellular levels (which are more likely to be evolutionarily conserved) and culminates at the systems and behavioral levels that can be employed to dissect complex phenotypes into quantifiable components.

THE TRANSMEMBRANE DOMAIN NEUREGULIN 1 MUTANT MOUSE – A VALUABLE TOOL FOR SCHIZOPHRENIA RESEARCH?

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Neuregulin 1 (NRG1) is one of the most promising susceptibility genes for schizophrenia and is known to influence neurodevelopmental processes in the CNS potentially related to schizophrenia. The neurodevelopmental theory of schizophrenia suggests that interactions between genetic and environmental factors are responsible for biochemical alterations leading to schizophrenia. To investigate these interactions, we applied a comprehensive behavioural phenotyping strategy for the domains motor activity, exploration, and anxiety in a heterozygous transmembrane domain Nrg1 mutant animal model (Nrg1 TM HET). We examined the effect of "age" (3-4 months vs. 4-6 months) and of housing conditions in Nrg1 mutant mice behaviourally. Furthermore, we analysed the expression profile of different neurotransmitter systems (e.g. serotonergic receptors) in wild type-like and Nrg1 hypomorphic littermates. We discovered an age-dependent exploration- and locomotion-related hyperactive phenotype in Nrg1 hypomorphic mice. Minimal environmental enrichment (EE) had a significant impact on the behavioural performance of wild type-like and Nrg1 TM HET mice, although Nrg1 mutant mice were more sensitive to the locomotion-stimulating and anxiety-decreasing potential of EE. Anxiety levels appear to be moderately reduced in Nrg1 TM HETs. We also found moderate changes in the expression profile of certain neurotransmitters (e.g. 5-HT2A) for Nrg1 TM HET mice. Mice mutant for the transmembrane domain Nrg1 isoform are an important tool to investigate the interaction between genetic and environmental factors of schizophrenia. Interactions are consistent with the pathophysiology of schizophrenia and the neurodevelopmental theory.

CHARACTERIZATION OF TRANSCRIBED HERV-W ELEMENTS *IN VITRO* AND *IN VIVO*

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Aberrant expression of elements related to the human endogenous retrovirus (HERV)-W family has previously been associated with the first manifestation of schizophrenia. Our current studies aim to

identify the disease-associated HERV-W elements and investigate possible mechanisms regulating their transcriptional activities. Using specific real-time PCR assays, *gag* transcripts mapped to a HERV-W element on chromosome 11q13.5 were detected at 1.6-fold elevated levels ($p < 0.05$) in peripheral blood mononuclear cells of recent-onset schizophrenia patients as compared to healthy controls. In cell cultures, certain HERV-W elements, including that on 11q13.5, were transactivated by influenza A/WSN/33 virus in some but not all cell-lines investigated. The HERV-W element on 11q13.5 is inversely inserted in the second intron of the gene encoding the putative protein PTD015. Strand-specific reverse transcription revealed the presence of transcripts from both strands of this HERV-W element. Correlations between the levels of transcripts encoding PTD015 and HERV-W gag transcripts in patients suggest coregulation. In conclusion, specific HERV-W elements appear to be activated in patients suffering from the first manifestation of schizophrenia and related disorders. *In vitro,* the levels of such transcripts may be modulated by infectious agents. The functional significance of expression of some HERV-W elements may be related to regulatory functions of the RNA.

THE POINT MUTATION IN DISC1 GENE IS ASSOCIATED WITH SCHIZOPHRENIA-LIKE BEHAVIOR AND NEUROANATOMICAL ABNORMALITIES IN MICE

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DISC1 (disrupted in schizophrenia 1) is a strong gene candidate for such psychiatric disease as Schizophrenia and Depression, identified in several independent human populations (Millar et al 2002). We found one missense mutant allele that introduces amino acid substitutions (L100P) to the Disc1 protein. Carriers of L100P mutation have normal levels of Disc1 protein in the brain, but exhibit behavioral and neuroanatomical abnormalities relevant to schizophrenia. L100P Disc1 mutants exhibited the pronounced Pre-pulse Inhibition (PPI) and Latent Inhibition (LI) deficits, which were improved by clozapine. Importantly, PPI deficit was completely reversed by rolipram (an inhibitor of phosphodiestirase 4B (PDE4B), protein interacting with Disc1). Hence, the pharmacological data indicate the altered Disc1-PDE4B interaction in L100P Disc1 mutants. In addition to the PPI and LI deficits, L100P Disc1 mutants display the pronounced hyperactivity in the open field during all tested time intervals. In parallel with behavioral data, magnetic resonance imaging (MRI) revealed reductions in overall brain size of 13 % in both hetero- and homozygous L100P mutants, which were coupled with tissue shrinkage in the cortex, enthorinal cortex, thalamus and cerebellum. The similarity in magnitude of the neuroanatomical and behavioral abnormalities suggests that these effects are related. Our results on mouse model support the notion that amino acid substitutions in Disc1 can increase the risk for schizophrenia with changes of the brain structures.

ASSOCIATION BETWEEN THE NEURONAL PAS GENE, NPAS3, AND SCHIZOPHRENIA

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We previously identified *NPAS3*, a gene on human chromosome 14, as a potential susceptibility gene for schizophrenia. A proband with schizophrenia and her affected mother were identified as carriers of a translocation between chromosomes 9 and 14 that disrupted the *NPAS3* gene(Kamnasaran et al, Med Genet. 2003, **40**:325). NPAS3 belongs to the bHLH-PAS (basic helix-loop-helix-Per-Arnt-Sim) family of transcription factors that have regulatory functions in an array of biological processes: circadian rhythms, cell differentiation, and nervous system development and function. bHLH-PAS proteins have both DNA and protein binding domains, and function as homodimers, and as hetero-dimers with other family members. The *NPAS3* gene is composed of twelve exons, and these were sequenced in fourteen patients with an affected first-degree relative and two controls to identify potential disease-associated mutations in patients. We have examined the association of the observed patient-specific single nucleotide polymorphisms (SNPs) in the *NPAS3* gene with schizophrenia. To date, DNA samples from 75 patients with schizophrenia (DSMIII or DSMIV) and 54 ethnically matched, healthy controls have been analyzed. Synonymous and non-synonymous changes found only in the patient group were then investigated in the remaining samples. Two potentially deleterious changes were consistently observed in patients. The first SNP appears to be in linkage disequilibrium with two additional SNPs, and was observed at a significantly higher frequency in the patient group and may disrupt an important functional domain ($p<0.03$). A second SNP may cause an RNA splicing defect and was observed only in the patient group. These changes may be pathogenic or be in linkage disequilibrium with a disease-causing variant elsewhere in the gene. Studies are underway to assess the consequences of these changes on NPAS3 function. In our small scale study, we have identified a positive association between four SNPs in the *NPAS3* coding sequence and schizophrenia. The changes may directly affect the production of functional NPAS3 and contribute to the development of schizophrenia in a subset of patients.

COGNITIVE FUNCTION IN SCHIZOPHRENIA AND EFFECTS OF NEUREGULIN 1

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Background: Several recent studies have found an association between Neuregulin 1 (NRG1) and schizophrenia. NRG1 is involved in the expression and metabolism of NMDA glutamate receptors and negative symptoms of schizophrenia have been linked to glutamate dysfunction. Negative symptoms have also been linked to poor cognitive function and worse clinical outcome. The aim of this study is to test the effects of the at-risk NRG1 haplotype on cognitive function in schizophrenia. Methods: Patients and controls were selected on the basis of their genotype and were divided into two groups based on their carrier status of the Icelandic " 5 SNP at-risk" core haplotype of Neuregulin, 77 schizophrenic patients (38 with and 39 without the "at-risk" haplotype) and 76 healthy controls (28 with and 48 without the "at-risk" haplotype). A comprehensive neuropsychological test battery assessed cognitive domains, such as memory, executive function and attention. Results: Results show no significant difference in performance on neuropsychological tests in schizophrenic patients with the "at-risk" haplotype compared with patients without the "at-risk" haplotype. There was although a non-significant trend towards the schizophrenic patients with the "at-risk" haplotype showing worse performance on most of the tests. There was not found a significant difference in performance on tests when the control group with the "at-risk" haplotype was compared with the other control

group. Conclusion: The results indicate that NRG1 function does not significantly influence cognitive function, neither in schizophrenic patients nor healthy controls. A trend towards poorer outcome of schizophrenic patients with the "at-risk" haplotype suggests that this needs to be studied further.

APPLYING AN OLFACTORY NEUROEPITHELIAL MODEL OF NEURODEVELOPMENT TO FAMILIAL SCHIZOPHRENIA

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Biopsy of olfactory neuroepithelium provides an opportunity to examine the dynamic process of neurodevelopment in living neural tissue from individuals with neuropsychiatric disorders. Previous studies showed that olfactory cultures from individuals with schizophrenia (SZ) have increased cell proliferation compared to cultures from healthy controls, and expression microarray analysis of olfactory biopsies revealed alterations to the cell cycle, neurogenesis and nucleic acid metabolism pathways in SZ. However, olfactory biopsies are limited in their usefulness for gene expression studies of neurodevelopment because they contain multiple cell types, including both neural and non-neural (e.g. glandular, vascular) cells, and each cell type has its own unique gene expression profile. Recently, a method has been developed to generate clusters of olfactory neural precursor cells or 'neurospheres'. These neurospheres can self-replicate, give rise to populations of neurons and glial cells and are free of contaminating non-neural cell types. Using this method and olfactory biopsies from 4 unaffected individuals undergoing scheduled rhinological surgery we have successfully generated neurosphere cultures. Neurospheres were harvested from each sample, cryopreserved and stored at – 80 °C for up to 4 weeks. Cryopreserved neurospheres were reanimated in serum-free medium containing either 50 ng/ml bFGF and 25 ng/ml EGF (proliferating-condition) or 5 ng/ml IGF-I (differentiating-condition). After 4 days under proliferating conditions our cultures generated new neurospheres, while under differentiating conditions new neurons (β-tubulin III-positive) were seen. We are currently applying this method to a familial SZ population that show significant association to the CAPON gene. Using Affymetrix Exon Arrays we will assess differences in gene expression in these neural precursor cells between SZ and unaffected first-degree relatives carrying high and low risk CAPON haplotypes respectively. Advances in these techniques open the door to testing the impact of specific stressors on multiple stages of nerve and/or glial cell development. The results promise to increase our understanding of the pathogenesis of SZ. We gratefully acknowledge the support of the Canadian Psychiatric Research Foundation, Centre for Addiction and Mental Health, NARSAD, Canadian Institutes of Health Research and the Canada Research Chairs Program.

TESTING GENE-ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA GENESIS

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To investigate the etiology of schizophrenia (SZ), we have used models based on exposure to putative infectious risk factors and host gene variation. Exposure to Herpes Simplex viruses (HSV1 and HSV2) and cytomegalovirus (CMV) was estimated simultaneously, with variation in genes localized to SZ linked regions. We used a pathway-oriented approach to focus separately on genes in the IL-18 signaling pathway and HLA genes (n = 8 genes). Representative 'tag' SNPs were analyzed in two independent samples: Pittsburgh, 478 cases, 501 controls, and available parents; Baltimore, 272 cases, 108 controls. The results for the two gene pathways were as follows: IL18 studies: Nominally significant associations with SZ were noted in the Pittsburgh sample with 5 SNPs at *IL18RAP, IL18R1, IL-18,* and *IL12B.* At *IL18RAP,* the C allele of rs2272127 was associated with SZ, while the G allele was over-represented among patients seropositive for HSV1. Similar patterns were observed at rs11465702, which is correlated with rs2272127. HLA studies: Significant associations were noted at 4 SNPs at *MICB* (Pittsburgh sample). A significant association with seropositivity for HSV1 was also noted at rs1051788, a *MICB* exonic SNP among unaffected parents but not SZ cases. In agreement with the Pittsburgh results, the association with HSV1 seropositivity at rs1051788 was present among controls but not cases. The association with SZ was not detected in the smaller Baltimore sample. In conclusion, we have detected suggestive associations with SZ, as well as seropositivity. The pleiotropic effects at some SNPs noted here suggest a plausible, testable hypothesis linking HSV1 exposure with IL-18 signaling and *MICB* variation in SZ pathogenesis. Replicate studies are warranted.

MAPPING GENE EXPRESSION IN SCHIZOPHRENIC BRAIN

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A number of risk factors have been identified to contribute to the development of schizophrenia. Yet, it is possible that genes that modify the dynamics of the central nervous system, causing the disease, act in different times of brain development, modifying other genes and generating a cascade of effects. In this study, we have studied three candidate genes – S100B, NRGN and MT3 - previously selected by SAGE (Serial Analysis of Gene Expression). The S100B protein is highly found in brain and is primarily present in astrocytes. It accumulates during the maturation of the mammalian brain and promotes viability, neurite extension and morphological differentiation in cultured neuronal cells. Neurogranin is an important protein involved in signal transduction and is an upstream regulator of calcium and calmodulin. This protein is believed to play a role in processing and transmitig information. The gene encoding the ion binding protein MT3 was originally designated growth inhibitory factor. It is involved in different biological signaling pathways. In order to study the expression of S100B, NRGN and MT3 in schizophrenic and normal brains we have evaluated them in pre-frontal cortex, frontal cortex and temporal cortex of schizophrenic patients and controls. The gene expression analysis has been developed by Real-time PCR using 3 endogenous controls (ACTB, GUSB and BCR). From these preliminary results, we have concluded that the expression of these genes varies from region to region of the brain. The gene expression profiles of S100B in pre-frontal, frontal and temporal cortex of schizophrenic patients tends to be lower in patients when compared to controls, although it was not statistically different. Considering the gene expression of NRGN, we observed it was lower in schizophrenic patients in frontal cortex and higher in pre-frontal and temporal cortex, but it was not statistically different. Finally, the gene expression of MT3 is almost the same (but tends to be a little higher) in the frontal cortex of schizophrenic patients when compared to

controls and lower in the pre-frontal cortex and temporal cortex. The values was not statistically different either. The results confirm our findings using SAGE, but the number of patients and controls is quite low until now. We have been studying the expression of other previously selected genes to identify their expression across the schizophrenic brain. Acknowledgements: ABADHS/FAPESP/CAPES/CNPq.

RT-PCR ANALYSIS OF NEUREGULIN-1 ISOFORMS IN THE DORSOLATERAL PREFRONTAL CORTEX AND HIPPOCAMPUS IN SCHIZOPHRENIA

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Several studies identified neuregulin-1 gene (NRG-1) as a candidate gene for schizophrenia. Data showed that NRG-1 single nucleotide polymorphisms may be regulatory, affecting disease susceptibility by altering NRG-1 isoform expression. Aim of the present study was to quantify mRNA expression of type I, II and III NRG-1 isoforms, as well as of total NRG-1 in the dorsolateral prefrontal cortex and hippocampus. Postmortem BA9, BA10 and hippocampal tissues were collected from schizophrenic patients and matched healthy controls. Expression levels of β-actin and GAPDH were used as internal controls. Total RNA was isolated using TRIzol. Commercially available and verified primer sets were used for β-actin, GAPDH and NRG-1, while the primers used for NRG-1 isoforms type I, II and III were replicated as described elsewhere. mRNA quantification was performed using SYBR green I real-time RT-PCR. In BA10 there was no significant difference of NRG-1 total gene expression between the two groups. Type I isoform expression was however significantly reduced in schizophrenics compared to controls when normalized with both β-actin and GAPDH (multivariate: p=0.046), while type II isoform expression was significantly increased in schizophrenic patients when normalized with both β-actin and GAPDH (multivariate: p=0.002). No significant differences were observed in BA9 and hippocampus. This data indicates that differential expression of NRG-1 isoforms in BA10 of schizophrenic patients might be implicated in the molecular pathology or may be the result of a cascade reaction in the pathophysiology of schizophrenia.

SCHIZOPHRENIA-LIKE PHENOTYPES DISPLAYED BY GPR88 KNOCK-OUT MICE: BEHAVIORAL AND NEUROCHEMICAL PROFILE

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The orphan G protein-coupled receptor (oGPCR), GPR88, is expressed predominantly in human and mouse nucleus accumbens and striatum (Mizushima, et al., Genomics 69:314, 2000), brain regions that are implicated in the pathophysiology of schizophrenia (SZ) and the modes-of-action of antipsychotic drugs. Interestingly, GPR88 was identified via transcriptional profiling as a gene whose expression is altered in rats treated with lithium or valproate (Ogden, et al., Mol. Psychiatry 9:1007, 2004; Brandish et al., Neuron 45:861, 2005). Thus, the potential for GPR88 to be involved in the pathophysiology of and/or the response to therapy for SZ and bipolar disorder (BPD) makes it an interesting candidate for further evaluation. The performances of GPR88 knockout (KO) mice were compared to wild type (WT) animals in behavioral assays that are models for the endophenotypes of schizophrenia. GPR88 male and female KO mice displayed decreased prepulse inhibition of the startle response (PPI) relative to the WT mice. This PPI deficit was normalized by the first-generation anti-psychotic haloperidol and second-generation drug risperidone. In the apomorphine-induced climbing and stereotypy assay, KO mice exhibited more climbing and stereotypic behavior at a 0.3 mg/kg dose of apomorphine than the WT mice. In addition, the response of GPR88 KO mice to the locomotor activity-stimulating effects of amphetamine was greater than that produced by the WT mice. The GPR88 mice were also more sensitive to haloperidol-induced catalepsy. In order to investigate molecular mechanisms that underlie the apparent elevated dopamine (DA) responsiveness observed in the behavioral assays, a series of neurochemical and biochemical studies were conducted. In vivo microdialysis measurements in the striatum revealed significantly lower baseline DA levels in the KO mice compared to WT, while KO and WT animals exhibited a similar degree of DA release when amphetamine was administered. In ex vivo tissue DA and DA metabolite determinations, no differences between KO and WT mice in the levels of DA and DA metabolites in the striatum were detected. Based on the data reported here on the behavioral profile of GPR88 KO mice in models of schizophrenia endophenotypes, the ability of antipsychotic drugs to normalize the schizophrenia-like behavior of the GPR88 KO mice, and the neurochemical profile, the GPR88 KO mice may be useful as a novel animal model of schizophrenia.

NEURONAL PAS DOMAIN PROTEIN 3 (NPAS3) IN HIPPOCAMPAL NEUROGENESIS AND SCHIZOPHRENIA

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A family with schizophrenia has been found to carry a genetic translocation that selectively disrupts the gene for NPAS3, and we have shown that mice bearing targeted lesions in npas3 exhibit behavioral and neuroanatomical abnormalities reminiscent of certain aspects of human schizophrenia. These phenotypes include impaired social recognition, increased open-field locomotor activity, stereotypic darting behavior, reduced prepulse inhibition and decreased brain levels of reelin protein. In the hippocampus dentate gyrus, npas3-/- mice bear selectively attenuated expression of FGF receptor subtype 1, which mediates hippocampal neurogenesis, as well as selectively enriched expression of Sprouty4, a known antagonist of FGF signaling. These findings correlate with an 85% reduction in baseline adult neurogenesis in the dentate gyrus of npas3-/- mice. Whereas hippocampal neural precursor cells in npas3-/- mice significantly proliferate with electroconvulsive seizure stimulation, these cells remain unresponsive to intracerebroventricular FGF infusion. Wild type animals, however, exhibit robust hippocampal neurogenesis in response to both stimuli. Thus npas3-/- mice are selectively deficient in FGF-mediated hippocampal neurogenesis. We are currently utilizing inducible npas3-/- mice in order to eliminate npas3 in a temporally specific manner during development and adult life. The etiology and pathophysiology of schizophrenia lie in both early devel-

opmental stages and adulthood, and this novel approach will thus enable us to more rigorously explore the role of NPAS3 in hippocampal neurogenesis and schizophrenia. Aberrations in hippocampal structure and function have been well-characterized in individuals with schizophrenia, and evidence of diminished hippocampal neurogenesis has also been demonstrated in brains from patients with schizophrenia. Furthering our understanding of the role of NPAS3 in neuronal functioning may thus lead to the identification and clarification of novel molecular pathways involved in schizophrenia.

NEUROBIOLOGICAL BASIS OF BEHAVIORAL DYSFUNCTION IN SCHIZOPHRENIA: INTERACTION BETWEEN GENES AND ENVIRONMENT

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Psychiatric disorders of neurodevelopmental origin, including schizophrenia, are disabling brain disorders that likely result from complex interactions between susceptibility genes and environment during early development. Dysfunction of dopamine circuitry, including increased activity of striatal D2 receptors, has been implicated in schizophrenia's pathogenesis. In order to determine the behavioral and physiological consequences of increased D2R function in the striatum, mice with reversibly increased levels of D2Rs restricted to the striatum were recently developed. Analysis of these mice revealed behavioral deficits that endure even when D2 overexpression is restricted to prenatal development, suggesting that prenatal D2R overexpression is sufficient to produce the adult phenotype. To model the further hypothesis that the full syndromal expression of schizophrenia results from an interaction of vulnerability genes and environmental insults, especially during prenatal development, the transgenic animals were subjected to a prenatal stress treatment. Methods and results of these studies will be presented to elucidate both the behavioral changes and molecular mechanisms involved in this gene/environment interaction. This research sheds new light on how dopamine-related susceptibility genes and early environmental stress can converge to cause core symptoms in schizophrenia. New avenues for improved treatment or prevention of this disorder may emerge from these studies.

BEYOND POSITIONAL CLONING AND ASSOCIATION IN SCHIZOPHRENIA: THE SEARCH FOR CAUSAL VARIATION IN DTNBP1 AND POTENTIAL INTERACTIONS WITH GENE PRODUCTS IN THE BLOC1 AND AKT1 PATHWAYS

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We have shown association of the dystrobrevin binding protein 1 (DTNBP1) gene with schizophrenia and identified a DTNBP1 high risk haplotype (HRH) in the ISHDSF. Sequencing of the 140 Kb genomic locus on genetically independent HRH backgrounds is complete, and identifies 293 polymorphisms (86 novel) of which 261 (89.1%) can be mapped to specific haplotypes. The sequence dataset provides several insights to the DTNBP1 association data, including 1) the demonstration that published associations cluster on 3 specific haplotypes, 2) the identification of 26 SNPs (21 novel) specific to the Irish HRH, 3) the identification of 22 SNPs (2 novel) with alleles shared by all three associated haplotypes, even though one is evolutionarily distant from the others, 4) the general absence of coding variation within the gene, 5) identification of a number of evolutionarily conserved regions (ECRs) in introns and upstream regions containing identified SNPs and 6) the identification of alleles which may have been under positive selection. Multiple bioinformatic analyses are underway currently to assess functional potential of these variants, including their potential to affect interactions with other molecules. We have additionally assessed two groups of genes with potential interactions with DTNBP1, those defining the BLOC1 complex, and those related to the AKT1 cell-survival signalling pathway. Analyses of BLOC1 genes are in progress currently. AKT1 is modestly associated with broad spectrum diagnoses in the ISHDSF ($0.002 < \text{global-p} < 0.046$). We also assessed expression of genes in the AKT1 cell-survival pathway in the Stanley Foundation brain series. Although we observe few significant diagnostic group mean differences for individual loci, we observe highly significant differences in the patterns of correlated expression of these genes between controls and schizophrenia or bipolar cases ($1.34E\text{-}15 < p < 2.15E\text{-}11$, $0.007 < P < 0.044$).

MODEL SYSTEMS TOWARDS UNDERSTANDING OF SCHIZOPHRENIA NEUROPATHOLOGY: CANDIDATE GENES AND OLFACTORY BIOPSY

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It is very important to elucidate genetic and neurobiological processes for understanding of the pathophysiology of schizophrenia. Several promising susceptibility genes for schizophrenia have recently become available, including neuregulin-1, dysbindin, and DISC1. Generation and characterization of genetically-engineered mice for these genes may provide us mechanistic insight associated with the pathology of schizophrenia. Use of patient tissues is also important in addressing the pathophysiology of schizophrenia. Autopsied brains, however, may not fully reflect the disease processes, especially those linked to neurodevelopment, due to the secondary confounding factors, such as long-term medication. To overcome this issue, we will propose use of olfactory epithelium biopsied from patients. Patient neurons originated from olfactory epithelium may be an alternative strategy in building model systems for schizophrenia. I will overview the updates of both strategies, including our own data, in this presentation.

GENETIC DISSECTION OF WHITE MATTER ABNORMALTIES IN SCHIZOPHRENIA

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White matter abnormalities have been hypothesized to play a role in the pathophysiology of schizophrenia. Technical advances in brain

imaging and neuropathology have made it easier to identify these abnormalites. Furthermore, genetic studies focusing on the development of myelin-forming oligodendrocytes suggest a positive association between schizophrenia and several white matter genes, including 2', 3'-cyclic nucleotide-3'-phosphodiesterase (CNP) and oligodendrocyte lineage transcription factor 2 (OLIG2). In addition, interaction effects on disease risk between OLIG2 and CNP with ErbB4, a receptor for Neuregulin-1, have been reported. In this symposium we will provide an overview of genetics data in association with expression studies in schizophrenia that focus on the white matter and discuss how cell and animal models based on genetic data can be generated to explore possible disease pathways at the mechanistic level.

REGULATORY AND STRUCTURAL FUNCTIONING OF α7 NICOTINIC ACETYLCHOLINE RECEPTOR SPLICE VARIANTS IN SCHIZOPHRENIA

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A new therapeutic compound, the anabaseine derivative (DMBX-A), is an α7 nicotinic acetylcholine receptor (nAChR) agonist that has been shown clinically to improve auditory gating and cognitive deficits in individuals with schizophrenia. The molecular mechanisms underlying α7 cholinergic deficiencies in this disease, however, are not known. We have previously reported finding a series of splice variants of the α7 nAChR, including a novel family of variants that incorporate a 124-127 base insertion between exons 4 and 5 of the 10-exon α7 gene. In qRT-PCR studies, a transcript containing the novel exon (α7-2) was found to be significantly down-regulated in the prefrontal cortex of individuals with schizophrenia compared to unaffected controls. We hypothesize that either structural or regulatory mechanisms are responsible for the α7-2 transcript deficit in schizophrenia. The transcript must either be (1) translated and take part in the formation of a novel subunit, or (2) transcribed as antisense mRNA that modulates α7 gene expression. We used RT-PCR and α7 gene- and strand-specific primers to isolate sense and antisense α7 transcripts from post-mortem brain samples of the Stanley Array Collection. We tested various sites within the targeted sequences as origin points of cDNA syntheses to eliminate the possibility that RNA secondary structure hindered cDNA production. We found that the splice deletion of exon 4 and the combined deletion of exons 4 and 5, both of which would encode non-membrane bound truncated peptide products, originated in substantial quantities from antisense pools of RNA. In contrast, the α7-2 and the α7 duplication (CHRFAM7A), which both translate to membrane-bound receptors with unique amino termini, originated predominantly from the protein coding, sense RNA collections. In conclusion, splice deletions of the α7 nAChR may act as antisense RNAs and control transcription through RNA masking or transcriptional interference. Conversely, the sense RNA-derived α7-2 and duplicated CHRFAM7A variants likely contribute to the physical structure of unique receptor species. These variant subunits could co-assemble with other α7 or non-α7 subunits to construct receptors with new structures, nicotine affinities and physiologies. Support was contributed by the Stanley Medical Research Institute.

PROTEOME ANALYSIS OF THE CORPUS CALLOSUM OF SCHIZOPHRENIA BRAINS

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Aim: Abnormalities within the corpus callosum (CC) are thought to affect inter-hemispheric communication and this in-turn is postulated to underlie some schizophrenia (SCZ) symptoms. A significant reduction in the size of the CC, disruptions in the axonal density and integrity has been identified in SCZ post-mortem brains (PMB). In this study we employed 2D-gel electrophoresis (2DE) proteomics approach to identify proteins differentially expressed in the genu, body and splenium of the CC that may underlie white matter abnormalities. Method: Proteins were extracted from 10 SCZ and 10 control PMB provided by the NSW Tissue Resource Centre, matched for age, gender, hemisphere and post-mortem interval. Proteins were separated by 2DE on 11cm pH 4-7 immobilized gradient strips and then on 6-15% 2D GelChips; samples run in duplicates. Protein/isoform spots were visualized using Coomassie stain. Protein profiles were analysed using Nonlinear Phoretix 2D Expression software and proteins identified using MALDI-TOF mass spectrometry (MS) on the basis of peptide mass fingerprinting. Results: We examined and compared the expression levels of approximately 800 protein spots varying in intensity in the genu, body and splenium. Differentially expressed protein/isoform spots involved in a number of cellular processes including myelination, microtubule formation and cytoskeleton regulation were identified. The results of these independent analysis and other comparisons will be presented. Conclusion: 2DE in combination with MS is an approach that can be successfully applied to identifying molecular factors that may underlie SCZ neuropathology.

ALTERED GENE EXPRESSION IN THE SUPERIOR TEMPORAL GYRUS IN SCHIZOPHRENIA

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The superior temporal gyrus (STG), which encompasses the primary auditory cortex, is believed to be a major anatomical substrate for speech, language and communication. MRI studies have consistently reported the left STG volume decreased in patients with schizophrenia compared to healthy controls and significant evidence suggests the STG plays an important role in the pathophysiology of some symptoms of schizophrenia. In this study 19000 gene oligo microarrays were used to identify altered gene expression in 7 age, gender, PMI and pH matched pairs of post-mortem STG tissue from individuals with schizophrenia and healthy controls. To confirm altered gene expression of 4 genes, Phosphoinositide-3-kinse regulatory subunit polypeptide 1 (PIK3R1), AT-binding transcription factor 1 (ATBF1), Lin-7 homolog b (Lin-7b) and calcium-independent phospholipase A2 gamma (IPLA2γ), an additional 6 matched pairs (n=13) were included in relative real-time PCR confirmation studies. The results identified a trend towards overall down-regulation in the STG in schizophrenia. Some of the genes that were significantly altered in the STG are located within the most reproduced schizophrenia linkage loci as were genes with known functions associated with schiz-

ophrenia such as neurotransmission, myelination and neurodevelopment. In conclusion this study will assist in furthering the biological mechanisms underlying the involvement of the STG in schizophrenia.

HOW GENES INFLUENCE INFECTIOUS AGENTS

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The interaction of genes and infectious agents is well known to occur in animal and human diseases. Genes may influence the infectious process either by encoding variant proteins that affect cellular attachment and penetration of the infectious agent, or by modulating the host's immunological response to the infectious agent. A literature search was carried out for specific illustrations of how genes influence infectious agents. An example of the cellular attachment mechanism is the utilization of chemokine receptors for cell attachment of HIV; some individuals with genetic CCR5 receptor variations are resistant to HIV infections. Similarly, individuals lacking the cellular receptor erythrocyte P antigen are resistant to parvovirus B19 infection and associated diseases. Genetic modulations of the host's immunological response can occur at myriad points, including T-cells, B-cells, or various mediations of inflammation. Variations in the NRAMP1 gene determine susceptibility to the bacteria causing tuberculosis. Variations in the HLA-DR2 and HLA-DR4 alleles determine susceptibility to the bacteria causing Lyme disease. Polymorphisms in a number of cytokine, chemokine, interferon, and T-cell determinants are associated with susceptibility to *Helicobacter pylori*, which causes ulcers and stomach cancer. In conclusion, genes and infectious agents have so far largely been studied separately in schizophrenia. Given what is known about other human diseases, it would seem wise to integrate these etiological approaches to contribute both to an understanding of etiology and to new approaches to treatment.

MAPPING SCHIZOPHRENIA SUSCEPTIBILITY LOCI

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The high heritability of schizophrenia has stimulated much work aimed at identifying susceptibility genes using positional genetics. As a result several strong and well-established linkages have emerged and more recently, evidence implicating individual genes has been reported and more importantly replicated. However, the complex nature of the data means that work remains before we understand precisely how genetic variation at each locus confers susceptibility and protection. While it is essential that further replications are established, the role of rare genetic variants, submicroscopic DNA copy-number variants, the respective contributions of each gene, relationships with aspects of the phenotype, the possibility of epistatic interactions between genes and functional interactions between the gene products will need to be addressed in current and future gene mapping studies.

SCHIZOPHRENIA: FROM GENE ARRAYS TO NOVEL DRUG TARGETS

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The aim of this study was to identify genes associated with prefrontal cortex dysfunction using a rodent model of the cognitive deficits of schizophrenia. Schizophrenia is a multifactorial disease involving the interaction of multiple genes of small effect and their interplay with the environment. Understanding the number of genes and their role and interaction in the pathophysiology, susceptibility to the disease or particular clinical symptoms and antipsychotic metabolism remains a crucial issue in developing novel drug strategies. The cognitive deficits of schizophrenia are considered a core feature of the disease resulting from dysfunction in the prefrontal cortex in particular. We therefore performed a global transcriptome screen using RNA isolated from the prefrontal cortex of a rodent phencyclidine (PCP) model of the cognitive deficits of schizophrenia developed in our laboratory (Cochran et al., 2003, Neuropsychopharmacology. 28 (2):265-275) and Affymetrix GeneChips. This PCP model produces a pattern of metabolic hypofunction, neurochemical changes and behavioural deficits in the prefrontal cortex that closely mirror the cognitive deficits of schizophrenia (Cochran et al., 2003 and Morris et al., 2005, Current Opinions in Pharmacology 5: 101-106). Applying sophisticated data analyses and bioinformatics, 327 differentially expressed transcripts were identified. Many of these genes map to key schizophrenia loci, have been previously implicated in schizophrenia and are consistent with current theories of prefrontal cortex dysfunction, suggesting a multifactorial neurobiological basis of the disease. Data mining of this study along with previous data from a human schizophrenia microarray allowed the identification of novel pathways that we hypothesise might be important in the cognitive deficits associated with schizophrenia.

SEARCHING FOR SUSCEPTIBILITY GENES OF SCHIZOPHRENIA USING MICROARRAY ANALYSIS

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Introduction) The etiology and genetic risk factors for schizophrenia is complex. Genome-wide gene expression analysis using DNA microarrays is a potential tool to find unanticipated susceptibility genes for complex diseases. In this study, we examined genome-wide gene expression in the postmortem brains of schizophrenia using a DNA microarray, HU133A chip (Affymetrix). Subsequently, we examined genetic association with schizophrenia depending on the result of microarray analysis. **Method)** Total RNA was extracted from the frozen blocks of orbital prefrontal cortex using ISOGEN (Nippon Gene). The purity of total RNA was evaluated by the OD260/OD280 ratio and its integrity was evaluated by denaturing agarose gel electrophoresis. Microarray analysis was performed according to the manufacturer's protocol (Affymetrix). Peripheral blood was drawn from patients and controls for the genetic study. The population consisted of 328 patients (156 males, 172 females) and 378 control subjects (162 males, 216 females). DNA was extracted from whole blood with the sodium iodide method using a DNA

Extractor WB kit (Wako Chemicals). We performed genetic association study with these samples using PCR- RFLP (restriction fragment length polymorphism) depending on the result of microarray analysis. The present study was approved by the ethics committee of Kobe University School of Medicine and the Ethical Committee for Genetic Studies of Kobe University Graduate School of Medicine. **Result and Discussion)** The genes of interest were chosen under the criteria that (1) their expression levels were less than half in the patients against controls and (2) genetic loci were on 8p, 13q or 22q that is reported to have the strong evidence for susceptibility loci for schizophrenia in meta-analysis [1]. Of 22,284 probe sets examined, 6 genes satisfied both criteria. These genes consisted of two intracellular signaling molecules, two transcription factors, one cell adhesion molecule and one nucleocytoplasmic shuttling protein. We found an association of one of these genes with schizophrenia. This gene may have be involved in the susceptibility to schizophrenia, although it needs further replication studies with larger sample size. **Reference)** 1) Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry. 2002;7(4):405-11.

HUMAN ENDOGENOUS RETROVIRUSES AND RISK OF DIABETES IN INDIVIDUALS WITH SCHIZOPHRENIA

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Human Endogenous Retroviruses (HERVs) are components of the human genome that arose by retrotransposition of viruses into the genomes of human or other primate progenitors. Many HERVs have retained the biological functions of both viruses and human genes. Activation of HERVs has been associated with alterations in immune function and with increased risk of autoimmune disorders, probably on the basis of superantigen generation. Individuals with schizophrenia are at an increased risk for autoimmune disorders, particularly diabetes. We investigated whether the human endogenous retrovirus K18 (HervK18) is associated with diabetes in this population. This HERV was selected for study because it has been shown to encode a superantigen and is located in an intron of CD48, which is involved in the immune response to external antigens. HervK18 is also located in a region of chromosome 1 that has been associated with increased risk of schizophrenia in genetic linkage studies. We measured polymorphisms in HervK18 and CD48 in 422 individuals with schizophrenia, 49 (11.6%) of whom had diabetes. We identified a G/A polymorphism at position 8146 of HervK18, which had a strong association with diabetes independent of age, race, gender, educational level, or the use of atypical antipsychotic agents (odds ratio 5.3, 95% confidence interval 2.3–12.3). This polymorphism was tightly linked with other polymorphisms in HervK18 and CD48. Preliminary studies indicate that this polymorphism is associated with the alternative splicing of CD48 exons and alterations in CD48 expression. These studies indicate that polymorphisms in an endogenous retrovirus are highly associated with diabetes in individuals with schizophrenia. The mechanism of action is likely to involve the differential expression of the encoded superantigen and of the immune response molecule CD48. The further characterization of these polymorphisms may provide a practical method for the early assessment of diabetes risk for individual with schizophrenia and for the development of effective interventions.

CONFIRMATION AND FINE MAPPING OF CHROMOSOMAL REGIONS INFLUENCING THE CORTICAL VOLUME IN MICE

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Volume reductions in two highly interconnected structures of the brain, the cerebral cortex and thalamic complex, have been associated with the pathogenesis of schizophrenia. Reduced cortical and thalamic volumes have been reported in schizophrenia subjects as well as their non-psychotic siblings. Our previous work has identified several QTLs that influence thalamus volume and cortical gray matter volume in recombinant inbred mice. One overlapping QTL was identified for both thalamus volume and cortical gray matter volume on chromosome 16, peak marker was D16Mit100. In order to confirm our previous findings and to reduce the interval length of the overlapping QTL, a recombinant inbred segregation test (RIST) was conducted. Mice were selected from two strains, BXD38 and BXD40. Both strains have a recombination in the middle of the QTL support region. The strains were intercrossed with C57BL/6J and DBA/2J and 200 F2 offspring from each of these intercross pairs were used for this study. After breeding, the offspring were genotyped at 6 markers in the proximal portion and 4 markers in the distal portion of the QTL region. Animals were perfused at 3 months of age, the body and brain weights were measured for each animal. Brain tissue was then prepared for sectioning, Nissl stained, and cortical volume was measured using Analyze 7.0. We determined the volumes of the entire cortical gray matter using point counting and Cavelieri's rule. Preliminary one-way ANOVAs for the 10 markers suggest that the QTL maps to the distal portion of the proximal half of the QTL support interval near D16Mit165. These results confirmed our previous findings of a QTL on chromosome 16 influencing cortical volume. This method of QTL fine mapping has narrowed the region of interest for genetic influence of chromosome 16 on cortical gray matter volume in BXD mice. We are currently replicating and confirming the segregation in these regions of chromosome 16 in the BXD38 intercrosses, and measuring thalamic volume in these animals.

ANALYSES BETWEEN THE GENETICS OF THE BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) AND SNAP25 GENES AND MRI OF EARLY-PSYCHOSIS PATIENTS

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Background: Schizophrenia and other psychotic disorders are a heterogeneous group of disorders, which share similar clinical and pathophysiological characteristics. The brain-derived neurotrophic factor (BDNF) and synaptomsome-associated protein of 25 kDa (SNAP25) genes are considered good candidates for early psychosis due to their significant association with schizophrenia and their importance in the postulated neurodevelopmental model. Hypothesis: The BDNF/SNAP25 gene variant(s) will predict grey matter abnormality in the brain of early psychosis patients when comparing with healthy controls, as measured by magnetic resonance imaging

(MRI). Method: Two polymorphisms in the BDNF gene, BDNF(Val-66-Met) and BDNF(HinfI), and 3 polymorphisms in the SNAP25 gene, SNAP25(DdeI), SNAP25(MnlI), and SNAP25(TaiI), were investigated for the possibility of association with total grey matter volume using 62 schizophrenic patients and 28 healthy controls. We compared allelic frequencies and genotype distributions between early psychosis patients and healthy controls, and total grey matter volume between alleles and genotypes of each of these polymorphisms. Results: In our preliminary analysis, we detected significant difference in total grey matter volume within early psychosis patients between genotype distributions of BDNF(Val-66-Met) (P=0.003) and SNAP25(DdeI) (P=0.015), as well as with the total sample in BDNF(HinfI) (P=0.033) and SNAP25(DdeI) (P=0.009). Conclusion: Our results showed an interesting correlation between genotypes and grey matter volume and required further investigation with larger samples and sub-regional grey matter volumes.

9. Neurochemistry, Clinical

PHOSPHOLIPASE-A2 (PLA2) ACTIVITY PREDICTS SHORT-TERM OUTCOME IN FIRST EPISODE PSYCHOSIS (FEP)

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The aim of our research was to investigate PLA2 activity in first episode psychosis patients and test if PLA2 activity may predict behavioral and functional outcome. Sixty-three FEP patients aged 15 to 30 and 33 healthy controls (CTL) from the North Western Metropolitan area of Melbourne, Australia were recruited into the study. Assessments of serum PLA2 (including protein amount and activity) and behavioural and functional outcome were conducted at baseline and after 12 weeks. FEP patients were either drug-naïve or commenced antipsychotic medication within 7 days of analysis at baseline. We performed cross-sectional analysis comparing the baseline PLA2 amount and activity between CTL and FEP using t tests. We performed bivariate correlational analysis of PLA2 amount and activity covariing for demographic variables, medication status, substance abuse, duration of untreated psychosis and family history of mental illness and performed a bivariate correlational analysis within the FEP group, correlating the baseline PLA2 amount and activity (dependent variables), with baseline measures, 12 week outcome measures and change scores between baseline and 12 week follow up for symptomatic and functional outcome measures (independent variables). Cross-sectional comparison revealed that the baseline activity of PLA2 was higher (t-test, p= 0.007) in the FEP compared to the CTL (713.106 ±181.505 vs 610.514 ± 157.107 arbitrary units [a.u.]). However, the baseline PLA2 amount (FEP = 79.254 ±4.833 vs. CTL = 79.997± 4.694 a.u.) did not differ (p= 0.472) between the groups. The baseline PLA2 amounts were inversely associated with functional outcome at 12-week measured with Global Assessment Functioning Score (Pearson correlation=-0.311, p=0.042). Furthermore, baseline PLA2 activity was moderately positively associated with overall symptomatology (i.e., BPRS total, PANSS total and PANSS general) at 12-weeks, in particular with negative symptoms (i.e., BPRS negative score, PANSS negative score) but not positive psychotic symptoms as assessed with the PANSS positive subscale. Our study suggests that baseline PLA2 activity may be able to predict symptomatic response characteristics, whereas the actual amount of PLA2 may be more relevant for functional outcome. Our findings support the importance of the phospholipid-arachidonic acid cascade in understanding the underlying neurobiology of the onset of psychotic disorders.

PREGNENOLONE REDUCTIONS IN PARIETAL CORTEX ARE ASSOCIATED WITH SUICIDE IN PATIENTS WITH SCHIZOPHRENIA

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BACKGROUND: The neurosteroid pregnenolone is markedly elevated in rat hippocampus, cerebral cortex, and serum following clozapine administration, and we have hypothesized that pregnenolone induction may contribute to the superior efficacy of this antipsychotic. Clozapine is FDA-approved for the treatment of suicidal behaviors in patients with schizophrenia or schizoaffective disorder, but the precise mechanisms contributing to clozapine effects on suicidality are unknown. We therefore determined if pregnenolone levels are altered in parietal cortex and posterior cingulate in patients with schizophrenia who died by suicide. Since pregnenolone levels are similarly elevated in patients with schizophrenia and bipolar disorder in both parietal cortex and posterior cingulate compared to control subjects (Marx et al 2006), we also determined if pregnenolone is altered in patients with schizophrenia and bipolar disorder who died by suicide. METHODS: Postmortem tissue was generously donated by the Stanley Foundation. Pregnenolone levels were determined by gas chromatography/mass spectrometry preceded by HPLC purification. Pregnenolone levels were analyzed by Mann-Whitney U test statistic. RESULTS: Median pregnenolone levels in parietal cortex are significantly reduced in subjects with schizophrenia who committed suicide (19.01 ng/g; n=4) compared to patients with schizophrenia who died of other causes (41.86 ng/g; n=11), p=0.04. Median pregnenolone levels in posterior cingulate are not significantly different in patients with schizophrenia who died by suicide (p=0.21). When patients with schizophrenia and bipolar disorder are combined, median pregnenolone levels are significantly lower in parietal cortex in patients who died by suicide (23.38 ng/g; n=13) compared to patients who died of other causes (52.57 ng/g; n=17), p=0.02, and also tend to be reduced in posterior cingulate in patients who committed suicide in this combined group (p=0.06). CONCLUSIONS: Pregnenolone levels are significantly reduced in parietal cortex in patients with schizophrenia who died by suicide compared to patients with schizophrenia who died of other causes. Pregnenolone levels are also reduced in parietal cortex (significantly) and posterior cingulate (trend) when patients with schizophrenia and bipolar disorder are combined. Pregnenolone may be relevant to the neurobiology of suicide in schizophrenia and bipolar disorder.

NO CHANGES IN CANNABINOID CB1 RECEPTOR BINDING DENSITY IN THE SUPERIOR TEMPORAL GYRUS IN SCHIZOPHRENIA

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Background: In recent years, abnormal changes in the endocannabinoid system have been found in schizophrenia. Previously, we have found that schizophrenic patients had increased density of cannabinoid CB1 receptors in the anterior cingulate cortex and posterior cingulate cortex. Superior temporal gyrus (STG) is strongly implicated in the pathophysiology of schizophrenia, particularly with regards to auditory hallucinations. It is well known that hallucinations can occur in cannabis users, especially with an excessive dose. Since a high density of cannabinoid CB1 receptor is found in the STG, these receptors may play a role in the hallucinations associated with schizophrenia. Purpose: In this study, we investigated the binding density of CB1 receptors in the STG of schizophrenia patients compared to control subjects. Methods: We used quantitative autoradiography to investigate the binding of [3H]SR141716A and [3H]CP-55940 to CB1 receptors in the STG. Post-mortem brain tissue was obtained from the NSW Tissue Resource Centre (TRC). Results: There were no differences in age, postmortem interval, and brain pH between the schizophrenia (n=8) and control (n=8) groups. [3H]SR141716A

binding was homogeneously distributed through all layers of the STG in both schizophrenic and non-schizophrenic subjects. However, [3H]CP-55940 binding sites showed a laminar distribution in the STG, with a greater binding density in the superficial cortical layers (layers I-II) and deep layers (layers V-VI) compared with the middle layers (layers III-IV). For both [3H]SR141716A and [3H]CP-55940 binding density, no significant difference was found between the schizophrenia and control cases (both $p>0.05$). In the schizophrenic cases, there were no relationships between the binding density and the final recorded dose of antipsychotic drugs. Conclusion: In the present study, no significant difference was observed in the STG of schizophrenia subjects compared to controls. In contrast, previous studies have reported altered CB1 receptor density in the prefrontal, and anterior and posterior cingulate cortices in schizophrenia, which was suggested to be associated with impaired cognitive function. We suggest that alterations of the cannabinoid receptors in the cortex of schizophrenia are region specific and might be related to specific symptoms.

COVARIANCE ANALYSIS OF CSF AMINO ACIDS IN HEALTHY NORMAL AND SCHIZOPHRENIA

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Differences in CSF amino acid (AA) metabolism between schizophrenics and matched normal controls have the potential to uncover important physiological causes or effects of schizophrenic illness. Determination of many analyte concentrations for each sample permits study of metabolic relationships across and between populations, as distinct from mean differences. In this study, we measured CSF-AA levels from patients with schizophrenia on and off haloperidol, and from age-, gender-, and race-matched control subjects. Data on 17 AA from 18 controls and 18 patients were log transformed as needed to achieve approximate univariate and multivariate normality, and freedom of extreme outliers. The 2 covariance matrices of controls and schizophrenia subjects off drug were tested for equality and this null hypothesis was rejected at $p=0.00033$. The null hypothesis for equality of covariance matrices of controls and schizophrenics on drug was rejected at $p=0.032$. The test for equality of covariance matrices of schizophrenics on and off drug was rejected at $p=0.027$. Since the covariance matrices were unequal, the Hotelling T2 test on mean vectors was not justified. Instead, we identified significant contributing variables in a logistic regression classifier of the groups by pairs. Covariance models were introduced to reduce the number of parameters and to efficiently describe the group differences. Truncation of principal components and related models encountered a large number of significant components when all variables were entered (though they worked well for small groups of variables). We performed a "clustering" of variables (using $1-|r_{ij}|$ as distance between variables i and j) to identify variable groupings, and 2 major groupings emerged: a branched-chain amino acid (BCAA) and alanine group, and a group with glutamate, asparagine, threonine, methionine, and serine. Changes in both variance and correlation between controls and patients were verified by the method of Manly and Rayner. Mutually high correlations are found among the BCAA and alanine. No correlation differences between controls and schizophrenics are found in the branched-chain and alanine group, but a trend was seen for the other group. Combining the groups resulted in a significant difference in the 2 correlation submatrices, suggesting that greater differences lay in correlations between the two major groupings' variables. (Supported by Dept. of Veterans Affairs, Merit Review Grant)

HALOPERIDOL ACTIVATES AKT AND REDISTRIBUTES IT TO THE SYNAPTIC MEMBRANE

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AKT/PKB is a serine/threonine protein kinase that functions as a critical regulator of cell survival and proliferation. Impairment of AKT signaling pathway is known to be directly associated with several diseases, including cancer, neurodegenerative and psychiatric brain disorders. Using a multidisciplinary approach, we reported convergent evidence for impairment of AKT signaling pathway in schizophrenia (Emamian et al., 2004). Specifically, we presented evidence for a decrease in AKT1 protein levels in peripheral lymphocytes and brains of schizophrenic patients, a significant association between schizophrenia and an AKT1 gene haplotype and an increased sensitivity to the sensorimotor gating-disruptive effect of amphetamine, conferred by AKT1 deficiency. Here we show that treatment with haloperidol results in activation of AKT, both in vivo and in frontostriatal slices, in a dose dependent manner. Biochemical fractionation of the frontal cortex tissue from C57Bl/6 mice shows the highest amount of AKT in the soluble cytoplasmic fraction. However, after in vivo administration of haloperidol there is a decrease in the level of phosphorylated AKT (Ser-473) in the cytosolic fraction and a significant increase in the synaptic membrane fraction. This suggests that activation of AKT in neuronal cells is associated with its redistribution from cytosol to the membrane fraction, similar to the mechanism described for the AKT activation in non-neuronal cells. We also show that this redistribution is accompanied with stable binding of phosphorylated AKT with other proteins. Finally, we show that redistribution of AKT to the synaptic membrane by haloperidol is associated with increased phosphorylation of synaptic substrates for AKT. This study suggests a novel mechanism for haloperidol's antipsychotic effect, i.e., activation and complex formation of AKT as well as redistribution of this complex from neuronal cell body to synaptic membrane, where it phosphorylates several synaptic membrane proteins. In conclusion, consistent with the findings of Wang et al. (2003), our data supports the hypothesis that AKT regulates the specificity and efficacy of neurotransmitter release in nerve terminals by phosphorylation of several synaptic proteins, contributes to synaptic plasticity and ultimately to the cognitive and executive function of mammalian brain.

PERIPHERAL IMMUNE ACTIVATION IN SCHIZOPHRENIA USING QUANTITATIVE REVERSE-TRANSCRIPTION POLYMERASE CHAIN REACTION (RT-PCR)

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The anti-inflammatory agent, celecoxib has been reported to be of therapeutic benefit in schizophrenia, suggesting that chronic inflammation might play an active role in schizophrenia (1). To better characterize the state of immune activation in this population, we examined the pattern of gene expression in peripheral blood cells for key pro-inflammatory cytokines and a central enzyme of tryptophan metabolism, indolamine 2,3-deoxygenase

(IDO), which is subject to regulation by the immune system. In a cross-sectional study, we obtained peripheral blood mononuclear cells (PBMCs) from 20 patients with schizophrenia and 10 matched control subjects. We measured expression of interferon-gamma, tumor necrosis factor-alpha, and IDO by quantitative RT-PCR. Schizophrenia subjects were further characterized clinically with standard scales of psychopathology. In a preliminary analysis of the first five subjects, four patients had significantly increased mRNA expression of IDO, and all patients had substantially elevated mRNA expression of interferon-gamma; some differences were more than 1000-fold compared to healthy controls. Results for the full cohort will be presented. Our finding of increased immune activation in peripheral blood cells of schizophrenia patients suggests that mRNA expression of cytokines in peripheral blood cells should be further studied as a potential, very sensitive bio-marker. A valid assessment of inflammation would allow to 1) delineate subgroups of patients where immune activation is present, and 2) to measure treatment response to anti-inflammatory agents. Reference: 1. Muller N, Riedel M, Scheppach C, Brandstatter B, Sokullu S, Krampe K, Ulmschneider M, Engel RR, Moeller HJ, Schwarz MJ: Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. Am J Psychiatry 2002; 159:1029-1034

NEUROCHEMICAL MEASURES OF SYNAPTIC PLASTICITY IN THE ANTERIOR HIPPOCAMPUS IN SCHIZOPHRENIA

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The anterior hippocampus (AH) has been implicated in the pathophysiology of schizophrenia by several convergent lines of evidence. We are examining candidate molecular targets in human post mortem brain tissue that may differ in their rostrocaudal representation in schizophrenia. Our working hypothesis is that glutamatergic neurotransmission is reduced at the NMDA receptor in schizophrenia in the anterior (AH) but not the posterior hippocampus (PH). Given the dynamic interactions between the NMDA receptor, BDNF, and GABA system, we investigated expression levels and correlations between NR1, BDNF exon 5 and GAD67 mRNA in the AH and PH. We have completed an initial set of in situ hybridization studies with probes for NR1 and BDNF exon 5 in serial sections of the AH and PH obtained from matched post mortem tissue in 14 individuals with schizophrenia (SCH) and 14 normal controls (NC). Studies are underway in a second cohort. We performed quantitative densitometric analysis by layer within the CA1, CA3 and the dentate gyrus (DG). BDNF exon 5 is decreased in the CA3 polymorphic subregion in the AH of cases with schizophrenia (50.7 + 43.1 nCi/g) compared to controls (91.3 + 63.15 nCi/g; $p = 0.05$). There were no significant differences in any of the other regions. Correlational analyses reveal a strong positive relationship in expression between NR1 and BDNF exon 5 in the AH of controls ($r = 0.61$) but not cases of schizophrenia ($r = 0.1$). This pattern is not seen in the PH of tissue from control and cases of schizophrenia. These data suggest there are region-specific changes in BDNF expression as well as a disruption of NMDA – BDNF coupling in the AH in schizophrenia. This may contribute to schizophrenia-associated alterations of hippocampal synaptic function and plasticity in the DG.

DOUBLE BLIND, CONTROLLED CLINICAL TRIAL OF CANNABIDIOL MONOTHERAPY VERSUS AMISULPIRIDE IN THE TREATMENT OF ACUTELY PSYCHOTIC SCHIZOPHRENIA PATIENTS

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Background: The human endocannabinoid system has been linked to the pathogenesis of acute schizophrenia, where elevated levels of the endocannabinoid anandamide were found inversely correlating to psychopathology (Giuffrida et al. 2004). It interacts with various neurotransmitter systems including the dopaminergic, glutamatergic and GABAergic. While delta-9-tetrahydrocannabinol, the psychoactive compound of Cannabis sativa, shows psychedelic properties, the major herbal cannabinoid compound cannabidiol was reported to act as a re-uptake inhibitor of anandamide with potential antipsychotic properties. Methods: We performed an explorative, 4-week, double-blind, controlled clinical trial on the effects of purified cannabidiol in acute schizophrenia compared to the antipsychotic amisulpride. The antipsychotic properties of both drugs were the primary target of the study. Furthermore, side-effects and anxiolytic capabilities as well as cognitive effects of both treatments were investigated. Results: 42 patients fulfilling DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis participated in the study. Both treatments were associated with a significant decrease of psychotic symptoms after 2 and 4 weeks as assessed by BPRS and PANSS. However, there was no statistically significant difference between both treatment groups. In contrast, cannabidiol induced significantly less side effects (EPS, increase in prolactin, weight gain) when compared to amisulpride. Conclusions: Cannabidiol proved to offer substantial antipsychotic properties in acute schizophrenia most likely by modulating the endocannabinoid system. This is in line with our suggestion of an adaptive role of anandamide in paranoid schizophrenia, and raises further evidence that this endogenous adaptive mechanism towards psychosis may represent a valuable target for antipsychotic treatment strategies in the future. Funding Source: This study was supported by Stanley Medical Research Institute (00-093 to FML) and the Koeln Fortune Program (107/2000 + 101/2001 to FML).

ABNORMALITIES IN THE DISC1 PATHWAY IN SCHIZOPHRENIA

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DISC1 is a promising candidate susceptibility gene for schizophrenia and affective psychosis with protean molecular effects related to development and neuroplasticity. DISC1 was discovered from a chr 1:11 balanced translocation in a Scottish family which strongly segregated with psychosis. SNP association studies and clinical data suggest that risk SNPs impact on hippocampal structure and function. In cell and animal models, C-terminus-truncated DISC1 disrupts intracellular transport, neural architecture and migration, perhaps because it fails to interact with binding partners involved in neuronal differentiation. We hypothesized that altered expression of DISC1 and/or its molecular partners may underlie its pathogenic role in

schizophrenia and explain its genetic association. Using quantitative RT-PCR, we examined the expression of DISC1 and the selected binding partners (NUDEL, FEZ1, LIS1, PDE4B, ATF4/5, Nde1, kendrin, citron) as well as reelin, a protein in a related signaling pathway, in the hippocampus and dorsolateral prefrontal cortex (DLPFC) of postmortem human brain of schizophrenic patients and controls (N=30 schizophrenics and 70 controls). We found no difference in the expression of DISC1 or reelin mRNA in schizophrenia and no association with previously identified risk SNPs. However, the expression of NUDEL, FEZ1 and LIS1 was each significantly reduced in the samples from patients with schizophrenia ($p<0.05$) and expression of each showed association with high risk DISC1 polymorphisms. The expression of PDE4B was reduced in the hippocampus of patients but not affected by DISC1 SNPs. The expression of other interacting molecules was not significantly altered. These data implicate genetically linked abnormalities in the DISC1 molecular pathway in the pathophysiology of schizophrenia. Putative aberrant DISC1 protein in individuals carrying high risk mutations may engage in abnormal interactions with specific binding partners and cause abnormalities in a DISC molecular pathway involved in mitochondrial transport and synaptic development and plasticity.

TRANSMITTER GLUTAMATE AND SCHIZOPHRENIA: A REINTERPRETATION IN TERMS OF LOSS OF RAPIDLY-CONDUCTING CORTICO-CORTICAL AXONS

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In recent schizophrenia congresses, components of a theory have been presented, explaining enduring trait aspects of schizophrenia in terms of a relative absence of rapidly-conducting cortico-cortical axons (Miller,R. Schiz Res. 37,177,178; 49,140; 53,222; 60,255-6; 67,104; 81,112). The theory covers psychological, electrophysiological and morphological findings in schizophrenia, and is compatible with recent evidence that several genetic factors related to schizophrenia are involved in the control of myelination. A separate body of evidence has shown that negative symptoms, and many of the enduring trait aspects of schizophrenia (impairment in sustained attention, smooth pursuit eye movements, recognition memory, verbal fluency) are mimicked in normal subjects given antagonists at the NMDA glutamate receptor (e.g. ketamine or PCP). From this has developed a "glutamate hypothesis" of the disorder. However, much of this evidence can be reinterpreted as a consequence of loss of rapidly-conducting cortico-cortical axons. Specifically, if rapidly-conducting axons are replaced by slowly-conducting ones, there will be an increase in the temporal dispersion of signals transmitted between any two cortical loci. As a result post-synaptic summation within any neuronal integration interval will be reduced, resulting, overall, in attenuation of excitatory synaptic transmission across the cortex. This can be seen as the basis for most negative symptoms and associated abnormal traits discovered in psychological tests. The attenuation of signal transmission between cortical loci is expected to be similar in many (but not all) respects to the effects produced by an NMDA-glutamate antagonist. One area where evidence reveals discrepancies in detail between abnormal traits in schizophrenia and effects of ketamine in normal subjects is in the latency of smooth pursuit eye movement. This discrepancy is predicted by the axonal conduction-time hypothesis. This hypothesis also explains many other trait features of schizophrenia, and appears to be more broadly-applicable than the glutamate hypothesis for construction of a comprehensive theory.

NIACIN RECEPTOR PROTEIN IS DECREASED IN ANTERIOR CINGULATE TISSUE DERIVED FROM INDIVIDUALS WITH SCHIZOPHRENIA VERSUS CONTROLS

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Niacin is an endproduct of tryptophan metabolism that occurs through the kynurenine pathway, a pathway upregulated in schizophrenia and psychotic bipolar disorder. The cause of this upregulation is not yet known, but one possible mechanism would be a loss of feedback inhibition by kynurenine endproducts. Niacin has been shown to exert feedback regulation in in vitro studies of an initiating enzyme of the pathway, tryptophan dioxygenase. Other feedback mechanisms of niacin, including receptor-mediated effects, have not yet been investigated. Receptors responsive to niacin have only recently been identified (HM74A and HM74B) and are characterized as high-affinity and low-affinity receptors, respectively. In this work, realtime RT-PCR and Western blots (chemiluminescence with film detection) were utilized to measure the expression of these receptors in sections of anterior cingulate cortex obtained postmortem from individuals with schizophrenia (N=12), from those with bipolar disorder (N=14) and from normal controls (N=14). A disparity emerged between the quantity of transcript measured for the combined expression of the receptors, which trended higher in the schizophrenia group (median value 2.3-fold that of normal controls, $p=0.08$) and the quantity of the full-length protein, which was significantly lower in the schizophrenia group (median value 0.15-fold that of that for controls, $p=0.008$), as measured with a commercially-available antibody to a region common to both niacin receptor subtypes. No significant differences were found between the bipolar group and the control group for these measures. The data show that the mRNA for the HM74A plus B receptors is represented by full-length protein product to a much lesser extent in the schizophrenia group (0.06-fold the median proportion of protein/mRNA in controls, $p=0.03$). The significant decrease in the 44 kD, full length receptor in schizophrenia is being investigated further through RT-PCR and Westerns specific for the receptor subtypes and through assays for functional SNPs that might affect protein translation, protein processing and/or stability. The relevance of the results will be placed in the context of epidemiological and clinical findings reported by other researchers who have demonstrated a blunted niacin flush response in schizophrenia and a decreased incidence of rheumatoid arthritis, a disease exacerbated by the signaling cascade initiated by the HM74A niacin-responsive receptor.

CONVERGENT EVIDENCE THAT OLIGODENDROCYTE LINEAGE TRANSCRIPTION FACTOR 2 (OLIG2) AND INTERACTING GENES INFLUENCE SUSCEPTIBILITY TO SCHIZOPHRENIA

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Abnormal oligodendrocyte function has been postulated as a primary etiological event in schizophrenia. ligodendrocyte lineage transcrip-

tion factor 2 (OLIG2) encodes a transcription factor central to oligodendrocyte development. Analysis of OLIG2 in a case-control sample (n=approximately 1,400) in the U.K. revealed several SNPs to be associated with schizophrenia (minimum P=0.0001, gene-wide P=0.0009). To obtain independent support for this association, we sought evidence for genetic interaction between OLIG2 and three genes of relevance to oligodendrocyte function for which we have reported evidence for association with schizophrenia: CNP, NRG1, and ERBB4. We found interaction effects on disease risk between OLIG2 and CNP (minimum P=0.0001, corrected P=0.008) for interaction with ERBB4 (minimum P=0.002, corrected P=0.04) but no evidence for interaction with NRG1. To investigate the biological plausibility of the interactions, we sought correlations between the expression of the genes. The results were similar to those of the genetic interaction analysis. OLIG2 expression significantly correlated in cerebral cortex with CNP (P<10(-7)) and ERBB4 (P=0.002, corrected P=0.038) but not NRG1. In mouse striatum, Olig2 and Cnp expression also was correlated, and linkage analysis for trans-effects on gene expression suggests that each locus regulates the other's expression. Our data provide strong convergent evidence that variation in OLIG2 confers susceptibility to schizophrenia alone and as part of a network of genes implicated in oligodendrocyte function.

CLOZAPINE INVOKES THE EPIDERMAL GROWTH FACTOR SYSTEM TO ACTIVATE THE EXTRACELLULAR SIGNAL REGULATED KINASE CASCADE. A NOVEL TARGET IN TREATMENT RESISTANT SCHIZOPHRENIA?

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The atypical antipsychotic drug clozapine is superior to all other drugs in the treatment of refractory schizophrenia[1]. This may plausibly involve clozapine inducing long-term neuronal adaptations contingent on drug-receptor activation of intracellular signalling systems that affect gene transcription. One candidate intracellular signalling pathway is the mitogen activated protein kinase-extracellular signal regulated kinase (MAPK-ERK) cascade. This pathway regulates synaptic plasticity and connectivity in frontal cortex, hippocampus and subcortical areas[2], processes and regions implicated in schizophrenia. However, the mechanism utilized by clozapine to modulate ERK in a manner distinct from other antipsychotic drugs is unknown. We have previously reported that although clozapine and haloperidol acutely inhibited ERK activation in cortical neurons, only clozapine stimulated ERK with continued treatment. This stimulation was not via the canonical dopamine D2-Gi/o-PKA or the serotonin 5HT2A-Gq-phospholipase C linked signalling pathways. We therefore examined alternative signalling pathways that clozapine could mobilise to activate ERK including growth factor receptor systems. Clozapine induced phosphorylation of ERK1/2 in the absence or presence of growth factor receptor specific inhibitors was measured in primary murine cortical cultures by Western immunoblotting. Results were normalized against vehicle and total ERK1 and 2 levels. The epidermal growth factor (EGF) receptor inhibitor, AG1478 caused significant dose-dependent inhibition of pERK1 (IC50 0.083μM) and pERK2 (IC50 0.106μM) in the presence of clozapine whereas the platelet-derived growth factor receptor inhibitor, tyrphostin A9 did not. This is the first evidence that the effects of clozapine may involve a neuronal signalling system not previously linked to antipsychotic drug action. This presents a novel target for the development of new therapeutics and one which may impart insight into the pathology of schizophrenia. 1. McEvoy et al (2006) Am J Psychiatry 163:600-610 2. Thomas and Huganir (2004) Nat Rev Neurosci 5:173-183

NEUREGULIN POLYMORPHISM ASSOCIATES WITH DENSITY OF THE VESICULAR GLUTAMATE TRANSPORTER 1 IN HUMAN STRIATUM AND HIPPOCAMPUS

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Background: There is substantial evidence for glutamatergic dysfunction in schizophrenia. This includes disturbances of the cortico-striatal pathway and hippocampal innervation, reflected by the deficits of the vesicular glutamate transporter 1 (VgluT1) we have identified in striatal and hippocampal regions. Several of the genes implicated in schizophrenia, including neuregulin and dysbindin, may influence function of glutamatergic synapses. We tested whether the neuregulin polymorphism providing the greatest contribution to risk in an Icelandic cohort might be associated with this indicator of glutamatergic dysfunction in human post-mortem tissue. Methods: Using tissue from the Stanley Neuropathology Consortium, we have determined density of VgluT1 in striatal and hippocampal regions by immunohistochemical staining and investigated the association of VgluT1 density with the SNP8NRG221533 neuregulin polymorphism. Results: Significant association with neuregulin genotype was found for VgluT1 density in putamen and in the dentate gyrus of the hippocampus in which subjects homozygous for the high schizophrenia risk C allele demonstrated lower densities of this glutamatergic marker. Reanalysis of CC homozygotes vs. the remaining sample generally increased significances, indicating a further significant association with VgluT1 in the nucleus accumbens. Conclusions: These findings demonstrate that genotype of a genetic risk factor for schizophrenia is associated with the density of a marker of cortico-striatal glutamatergic innervation and hippocampal glutamatergic terminals in which there are deficits in the disease. This suggests that these glutamatergic deficits may, in part, be genetically determined, either from early development or by the at-risk genotype imparting an increased vulnerability to subsequent damage of glutamatergic terminals.

ABNORMAL KYNURENINE PATHWAY METABOLISM IN THE STRIATUM OF INDIVIDUALS WITH SCHIZOPHRENIA

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The levels of two metabolites of the kynurenine pathway (KP) of tryptophan degradation, kynurenic acid (KYNA) and its bioprecursor L-kynurenine (L-KYN), are elevated in cortical regions in individuals with schizophrenia (SZ) (Biol. Psych., 50: 521, 2001). Nanomolar concentrations of KYNA, a preferential antagonist of NMDA and α7 nicotinic acetylcholine receptors, can reduce the extracellular levels of glutamate and dopamine in experimental animals. Increased levels of KYNA may therefore play a role in the pathophysiology of SZ. To examine if abnormalities in KP metabo-

lism also exist in the striatum, we now measured the tissue levels of L-KYN and KYNA and the activity of several KP enzymes in samples from five distinct striatal regions [dorsal caudate (DC), ventral caudate (VC), dorsal putamen (DP), ventral putamen (VP) and nucleus accumbens (ACC)]. Brains from 15 SZ patients and 14 matched controls (CTR), obtained from the Maryland Brain Collection, were used in this study. KYNA levels were increased in all regions tested (overall ANOVA $p<0.001$, SZ vs. CTR), and significant differences were observed in the VC, DP and ACC using Fisher's LSD multiple comparison test ($p<0.05$). L-KYN levels, too, were elevated in all regions (overall ANOVA $p<0.001$, SZ vs. CTR). These differences were significant in the VC and DP after Fisher's LSD corrections were applied ($p<0.05$). Using the same tissues, we then determined the activity of several enzymes involved in KP metabolism [indoleamine 2,3-dioxygenase (IDO), tryptophan dioxygenase (TDO), kynurenine aminotransferases I and II, kynureninase, kynurenine monooxygenase (KMO), 3-hydroxyanthranilate dioxygenase and quinolinate phosphoribosyltransferase]. IDO (+83%) and TDO (+61%) activity were increased in the SZ samples, while KMO activity was decreased (-26%) (overall ANOVA in all cases $p<0.001$, SZ vs. CTR). After Fisher's LSD corrections, significant differences ($p<0.05$) were seen in IDO (DC, DP, VP and ACC), TDO (all five regions) and KMO (DP and ACC). No other KP enzyme changes were observed. Our data indicate a pronounced impairment of striatal KP metabolism in SZ, where the synthetic machinery leading to L-KYN and KYNA is up-regulated, while a key degradative enzyme of L-KYN is down-regulated. These results justify a detailed study of the causes of these enzyme abnormalities, their relationship to elevated L-KYN and KYNA formation, and implications for various domains of SZ pathology and treatment responses.

CHROMATIN PLASTICITY AND REMODELING IN SCHIZOPHRENIA

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Chromatin can be viewed as the protein scaffolding that sheathes the DNA strand and regulates the access and attachment of transcriptional regulators (either activators or repressors) to the gene promoter. Whether chromatin is in a loose 'relaxed' configuration or alternatively in a condensed 'impenetrable' configuration will profoundly impact gene activity. Levels of acetylated Histone 3 and 4 proteins are strongly predictive of a chromatin structure that is conducive to gene expression and are robustly and reliably increased with the application of histone deactylase inhibitors (HDACi) providing an experimental tool to deconstruct the linear histone code. We have initiated a series of studies to investigate chromatin structure in schizophrenia subjects. A sample of schizophrenia and bipolar patients was treated with equivalent levels of valproic acid (Depakote ER®) over a period of 4 weeks. Acetylated H3 (acH3) and H4 (acH4) levels from lymphocyte nuclear protein extracts were measured by Western Blot. Genomic expression was analyzed using microarrays in an attempt to excavate genomic regions entombed in resistant chromatin. In addition to this in-vivo approach, we have developed in-vitro lymphocyte assays to use HDACi with increasing specificity in the nanomolar range. Treatment with valproic acid resulted in a significant increase of acH3 and acH4. Levels of valproic acid were positively and significantly correlated with percent increase in acH3 but not acH4. Schizophrenia patients were significantly less likely to increase their acH3 and acH4 levels after 4 weeks on valproic acid. In the lymphocyte cultures, HDAC inhibitors such as Trichostatin A demonstrate a reliable dose response effect in increasing H3 and H4. Increases in acH3 and acH4 can be demonstrated within 24 hours and the ED50 for TSA is approximately 100 nM. These results suggest that chromatin is 'less plastic' in schizophrenia blood lymphocytes. Our current approach using in-vitro lymphocyte cultures will examine the effects of chronicity, substance abuse and ongoing antipsychotic treatment on the structure and responsivity of chromatin. Because chromatin 'plasticity' can be modified by conventional pharmacology, a novel approach to the regulation of gene expression in clinical populations is possible.

INVESTIGATION OF AMINO ACIDS INVOLVED IN GLUTAMATERGIC NEUROTRANSMISSION IN FIRST EPISODE PSYCHOSIS

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NMDA glutamate receptor hypofunction is one of the leading hypotheses of schizophrenia pathophysiology. To further our understanding of neurochemical abnormalities during the early phase of the illness, the present study investigates peripheral levels of amino acids that affect glutamatergic neurotransmission, including glutamate, glutamine and glycine, in unmedicated first episode psychosis patients (FEPs). Blood was collected from 14 unmedicated, male FEPs (mean age±SD= 21.6±3.4) recruited from the Edmonton Early Psychosis Intervention Clinic, and from 15 age matched, male healthy control subjects (HCs) (mean age±SD=22.9±3.4), between 8 and 10 am following an overnight fast. The plasma was immediately separated by centrifugation and stored at -80°C until analysis. Plasma amino acids were quantified using high performance liquid chromatography with fluorimetric detection. Mean (±SD) glutamate, glutamine and glycine plasma levels were 3.57±1.82 and 3.66±2.18 μg/ml, 57.93±9.14 and 73.93±10.28 μg/ml, and 16.07±3.92 and 17.09±3.70 μg/ml, for FEPs and HCs, respectively. Glutamine plasma levels were significantly lower in FEPs when compared to HCs ($p<0.001$). Glutamate and glycine plasma levels were not significantly different between groups. Glutamine plays an important role in many metabolic processes, including glutamate metabolism. It is both a precursor for and a degradation product of glutamate, and also serves as the major transport form of glutamate in circulation. Our finding of abnormal plasma glutamine levels in FEPs suggests a dysregulation in the glutamatergic system in recent onset psychosis.

STUDIES OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN FIRST EPISODE SCHIZOPHRENIA

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There is much interest, derived from current neurochemical, genetic, and therapeutic research, in the role of brain neurotrophins in schizophrenia. Neurotrophins play key roles in neuronal development and differentiation (i.e., promoting dendritogenesis and synaptogenesis), and in orchestrating the neuronal response to stress/noxious stimuli. Additionally, neurotrophins are modulators across monominergic (dopamine and serotonin), gabaergic and cholinergic

systems. These roles focus on important areas of the etiopathophysiology of schizophrenia. Clinical studies show reductions in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NFG) in patient - normal control comparisons, as well as differences in patients receiving first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs). We now report on BDNF levels in patients with first-episode psychosis in comparison with normal, healthy subjects. Compared to normal controls (N = 14; 290.5 ± 38.81 pg/ml), patients showed significant reduction (N = 15; 135 ± 21.77 pg/ml; P = 0.001; f = 12.873) in plasma BDNF. Additionally, plasma BDNF levels showed a significant negative correlation (N=13, r=-0.584, p=0.0362) with positive symptoms scores at the baseline. These are replicated in another first episode cohort which we found low BDNF in both CSF and plasma. BDNF may be a neurobiological marker for active psychosis.

PLASMA PROTEOMIC BIOMARKERS IN SCHIZOPHRENIA

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Schizophrenia is an illness only partially responsive to treatment. Development of better treatment strategies may be enhanced by developing objective biological state and trait markers. The goal of this study was to investigate candidate peripheral proteins or protein patterns characteristic for schizophrenia. Source of material were plasma samples which were collected from patients with DSM-IV diagnosis of schizophrenia and gender, age, and smoking matched healthy control subjects. All patients with schizophrenia had a total PANSS score of >60. Two groups of samples were compared utilizing two separate proteomic techniques: DIGE and mass spectroscopy. METHODS: Blood was collected 8-9 AM and centrifuged at 4°C. Obtained plasma (with EDTA) was separated and frozen at -80°C until further analysis. Prior to DIGE (fluorescence 2D-differential gel electrophoresis) analysis, plasma was depleted from the 12 most abundant plasma proteins utilizing a commercial depletion kit (Beckman-Coulter Proteome Lab IgY 12 column). The samples were labeled with fluorescent dyes Cy3 or Cy5. The comparison of pooled schizophrenia and control 26 matched pairs were performed in a single gel and differential protein expression was analyzed (Amersham platform). For mass spectroscopy experiments, individual plasma samples were analyzed directly by MALDI-MS to produce reflectron and linear spectra which were later compared. RESULTS: DIGE and mass spectroscopy comparisons of plasma samples in schizophrenia and matched control subjects suggest that there are protein based differences in blood which may represent candidate state or trait biomarker(s) in schizophrenia. Current status of the identified protein pattern differences will be presented. The ultimate goal of these preliminary studies is to investigate candidate marker molecules in the periphery which may be used as state or trait markers in schizophrenia.

10. Neurochemistry, Animal

EFFECT OF THE POSITIVE ALLOSTERIC AMPA RECEPTOR MODULATOR, FARAMPATOR, ON 5-HT FUNCTION

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Farampator is a positive allosteric modulator of AMPA receptors and is a member of a class of compounds called Ampakines®. Ampakines have entered development for treatment of CNS disorders such as cognition, depression and schizophrenia. Here we report the effect of systemic administration of farampator on extracellular 5-HT levels in vivo and its effect on 5-HT synthesis, ex vivo. Furthermore, we have also begun to investigate the mechanism of action of farampator by studying its interaction with the AMPA antagonist CNQX and the 5-HT1A antagonist WAY 100635. In vivo microdialysis in the freely moving rat was used to determine 5-HT levels in the pre-frontal cortex. Farampator (10 mg/kg i.p.) significantly reduced 5-HT levels (54% +/- 14 of basal, $P<0.01$, n=6). Pre-treatment of rats with the AMPA receptor antagonist CNQX (2.5mg/kg i.p.), which by itself had no effect, completely blocked the inhibitory effect of farampator on 5-HT levels (100% +/- 25 of basal, $P>1.0$, n=6) demonstrating that farampator is acting directly via AMPA receptors. However, since AMPA itself increases 5-HT levels, enhancing the activity of AMPA receptors via positive modulation might not be expected to reduce 5-HT levels. Therefore it was postulated that any increase in 5-HT induced by farampator might be compensated for by an inhibitory action of 5-HT1A autoreceptors. Pre-treatment with the 5-HT1A receptor antagonist WAY100635 (0.63 mg/kg sc), that alone had no effect, completely blocked the inhibitory effect of farampator on 5-HT levels in the cortex (98% +/- 26 of basal, $P>1.0$, n=5), indicating that the decrease is mediated indirectly by 5-HT1A receptors. Interestingly, despite the apparent involvement of 5-HT1A receptors in the mechanism of action of farampator on 5-HT levels in the frontal cortex of rats, there was no significant effect on 5-HT synthesis (5-HTP (pg/mg tissue) veh = 140±6 & Org (10mg/kg) 144±6, n=6-7 per group). Although farampator reduces extracellular 5-HT via a 5-HT1A receptor-sensitive mechanism, it does not appear to induce a decrease in 5-HT synthesis. This suggests the tone induced on the 5-HT1A autoreceptors is not sufficient to reduce tryptophan hydroxylase activity. Compared with the SSRIs that reduce 5-HT synthesis considerably, it appears that the effect of farampator on the 5-HT system is more subtle. Whether this difference leads to a novel therapeutic activity remains to be seen.

THE PARVALBUMIN-INHIBITORY SYSTEM IN THE PREFRONTAL CORTEX OF AGED MICE PRESENTS AN INCREASED VULNERABILITY TO KETAMINE EFFECTS: A POSSIBLE MODEL FOR POST-ANESTHETIC DELIRIUM AND PSYCHOSIS IN THE ELDERLY

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Most individuals in the general population will undergo normal aging, usually accompanied by a mild memory deficit. However, under stressing conditions such as those observed in clinical situations, post-anesthetic amnesia, delirium, psychosis, and lasting cognitive decline are often observed in elderly patients. Age-dependent decreases in GABAergic cell number and function have been consistently reported in non-human primates and rodents. If this extends to the human brain, it is possible to postulate that aging would render individuals more susceptible to changes in GABAergic tone, which can lead to uncontrolled excitatory transmission, such as what has been suggested for the psychotomimetic effects of the anesthetics ketamine and phencyclidine (PCP) acting as NMDA receptor antagonists. At present, the best model of a psychotic episode across species is treatment with antagonists to a specific subtype of receptor for the neurotransmitter glutamate, the NMDA-type receptor. Non-competitive NMDA receptor antagonists, such as phencyclidine or ketamine, at sub-anesthetic concentrations induce a transient schizophrenia-like state in healthy individuals, and exacerbate psychosis in schizophrenic patients. In rodents, the same NMDA receptor antagonists producing psychosis in humans induce a behavioral syndrome that has been proposed as a valid experimental model for schizophrenia. We hypothesized that situations inducing a mild hypoglutamatergic condition in young adults will have more profound effects in old age, due to a specific vulnerability of the GABAergic system in the aged subject. We have characterized the effects of low concentrations of ketamine in old C57BL/6 male mice, as a model to study the subpopulation of parvalbumin-positive GABAergic interneurons in the aged brain. Our results show that exposure to low doses of ketamine (15 mg/kg on two consecutive days) induces a pronounced decrease in parvalbumin immunoreactivity in the prefrontal cortex, whereas calbindin and calretinin immunoreactivities were not affected. Furthermore, pre-treatment with an antioxidant reversed the effect of ketamine on parvalbumin immunoreactivity. These results suggest that ketamine effects in the aged brain is a suitable in vivo model for the study of age-related psychotic and delirium episodes, and will thus allow us to test approaches to prevent the development of these conditions that can be translated to therapeutic interventions in humans.

REGULATION OF NEDD4 BY CLOZAPINE, HALOPERIDOL AND OLANZAPINE IN THE MOUSE BRAIN

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Neural precursor cell expressed, developmentally downregulated gene 4 (NEDD4) is the prototypic member of a family of proteins that is conserved from yeast to mammals. NEDD4 is highly expressed in the granular cells of the olfactory bulb and cerebellum in adult mouse brain and in other adult tissues. Mouse NEDD4 protein consists of an amino terminal C2 Ca2+/lipid-binding domain, three WW protein–protein interaction domains, and a carboxyl terminal HECT domain. NEDD4 is involved in a number of diverse cellular processes including regulation of the trafficking, stability and signaling of membrane proteins. Mice were treated for 7-days with either clozapine, haloperidol or olanzapine. Control animals were treated with saline solution. Quantitative real-time PCR analysis was used to examine mRNA expression of NEDD4 in control and treated whole mouse brain total RNA preparations. Immunohistochemistry was used to determine qualitative and quantitative expression of NEDD4 protein in treated and control

mouse brain sections. The mRNA level of NEDD4 was found to be downregulated by all 3 antipsychotic drugs by greater than 1.5 fold, compared to controls. The most significant down regulation was by olanzapine, which downregulated NEDD4 mRNA by 1.66-fold. The qualitative and quantitative protein expression for NEDD4 protein was also investigated in mouse brain tissue from antipsychotic treated mice. Our results indicate that all three antipsychotic drugs down regulated the expression of NEDD4, which potential could be an important element in the mechanism of action of antipsychotic drugs. Understanding the molecular and cellular mechanisms by which commonly prescribed antipsychotics achieve their therapeutic action could represent a valuable step in clarifying the pathophysiology of schizophrenia.

MODELING SCHIZOPHRENIA RISK BY MANIPULATION OF GENES THAT MODULATE NMDA RECEPTOR FUNCTION DURING DEVELOPMENT

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Several putative risk genes for schizophrenia directly or indirectly affect NMDA receptor (NMDAR) function. These include D-amino acid oxidase (DAAO), the DAAO modulator G72, Neuregulin, Dysbindin, Proline Oxidase and mGluR3. To understand better how these genes might affect brain function and behavior, we have manipulated in mice the expression of two genes that modulate NMDA receptor function during development: glutamate carboxypeptidase 2 (GCP2) and serine racemase (SR). GCP2 catabolizes N-acetyl aspartyl glutamate (NAAG), which is an endogenous antagonist of the NMDAR and is an agonist at mGluR3 that inhibits glutamate release. GCP2 is of additional interest because it is also folate hydrolase 1 (FOLH1), which is critical for the absorption of dietary folate and could impact levels of homocysteine, another risk factor for schizophrenia, during development. Post-mortem studies indicate that GCP2 expression is reduced in the brain in schizophrenia. SR synthesizes D-serine, a co-agonist at the NMDAR that is reduced in schizophrenia, is critical to neuronal migration via NMDAR activation, and is catabolized by DAAO and G72. GCP2+/- mice have subtle abnormalities in cognition and behavior as compared to wild-type (WT) littermates. SR-/- and SR+/- mice exhibit normal survival but show gene dose effects on brain D-serine. Behavioral characterization of SR-/- is ongoing but points to reduced tolerance to stress.

GLUTATHIONE DEFICIT ALTERS DOPAMINE MODULATION OF NMDA-MEDIATED CALCIUM RESPONSES VIA D2 RECEPTOR-MEDIATED SIGNALLING PATHWAY: IMPLICATION OF RYANODINE RECEPTORS AND L-TYPE CALCIUM CHANNELS

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Synthesis of glutathione (GSH), an intracellular redox regulator, is compromised in schizophrenia. Patients show a deficit in GSH levels in cerebrospinal fluid and prefrontal cortex, and a decrease in gene expression of both modulatory and catalytic subunits of glutamate-cysteine ligase, the rate limiting enzyme of GSH synthesis. A polymorphism of the gene for the modulatory subunit is also associated with the illness. Such GSH deficit might affect neurotransmission via changes in the function of intracellular redox-sensitive proteins. Here, we investigated whether a GSH deficit affects intracellular pathways implicated in dopamine signalling. We studied the effect of GSH deficit on dopamine modulation of NMDA-mediated calcium responses in cultured cortical neurons. GSH deficit was induced by L-buthionine-(S,R)-sulfoximine (BSO), an inhibitor of glutamate-cysteine ligase. A GSH deficit reversed the direction of the modulation of NMDA responses by dopamine. Moreover, dopamine modulation of NMDA responses was mediated by different cellular mechanisms in control and BSO-treated neurons. In control neurons, dopamine (1μM) enhanced NMDA responses via presynaptic mechanisms. But in BSO-treated neurons, dopamine decreased NMDA responses via activation of D2 receptors and postsynaptic mechanisms. In BSO-treated neurons, the decrease of NMDA responses was abolished when intracellular GSH levels was replenished with GSH-ethylester or when L-type Ca2+ channels were blocked with nifedipine. This suggests that low intracellular GSH causes a change in modulation of L-type Ca2+ channels by dopamine. Blockade of ryanodine receptors with high ryanodine concentration fully reversed dopamine-induced decrease in BSO-treated neurons. Since caffeine, but also dopamine, evoked stronger calcium release from internal stores in BSO-treated than in control neurons, this indicates that ryanodine receptors, known to be redox-sensitive, are more functional under low GSH conditions. We postulate that an enhancement of the function of ryanodine receptors in GSH-depleted neurons favours D2R/D4R-mediated and calcium-dependent pathways, causing a change in the dopamine modulation of L-type Ca2+ channels in particular. As consequence, dopamine modulation of NMDA-mediated response is strongly altered. We could speculate that antipsychotics through their antagonistic action on D2R might prevent or attenuate the unbalance between signalling pathways induced by a GSH deficit.

DEVELOPMENTAL VITAMIN D DEFICIENCY; A CANDIDATE RISK FACTOR FOR SCHIZOPHRENIA

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Our group have been exploring the concept that developmental vitamin D (DVD) deficiency may be a plausible neuro-biological explanation for several important epidemiological correlates of schizophrenia namely; 1. The excess winter/spring birth rate; 2. Increased incidence of the disease in 2nd generation Afro-Caribbean migrants and 3. Increased urban birth rate. We have published two pieces of direct epidemiological support for this hypothesis in patients. DVD deficiency therefore is a plausible "Biological Marker" for schizophrenia. We have recently developed an extremely sensitive assay that will allow us to test this hypothesis in a major European long-term storage biobank. In order to establish the "Biological Plausibility" of this hypothesis we have established an animal model to study the effects of DVD deficiency on brain development. In order to do this we ensure maternal levels of the vitamin are deplete via dietary restriction prior to breeding. Maternal vitamin D levels are normalised within 1 week of birth via switching to normal vitamin D containing chow at birth. Adult offspring reproduce the gross pathological features of the disease i.e. ventriculomegaly (Feron et al., 2005) as well display sensitivity to amphetamine and MK-801 induced hyperlocomotion (Kesby et al., 2006) and have impairments in latent inhibition (Becker et al., 2005), behaviours analo-

gous to the positive and negative symptoms of the disease in patients. We are now studying what alterations in neurotransmission may contribute to this interesting behavioural phenotype. Our initial data in whole neonatal brain reflects abnormalities in dopamine metabolism. Firstly we show a 36 ± 11% reduction in the expression of catechol-o-methyltransferase (COMT) ($P<0.05$) and no change in monoamine oxidase mRNA. Consistent with this altered enzyme profile we also find a 24% increase in the ratio of the major dopamine metabolites DOPAC:HVA ($P<0.05$); (DOPAC and HVA are produced by MAO and COMT respectively). Brain regional studies have not yet been undertaken. Neurotransmitter studies in adult DVD deficient animals are ongoing. This animal model continues to provide good face and some construct validity with the disease in patients and illustrates how animal models can be used to progress plausible biological markers for schizophrenia. Feron et al., (2005) Brain res Bull 65:141-148 Kesby et al., Biol Psych (2006) in press accepted 24th May Becker A et al., (2005) Behav Brain Res 161:306-312

HISTAMINE H1 MRNA EXPRESSION IS DECREASED IN THE RAT HYPOTHALAMUS FOLLOWING OLANZAPINE TREATMENT

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Background: Olanzapine is a widely used antipsychotic which provides effective treatment of positive and negative schizophrenia symptomatology. However, it commonly produces side effects such as obesity, diabetes and other metabolic disorders. It has been suggested that this olanzapine-induced weight gain may be associated with its high specificity and affinity for the histamine H1 receptor. Purpose: The aim of this study was to test the hypothesis that antipsychotic drugs with high H1 receptor affinities, such as olanzapine, affect H1 receptor mRNA expression in energy balance brain areas. Methods: Using in situ hybridization, the level of H1 receptor mRNA expression was examined in rat brain following aripiprazole, olanzapine and haloperidol treatments for 1 and 12 weeks (2.25, 1.5 & 0.3mg/kg/day, respectively, n=5/group). Aripiprazole and haloperidol were used as they have lower H1 receptor affinities than olanzapine and have been shown not to produce significant body weight gains in the clinical setting. Results: The olanzapine group gained more body weight compared to the saline controls after both 1-week and 12-weeks of drug intervention. This group also showed increased food intake and increased fat accumulation. Compared to the controls, olanzapine treatment significantly decreased the levels of H1 receptor mRNA expression in the arcuate nucleus (Arc) and ventral medial hypothalamus (VMH) after 1-week and 12-weeks of drug treatment. The aripiprazole and haloperidol treated mice showed no significant differences in the levels of H1 receptor mRNA expression in the Arc and VMH after both the 1 week and 12 week treatments compared to the controls. Significant negative correlations were found between H1 receptor mRNA expression in the Arc and VMH and body weight gain, food intake, energy efficiency and fat accumulation. Conclusion: These findings support the hypothesis that down-regulated histamine H1 mRNA expression in the Arc and VMH in olanzapine treated mice may contribute to the drug-induced increases in body weight, food intake and accumulative fat mass. Antipsychotics with high H1 receptor affinity may therefore be predicted to have a high risk of causing metabolic disorder.

NMDA RECEPTOR HYPOFUNCTION DURING EARLY BRAIN DEVELOPMENT: RELEVANCE TO SCHIZOPHRENIA

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Background: Interruption to brain development at an early stage can alter chemically coded neural networks and can affect behaviour in later life. NMDA receptor antagonists, such as phencyclidine (PCP), disrupt brain development which leads to neuronal damage and causes behavioral alterations in rodents that mimic aspects of schizophrenia psychosis. Purpose: The aim of this study was to compare behaviour, dopamine receptor and transporter changes and apoptosis in rats treated with PCP before and/or after brain maturation. Methods: PCP (10mg/kg) or saline was administered to female rat pups on postnatal day (PN)7, 9 and 11. On PN12, 18, 32 and 96 brain tissue was collected for analysis of dopamine D2 receptor and transporter binding. Tissue was also collected on PN12 for analysis of apoptosis. Remaining rats underwent forced swim, open field and elevated plus maze tests 10 weeks after their last PCP injection. Results: D2 receptor expression did not follow a normal pattern of development in the PCP treated group. In the nucleus accumbens, changes in D2 receptor binding were evident by the early postnatal period, while in the caudate putamen, changes became evident during adolescence, with both areas showing decreased D2 receptor binding in adulthood. The pattern of expression of dopamine transporter did not change. PCP treatment significantly increased the number of apoptotic cells primarily in cingulate and frontal cortices. In the modified forced swim test, PCP treated rats showed increased climbing and decreased swimming time. These rats showed hyperlocomotion in an open field/holeboard test. There was no change in elevated plus maze scores. Conclusions: This study has shown that early insult to the brain from NMDA receptor hypofunction results in immediate changes including increased apoptosis in key brain areas involved in working memory and learning, as well as long-term changes in D2 receptor binding in the mesolimbic and nigrostriatal systems, which may have contributed to the behavioral deficits in later life found in this study. Clearly, the changes in some behaviors but not others indicate that selective and multiple systems are involved. We are currently investigating muscarinic, NMDA, tyrosine hydroxylase and GABAa receptors in this animal model. Overall, these results support the idea that schizophrenia is a neurodevelopmental disorder, involving NMDA receptor hypofunction.

5-HT2A AND 5-HT2C RECEPTOR STIMULATION ARE DIFFERENTIALLY INVOLVED IN THE CORTICAL DOPAMINE RELEASE IN 5-HT2A AND 5-HT2C GENETIC MUTANT MICE

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Both 5-HT2A and 5-HT2C receptors modulate cortical dopamine (DA) release, but in different directions. Microdialysis experiments in rats indicate that 5-HT2A receptor stimulation enhances, whereas 5-HT2C receptor stimulation diminishes cortical DA release. DOI, meta-chlorophenylpiperazine (mCPP) and MK-212 are drugs with affinities for both 5-HT2A and 5-HT2C receptors where they behave as agonists or possibly partial agonists. Their functional

effects in vivo vary in different systems, e.g. endocrine, behavioral, thermoregulation, sexual arousal, and hallucinogenesis in man. We have now compared the ability of these three 5-HT2A/2C agonists to modulate cortical DA release, using microdialysis in 5-HT2A and 5-HT2C genetic mutant (wild type: +/+ and knock out: -/-) mice. DOI (2.5 mg/kg, s.c) induced a slight but significant increase in cortical DA efflux only in the 5-HT2A +/+ mice; this effect was blocked by 5-HT2A antagonist M100907 (3.0 mg/kg). MK212 (2.5 mg/kg) reduced DA release below baseline in the mPFC of both 5-HT2A +/+ and -/- mice; this effect was attenuated by the selective 5-HT2C antagonist SB242084 (1.0 mg/kg) in both types of mice. MCPP, 2.5 mg/kg, had no effect on DA release in either type of 5-HT2A genetic mouse. In the 5-HT2C receptor genetic mice, DOI increased the cortical DA efflux in the +/+ mice, while slightly increased its efflux in the -/- type. Moreover, MK212 decreased the DA efflux in the +/+ but not the 5-HT2C -/- mice cortex. While additional dose-response data are needed, these findings suggest that DOI is more of a 5-HT2A than 5-HT2C agonist, while the opposite is true with regard to MK-212. MCPP on the other hand is more balanced. Of the three agents, only DOI is hallucinogenic in man, providing additional data that hallucinations are due, in part, to 5-HT2A rather than 5-HT2C receptor stimulation, although this does not rule out an important role for 5-HT2C receptors in establishing vulnerability to hallucinate. These findings may be relevant to the antipsychotic effects of atypical antipsychotic drugs.

TYROSINE AVAILABILITY AFFECTS PREFRONTAL CORTEX DOPAMINE SYSTEMS - IN VIVO MICRODIALYSIS IN THE RAT

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In schizophrenia, an abnormality of tyrosine transport has been linked to cognitive processes mediated at least in part by prefrontal cortex dopamine (DA) systems (Wiesel et al, 2005). To further delineate how tyrosine availability could affect dopamine (DA) neurotransmission, we conducted in vivo microdialysis studies in the medial prefrontal cortex of the awake (male, Zivic-Miller, 250-300g) rat. A guide cannula was stereotaxically implanted (AP ± 3.1, ML± 0.7). On the following evening a microdialysis probe was inserted. Probe perfusion started in the morning, 48h following surgery. In one group of animals, perfusate contained the decarboxylase inhibitor NSD1015 (20μM) and DOPA levels were assayed as an index of in vivo tyrosine hydroxylation. In another group DA, norepinephrine (NE) and tyrosine levels were measured. Desmethylimipramine (DMI) 10mg/kg IP did not affect DOPA levels but increased both DA (400% baseline) and NE (700% baseline) levels. IP administration of a tyrosine- and phenylalanine-free amino acid mixture lowered basal tyrosine levels (40% baseline), DOPA levels (< 50% baseline) and DMI-induced DA (175% baseline) and NE (230% baseline) levels. We repeated the studies, but administered DMI (10μM) via the perfusate rather than IP. The results were similar. We conclude that basal DA synthesis in the prefrontal cortex is dependent on tyrosine availability. Depletion of tyrosine in the prefrontal cortex lowers DA synthesis as well as pharmacologically-induced extracellular fluid levels of DA and NE. These data suggest that aberrant tyrosine transport could affect prefrontal cortex DA systems. Appropriate manipulation of brain tyrosine levels may provide a useful probe and/or adjunctive treatment in schizophrenia.

STRIATAL DOPAMINE D2 RECEPTORS AND NEGATIVE SYMPTOMS IN MICE

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Increased activation of dopamine D2 receptors in the striatum has been linked to the pathophysiology of schizophrenia. We previously reported that mice with increased levels of D2 receptors restricted to the striatum exhibit selective cognitive impairments that resemble some of the cognitive deficits described in schizophrenia (Neuron 2006 49,603-615). Here we address the question whether D2R transgenic mice may also show correlates of the negative symptoms of schizophrenia. We found that D2R transgenic mice suffer from deficits in social interaction and motivation. The deficit in social interaction is of developmental origin because it persists after normalizing D2 receptor levels in the adult animal. In contrast, the motivational impairment is due to concurrent over-expression of D2 receptors in the adult animal because it is reversed after switching off the transgene. To understand the underlying mechanisms that may explain the motivational deficit we analyzed the dopamine system in the striatum of D2R transgenic mice. We found no changes in the tissue levels of dopamine and their metabolites in the striatum. However, we observed that D1 receptor mRNA and binding sites were both decreased in this structure. Just as for the motivational deficits, the downregulation of D1 receptors was reversed after normalizing D2 receptor levels. Moreover, in a screen for altered gene expression in the striatum of D2R transgenic mice we found that another modulator of motivation, preproenkephalin was reversibly downregulated. Because both D1 receptors and enkephalin are known to positively affect motivational processes attenuated signaling in both pathways as a consequence of increased D2 receptor levels may be responsible for the observed deficit. In conclusion, we believe that mice with selective over-expression of D2 receptors in the striatum may help us to understand neural mechanisms underlying some of the cognitive and negative symptoms of schizophrenia.

REPLENISHMENT OF GLUTATHIONE LEVELS IN NEURONS AND ASTROCYTES WITH COMPROMISED GCL ACTIVITY: RELEVANCE TO SCHIZOPHRENIA

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In schizophrenia patients, a decrease in glutathione levels ([GSH]) in cerebrospinal fluid and prefrontal cortex was observed. Several evidences suggest a compromised GSH synthesis at the level of the rate limiting enzyme, glutamyl-cysteine ligase (GCL): association of allelic variants of GCL modulatory subunit (GCLM) gene with the illness; decrease of mRNA levels of both GCLM and GCL catalytic subunit (GCLC) in patients fibroblasts; decrease of GCLC protein expression and of GCL activity under oxidative stress conditions. The aim of this study is to find substances that could normalize [GSH] in cultured neurons and astrocytes with compromised GCL activity. First, GCL activity was inhibited with BSO, a blocker of GCLC. In both neurons and astrocytes, the decrease in [GSH] was prevented by a membrane permeable GSH analogue, GSH-ethylester, that bypasses the GCL synthesis step. As a second model, we

used neurons and astrocytes from GCLM knockout (-/-) mice. These cells show low [GSH] (-80%) and GCL activity (-25%). We tested natural antioxidants [Curcumin (polyphenol); quercetin (flavonoid)] and tert-butylhydroquinone (tBHQ), a quinone that generates free radicals. These substances are known for their capacity to increase [GSH] in various cell types. In wild-type (+/+) astrocytes, [GSH] and GCL activity were increased by curcumin (50mM; 50%; 140%; respectively), tBHQ (100mM; 80%; 150%), and quercetin (20-100mM; 60%; 100%) . In (+/+) neurons, curcumin was also efficient (10mM; 60%; 80%) and, while low [tBHQ] (20μM) increased [GSH] (20%), higher [tBHQ] and [quercetin] depleted [GSH] and led to cell death. These results suggest that neurons and astrocytes differ in their ability to regulate GSH synthesis and to cope with the toxic effect of some substances. In GCLM (-/-) astrocytes, tBHQ slightly increased [GSH] (25%), while curcumin and quercetin led to [GSH] depletion even at low concentrations. This indicates that GCLM might not be essential for tBHQ-induced increase in [GSH], while it is necessary for enhancement of GSH synthesis by curcumin and quercetin. Furthermore, it suggests that a compromised GSH synthesis due to a defect at the level of GCL might increase brain cells sensitivity to oxidative stress and substances known to be antioxidants might become prooxidants.

VASCULAR ENDOTHELIAL GROWTH FACTOR MEDIATES NEUROPROTECTIVE EFFECTS OF ANTIPSYCHOTIC TREATMENT IN CORTICAL NEURONAL CULTURE

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Vascular endothelial growth factor (VEGF), a key regulator of brain blood flow through vasodilatation and increased angiogenesis, is also a potent neuroprotective agent against a variety of neural injuries in the brain. We have recently reported in rats that VEGF expression was differentially regulated in the brain by time dependent treatment with first- and second-generation antipsychotics (FGAs and SGAs, respectively) (Pillai and Mahadik, Schizophrenia Research, 2006). Fourteen days of treatment with either FGAs such as haloperidol or SGAs such as olanzapine increased the expression of VEGF in both hippocampus and striatum, but after 45 days of treatment with haloperidol but not with olanzapine reduced the VEGF expression in both the brain regions. The changes in the levels of VEGF paralleled the changes in the angiogenesis. It was hypothesized that the VEGF levels in the brain may be critical for the beneficial as well as adverse/toxic effects of haloperidol in the brain. Since several studies have reported neurotoxic effects of haloperidol in neonatal neurons in culture, we examined the neuroprotective effects of VEGF against haloperidol toxicity in mouse cortical neuronal cultures. The optimum concentration of haloperidol to cause approximately 50 to 60% cell death (using MTT procedure) with 24 hrs of exposure was established as 50uM. Pre-treatment with VEGF (50 ng/ml) for 72 hrs significantly protected the neuronal cells from haloperidol toxicity. This neuroprotective effect of VEGF was mediated through induction of the expression of its receptor, flk-1 on neuronal cells and receptor-mediated kinase signaling mechanisms. This data suggest that the exogenous VEGF may enhance the beneficial effects and prevent / protect the adverse effects of antipsychotic treatment in psychiatric patients. This further suggests that VEGF may be potentially a novel therapeutic agent for the treatment of psychiatric disorders.

CLOZAPINE INCREASES THE NEUROSTEROID PREGNENOLONE IN RAT HIPPOCAMPUS, CEREBRAL CORTEX, AND SERUM: RELEVANCE TO SUPERIOR EFFICACY?

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BACKGROUND: Clozapine demonstrates superior efficacy in patients with refractory schizophrenia, but the precise mechanisms contributing to this distinct clinical advantage remain to be elucidated. Clozapine is also utilized for the treatment of suicidal behaviors in patients with schizophrenia and schizoaffective disorder. Clozapine and olanzapine increase the GABAergic neurosteroid allopregnanolone, and it has been hypothesized that neurosteroid induction may contribute to the therapeutic actions of these agents. Pregnenolone (a precursor to allopregnanolone) improves learning and memory in rodent models, and decreases in this neurosteroid have been associated with depressive symptoms in humans. Furthermore, we recently determined that pregnenolone levels in parietal cortex in patients with schizophrenia who died by suicide are significantly reduced compared to pregnenolone levels in patients with schizophrenia who died of other causes. Clozapine-induced pregnenolone elevations could thus potentially contribute to its therapeutic actions. METHODS: In the first set of experiments, intact, adrenalectomized, and sham-operated male rats received vehicle or clozapine (20 mg/kg) IP, n=6-10 rats per condition. In the second set of experiments, male rats received vehicle, olanzapine (5 mg/kg), quetiapine (20 mg/kg), ziprasidone (10 mg/kg) or aripiprazole (5 mg/kg) IP, n=9 rats per condition. Pregnenolone levels were determined by gas chromatography/mass spectrometry preceded by high performance liquid chromatography purification. RESULTS: Clozapine markedly elevates pregnenolone in rat hippocampus (13-fold), cerebral cortex (26-fold), and serum (34-fold). Pregnenolone levels in hippocampus are strongly correlated with pregnenolone levels serum ($r=0.987$, $p<0.0001$). Adrenalectomy prevents clozapine-induced elevations in hippocampal and serum pregnenolone levels. Olanzapine also elevates pregnenolone levels, but to a lesser degree compared to clozapine. CONCLUSIONS: Pregnenolone induction may contribute to the therapeutic actions of clozapine and possibly olanzapine. Given the magnitude of clozapine effects on pregnenolone levels in two brain regions and peripheral serum in these investigations, it is possible that marked pregnenolone induction following clozapine may contribute to mechanisms mediating its superior clinical efficacy. Pregnenolone induction may also be relevant to clozapine's therapeutic actions on suicidal behaviors.

CORTICAL CHOLINERGIC DEFICIENCY ENHANCES AMPHETAMINE-INDUCED DOPAMINE RELEASE IN ACCUMBENS BUT NOT IN STRIATUM

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Disturbances of cholinergic functions has been implicated as a putative contributing factor in the pathogenesis of schizophrenia. Recently, we showed that cholinergic denervation of cortex cerebri in adult

rats leads to a dramatic increase in the behavioral response to amphetamine in the form of increased locomotor activity. This increase was not mimicked by the administration of dopaminergic agonists, suggesting that the behavioral effect is due to an altered state of the dopamine neurons caused by the loss of cholinergic innervation of cortex cerebri. Therefore, the main objective of this study was to investigate if the enhanced locomotor response to amphetamine seen after cortical cholinergic denervation was paralleled by an increased amphetamine-induced release of dopamine in nucleus accumbens and/or striatum. We hypothesize that a possible consequence of cortical cholinergic dysfunction might be dysregulation of subcortical dopamine, which in turn could contribute to the psychotic symptoms seen in schizophrenia. The corticopetal cholinergic projections were lesioned by intraparenchymal infusion of 192 IgG-saporin into nucleus basalis magnocellularis of adult rats. Amphetamine-induced dopamine release in nucleus accumbens or striatum was monitored by in vivo microdialysis two to three weeks after lesioning. The results demonstrated that cholinergic denervation of the rat neocortex leads to a significantly increased amphetamine-induced dopamine release in nucleus accumbens. Interestingly, the cholinergic lesion did not affect amphetamine-induced release of dopamine in striatum. The relative levels of the dopamine metabolites DOPAC and HVA after amphetamine-challenge were not significantly altered in accumbens or striatum in saporin-treated rats. Neither did basal levels of dopamine, DOPAC and HVA differ between groups. Administration of nicotine before the amphetamine-challenge did not reverse the enhanced dopamine release in the cholinergically denervated rats, suggesting that loss of muscarinic receptor stimulation was likely to have caused the observed effect. The results suggest that abnormal responsiveness of dopamine neurons can be secondary to cortical cholinergic deficiency. This in turn might be of relevance for the pathophysiology of schizophrenia and provides a possible link between cholinergic disturbances and alteration of dopamine transmission.

AMISULPRIDE'S ANTIPSYCHOTIC ACTIONS IN ANIMAL MODELS FOLLOW A TIME COURSE REFLECTIVE OF ITS IN-VIVO $D_{2/3}$ OCCUPANCY

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Amisulpiride(AMI) is a substituted benzamide with high and selective affinity for dopamine D_2 (Ki 1.3nM) and D_3 (Ki 2.4nM) receptor subtypes. It is a very interesting 'atypical' antipsychotic as it shows no significant affinity for 5-HT_2 or $5HT_{1A}$ receptors, has a very high affinity for D_2, yet shows fast dissociation and is required in high doses (usually associated with drugs with low affinity). To understand its mechanism of efficacy, in animal models, we investigated the time course of D_2 striatal receptor occupancy($D2_{RO}$) using [3H]raclopride as a tracer, and correlated it to behavioral effects in models of amphetamine induced locomotor activity(AIL), conditioned avoidance response(CAR), catalepsy(CAT) and plasma prolactin levels(Prl). AMI over a dose range of 1-100mg/kg/s.c. resulted in a 'delayed' pattern of D^2RO: a maximal D^2RO of 42.98, 60.17 and 87.8% after 1, 2 and 6hrs respectively, after drug administration. AMI was ineffective 1hr after administration while inhibiting AIL & CAR 6hrs later. Even at 6hrs, despite high D^2RO, it showed no CAT. Prl levels (reflective of peripheral D^2RO) conversely showed a different picture - 1hr after administration the dose required for 200% elevation from baseline was 7.23mg/kg while at 6hrs there was no significant prolactin elevation even with 100mg/kg. Comparing it to haloperidol(HAL), risperidone(RIS) and clozapine(CLZ) (1hr after administration), HAL over a dose range of 0.025–1mg/kg showed a D^2RO range of 46-89%, while RIS 0.02–2mg/kg showed a range of 20-87% and CLZ 2.5–60mg/kg showed an occupancy range of 24-75% (ED^{50} values–refer table). HAL and RIS showed an increased propensity for catalepsy as D2RO crossed 80%. HAL, RIS and CLZ, 1hr after administration, were effective in inhibiting AIL as well as CAR. CLZ showed no prolactin elevation but, HAL and RIS significantly elevated prolactin levels 1hr after administration. The above study relates AMI's functional profile (delay in occupancy, increase in dose required and Prl elevation) to poor penetration of the BBB.

Table: D_2RO occupancy and efficacy indicators among antispychotics

Drug	D_2RO ED50	AIL ED50	CAR ED50	CAT ED50	Prolactin ED200
AMI	4.68(6hr)	4.97(6hr)	20.8(6hr)	>100(6hr)	7.23
HAL	0.02	0.02	0.01	0.3	0.15
RIS	0.19	0.38	0.79	1	0.15
CLZ	21.03	9.97	2.26	>60	-

Doses mentioned are in mg/kg,s.c. All values are for 1hr after administration except in cases where they are mentioned.

NEONATAL EXPOSURE TO NEUREGULIN-1 RESULTS IN DISTINCT BEHAVIORAL ABNORMALITIES IN MICE; COMPARISON WITH OTHER CYTOKINE TREATMENTS

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Neuregulin-1 (NRG1) belongs to the epidermal growth factor (EGF) family and is suggested to be a risk gene for schizophrenia, although etiological or pathological mechanisms remain to be characterized. We previously reported that neonatal exposure to the proinflammatory cytokines, EGF and interleukin-1 (IL-1), perturbs dopaminergic development as well as synaptic maturation, leading to the behavioral and cognitive impairments that are often implicated in schizophrenia animal models. In the present study, we examined influences of in vivo NRG1 administration on mouse brain development and neurobehavioral consequences, and compared their behavioral characteristics with those induced by other cytokines such as EGF and IL-1. We produced and purified mouse Ig-NRG1beta protein (MW 25000) using the bacterial recombinant system and subcutaneously administered it (1 microgram/ g body weight) to neonatal mice (C57BL/6J). Repeatedly injected Ig-NRG1beta penetrated the blood-brain barrier and activated ErbB4 receptors in neonatal brain. At the adult stage, the Ig-NRG1beta-treated mice showed normal response in the fear-conditioning task, but were impaired in its latent learning paradigm. Prepulse inhibition (PPI) of the Ig-NRG1beta-treated mice was modestly decreased and social interaction score was normal, which are distinct from the behavioral features of EGF- and IL-1-treated mice. These results suggest that endogenous production or release of NRG1 during brain development results in unique cognitive and behavioral abnormalities. This study is supported by research grants from Kyowa Hakkou Chem., JST, MECSST and MHLW.

THE POSTERIOR CINGULATE CORTEX: A SITE OF ALTERED NEURAL CIRCUITRY IN SCHIZOPHRENIA AND NMDA HYPOFUNCTION

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Background/Purpose: The posterior cingulate cortex (PCC), part of the limbic system, has recently been implicated in the pathophysiology of schizophrenia. In addition to recent functional imaging studies implicating this brain region, NMDA antagonist treatment in rodents has been shown to cause selective damage to this brain area. This study aimed to examine neural circuitry of the PCC in schizophrenia and in an NMDA hypofunction animal model. Methods: Schizophrenia subjects and matched controls (9 pairs on average) were used to investigate the binding of several important neurotransmitter systems (see table 1). Furthermore, the PCC was examined in mice treated chronically with PCP. The early treatment group was treated with PCP (10mg/kg/day) for 14 days and sacrificed 1 hour after the final PCP injection. The delayed treatment group was treated for 14 days with PCP (10mg/kg/day) and sacrificed 14 days after the final PCP injection. Results: The results as presented in table 1 show selective neurotransmitter receptor alterations in the PCC in schizophrenia and in the NMDA hypofunction animal model. Conclusion: These studies clearly show an involvement of the PCC in both the pathology of schizophrenia and in NMDA hypofunction. The delayed PCP treatment produces a state of NMDA hypofunction in the PCC, although this downregulation of NMDA receptors does not reflect what was found in the schizophrenia tissue. However, the delayed effect of PCP treatment on M1/4 receptor density is in line with that found in the schizophrenia PCC. This NMDA receptor hypofunction animal model may therefore represent some aspects of schizophrenia.

Table 1: Posterior cingulate cortex receptor changes in schizophrenia and in the chronic PCP mouse model

Human	Control	Schizophrenia	%change
NMDA	141.3±11.8	200.3±10.6	+41
AMPA	231.4±25.4	249.4±23.9	No change
Kainate	12.6±2.0	13.2±1.5	No change
M1/4	85.9±4.2	65.1±5.5	-24
M2/4	28.5±4.0	27.5±2.4	No change
GABAA	16.2±2.0	34.3±4.0	+112
CB1	49.2±5.0	61.3±2.6	+25
5HT2A	20.5±1.1	13.5±1.9	-34
Mouse model	Control	PCP	%change
NMDA-early	335.3±11.5	334.9±10.3	No change
NMDA-delayed	336.3±18.4	270.7±10.0	-20
M1/4-early	52.3±3.1	128.1±13.0	+145
M1/4-delayed	52.9±3.1	28.5±2.0	-46

A REDUCTION IN VENTRAL TEGMENTAL GABA TRANSMISSION IS ASSOCIATED WITH ABRUPT CLOZAPINE WITHDRAWAL

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Sudden discontinuation of clozapine causes rebound psychosis in 39% of patients but in only 6-11% of those taking typical antipsychotics (Meltzer at al., 1996). The present study investigated the effect of abrupt clozapine withdrawal on VTA GABA transmission in the maternally deprived and the socially isolated rat models of schizophrenia. Microdialysis was employed in the VTA to monitor dialysate GABA levels in vehicle and clozapine-treated (5mg/kg i.p. daily, 10 days) isolated and maternally deprived rats over a 6-day withdrawal period. Socially reared rats acted as controls. A two-factor ANOVA was employed for significance (n=7-8 animals per group). Basal dialysate VTA GABA levels (nM) were similar in the vehicle-treated social control and maternally deprived rat (14±4 and 11±3 respectively) but were reduced by 55±11% (v's social controls) in the isolated rat (6.5±1.5, p=0.0066 v's social control) and chronic clozapine had no effect on GABA levels in any of the groups. However, clozapine withdrawal reduced GABA release in the control and maternally deprived rats by 39-70% over a 6-day withdrawal period (p=0.029 v's vehicle-treated controls) without affecting it in the isolated rats. The reduction in VTA GABA release in both control and maternally deprived rats associated with clozapine withdrawal may reflect a clozapine-induced supersensitivity of inhibitory dopamine, serotonin and acetylcholine receptors on the VTA GABA interneuron while the absence of this effect in the isolated rats may reflect a lack of interneuronal GABA as indicated by the observed reduction in basal dialysate GABA levels. In conclusion, the findings indicate that chronic clozapine targets VTA GABA transmission and the observed reduction in VTA GABA release during clozapine withdrawal suggests that reduced VTA GABA transmission may play a role in rebound psychosis. Furthermore, the ability of ligands to reverse this clozapine-withdrawal induced decrease in VTA GABA transmission may represent a useful model for screening novel antipsychotic agents. References Meltzer H.Y., Lee M.A., Ranjan R., et al., Relapse following clozapine withdrawal: effect of neuroleptic drugs and cyproheptadine (1996) Psychopharmacology, (Berl), 124, 1-2, 176-187. Acknowledgements This work was supported by a Science Foundation Ireland award to W.T. O'Connor, NDP, HEA, PRTLI and Wyeth.

ACTIVATING THE IMMUNE SYSTEM OF PREGNANT MICE CAUSES CHANGES IN THE OFFSPRING RESEMBLING THOSE IN SCHIZOPHRENIA AND AUTISM

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Maternal viral infection is associated with increased risk of schizophrenia and autism in the offspring. In developing a mouse model based on this risk factor, we found that respiratory infection with influenza virus at mid-gestation leads to behavioral abnormalities in the adult offspring. These are consistent with abnormalities seen in schizophrenia and autism, including enhanced anxiety, as well as deficits in social interaction (SI), latent inhibition (LI) and prepulse inhibition (PPI). The latter is corrected by anti-psychotic and exacerbated by psychomimetic drugs. These adult offspring display neuropathology in the hippocampus and cerebellum that is similar to that found in schizophrenia and autism, respectively. There is also a striking abnormality in the migration of late-born cortical neuroblasts, which resembles that seen the knockdown of Disrupted in Schizophrenia-1. The cause of these abnormalities is likely to be the maternal response to viral infection, as we find no evidence of virus in the fetus, and treatment of uninfected, pregnant mice with the dsRNA, poly(I:C), which evokes an anti-viral-like immune response,

also induces SI, PPI and LI deficits in the offspring. We have identified the cytokine IL-6 as a key mediator of the effects of the activated maternal immune response on fetal brain development and subsequent behavior of the offspring. That is, injection of IL-6 in normal, pregnant mice causes PPI and LI deficits in the offspring. Conversely, injection of anti-IL-6 antibody along with poly(I:C) in pregnant mice strongly attenuates the effects of poly(I:C) on the behavior of the offspring. Similarly, anti-IL-6 blocks the changes in gene expression the brains of adult offspring elicited by maternal poly(I:C) treatment.

DO NEUROTROPHINS HAVE THERAPEUTIC POTENTIAL IN SCHIZOPHRENIA?: ERYTHROPOIETIN PREVENTS HALOPERIDOL TOXICITY THROUGH INCREASED EXPRESSION OF BDNF

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The key role of neurotrophic factors such as BDNF in neural development and cell repair has generated intense interest (and provocative data) now concerning their role in psychiatric disorders, including schizophrenia. Postmortem brain and clinical (csf and blood) studies point to marked decrements in BDNF in schizophrenia. Moreover, provocative results from studies in rodents have shown time dependent differential effects of first (FGA) and second-generation (SGA) antipsychotics on BDNF. BDNF levels increase by short-term (14 days) treatment with both FGAs and SGAs but decline, earlier with FGAs than SGAs, the BDNF expression when treated for long-term (i.e., 180 days) in adult rats. These studies suggest that agents acting as BDNF agonists (particularly in combination with SGAs) might sustain BDNF levels and thereupon be of potential therapeutic significance. We report here that in primary mouse cortical neurons, erythropoietin, a potent neuroprotective agent, could prevent haloperidol toxicity through increased expression of BDNF. Erythropoietin concentrations at 3 and 30 pm significantly protected neuronal cells from haloperidol toxicity by 18% and 50%, respectively. This effect resulted in a time-dependent parallel increase in BDNF expression. The reduction of haloperidol induced neuronal death by erythropoietin was partially, but significantly, prevented by neutralizing BDNF with anti-BDNF antibody (15 ug/ml). Erythropoietin also significantly protected the cellular morphology from haloperidol induced loss of dendrites and shrinkage of cell bodies. Haloperidol treatment showed time-dependent decrease in Akt as well as Erk phosphorylation, but increase in p38MAPK phosphorylation. But erythropoietin significantly reversed the phosphorylation. The finding that erythropoietin protects neuronal cells from haloperidol toxicity by increasing BDNF expression provides a heuristic rationale for clinical investigation of the therapeutic implications of BDNF-related agents in schizophrenia.

MODULATION OF NEUROTROPHIC FACTOR AND INTRACELLULAR SIGNALING PATHWAYS: A ROLE IN SCHIZOPHRENIA AND ANTIPSYCHOTIC RESPONSE

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One of these proteins is the neurotrophin BDNF: autoptic analyses have demonstrated reduced expression of the neurotrophin and of its high affinity receptor TrkB in the schizophrenic brain, primarily at cortical level. The expression of BDNF is similarly reduced in rats exposed to stressful event during development, which represent a putative animal model of the disease. Pharmacological studies have demonstrated that chronic treatment with antipsychotic drugs may counteract the reduced expression of neuroplastic genes: a significant increase of neurotrophin expression in selected brain regions was found mainly following treatment with second-generation antipsychotics (SGA), but not with haloperidol. Neuro-adaptive changes associated with drug therapy are not limited to the modulation of BDNF, but may also involve intracellular signaling pathways associated with the neurotrophin. We have demonstrated that chronic, but not acute, treatment with the SGA olanzapine increases the phosphorylation of ERK 1/2, a signaling cascade that regulates a broad range of fundamental cellular and can be considered a crucial integrator of multiple signaling pathways. Major changes in ERK activation are found is in selected cellular compartment of the prefrontal cortex, whereas no significant changes were observed with haloperidol, suggesting that these adaptive mechanisms may contribute to the amelioration of domains that show a better response to SGA. Moreover long-term olanzapine treatment produces a significant increase in the phosphorylation of αCaMKII in prefrontal cortex, primarily in the membrane fraction where the kinase can modulate glutamate function through the interaction with NMDA receptors. We believe that adaptive changes taking place following antipsychotic drug treatment may converge upon the modulation of neuroplastic molecules, such as BDNF, and intracellular signaling pathways leading to an improvement in brain plasticity and contributing to the functional recovery of schizophrenic patients.

ACTIVATION OF THE CANONICAL WNT PATHWAY BY THE ANTIPSYCHOTICS HALOPERIDOL AND CLOZAPINE INVOLVES DISHEVELLED-3

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Akt, glycogen synthase kinase-3 and members of the Wnt signal transduction pathway were recently found to be altered in schizophrenia and targeted by antipsychotic drugs. In the current study, selected Wnt signalling proteins were investigated to determine if they are altered by the antipsychotics clozapine or haloperidol in the rat prefrontal cortex. PC12 and SH-SY5Y cells were also used to elucidate how antipsychotics generated the pattern of changes observed in vivo. Western blotting revealed that treatment with haloperidol or clozapine caused an upregulation of Wnt-5a, dishevelled-3, Axin, total and phosphorylated glycogen synthase kinase-3 and β-catenin protein levels. Treatment of PC12 and SH-SY5Y cells with a variety of pharmacological agents as well as the overexpression of several Wnt related proteins failed to mimic the pattern observed in vivo following antipsychotic treatment. However, the overexpression of dishevelled-3 nearly perfectly duplicated the changes observed in vivo. Immunoprecipitations conducted using protein isolated from the rat prefrontal cortex indicated that dishevelled-3 is associated with the D2 dopamine receptor. Collectively, the data suggests that antipsychotics may act on dishevelled-3 via D2 dopamine receptors to initiate a cascade of downstream changes involving Axin, GSK-3 and β-catenin that may help to alleviate psychosis in schizophrenic patients.

CHRONIC HALOPERIDOL GRADUALLY AND PERSISTENTLY LOSES ITS ANTIPSYCHOTIC EFFICACY OVER TIME: PRE- AND POST-SYNAPTIC CHANGES IN DOPAMINE FUNCTION DURING TREATMENT

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Antipsychotics often fail in patients after inducing an initial remission, despite patients taking them regularly. Why this occurs is not known. However, it is known that antipsychotic withdrawal results in transient supersensitivity to the psychotogenic and psychomotor activating effects of dopamine (DA) agonists in humans and rats, respectively. Using therapeutically meaningful doses (0.25-0.75mg/kg/d) and modes of administration (continuous delivery for 14 d via minipump), we showed previously that haloperidol (HAL) gradually loses its ability to inhibit amphetamine (AMPH)-induced locomotion and conditioned avoidance responding in rats. This loss occurred in the face of persistently high levels (80%) of DA D2 receptor occupancy. Behavioural supersensitivity to DA agonists has been linked to elevated levels of striatal D2 receptors in the high-affinity state for DA (D2High). Indeed, we found that the loss of the antipsychotic effects of HAL was accompanied by 193% (0.25 mg/kg) and 224% (0.75 mg/kg) increases in the density of D2High. In addition, striatal D2 receptor binding capacity was increased by 20-40%, suggesting an increase in total receptor number. To further explore the processes whereby HAL gradually loses its antipsychotic effects, we used in vivo microdialysis techniques in freely moving rats to examine changes in extracellular DA and DA turnover during ongoing HAL treatment. Chronic HAL (0.75 mg/kg/d, 13d, via minipump) resulted in significant time-dependent changes in basal DA levels in the nucleus accumbens. Basal levels of DA, DOPAC and HVA were elevated during short-term (2-3 d) HAL treatment, and depressed during long-term (12-13d) HAL treatment. In spite of these changes, however, the increases in DA levels in response to acute AMPH were unaltered during the course of HAL treatment. These results suggest (1) that antipsychotic-induced supersensitivity to DA agonists is not due to pre-synaptic changes in DA releasability, and (2) that DA turnover is suppressed, and D2 receptor function is enhanced during long-term HAL treatment. These data demonstrate that the "breakthrough" sensitivity to DA agonists and the loss of antipsychotic efficacy seen during ongoing antipsychotic treatment might be mediated in part by altered D2 receptor signaling. These findings point to a neurobiological mechanism whereby antipsychotics lose efficacy in a number of patients, and to potential directions for the development of more effective treatments.

PHARMACOLOGICAL CHARACTERIZATION OF GLYCINE TRANSPORTERS 1 AND 2 USING NOVEL MOUSE CORTICAL AND SPINAL CORD SLICE ASSAYS

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Glycine is an important neurotransmitter in the mammalian CNS, acting on two distinct receptor systems. In spinal cord, glycine has an inhibitory effect mediated by the activation of strychnine-sensitive glycine receptors. In addition, glycine acts in the forebrain via a strychnine-insensitive regulatory site on the NMDA receptor complex as an obligatory co-agonist with glutamate. Glycine activity is terminated by a rapid, sodium-dependent, uptake system. Two distinct types of glycine transporters (GlyT1 and GlyT2) have been cloned and pharmacologically characterized in heterologous systems and in native synaptosome preparations. NMDA receptor hypofunction in schizophrenia may contribute to the positive, negative and cognitive symptoms of this disorder. Therefore, a selective increase of NMDA activity in the forebrain by increasing synaptic glycine via GlyT1 inhibition could provide a new approach to the treatment of schizophrenia. The aim of this study was to develop glycine uptake assays using tissue slices and to pharmacologically characterize the effect of selective glycine uptake inhibitors. Two 96-well plate assays were developed using mouse cortical and spinal cord slices to confirm the tissue distribution of these two distinct glycine transporters. Competition studies suggest that the sodium-dependent [2-3H]-Glycine uptake into these preparations has a narrow selectivity for glycine, with other amino acids producing minimal effect. Kinetic studies were performed and the parameters obtained were in accordance with published data using synaptosome preparations. The selective GlyT1 inhibitor ALX-5407 demonstrated robust inhibition of glycine uptake in cortical preparations, with an IC50 value of 7.2 + 0.55 nM. Interestingly, ALX-5407 at the highest concentration tested (30 μM) partially inhibited the glycine uptake in spinal cord slices, consistent with the presence of both GlyT1 and GlyT2. In contrast, the selective GlyT2 inhibitor ORG-25543 inhibited glycine uptake into spinal cord preparations with an IC50 value of 6.6 + 0.33 nM, while glycine uptake into cortical preparations was not inhibited. These functional and pharmacological studies with native preparations confirm the tissue distribution of glycine transporter subtypes and can be used to understand the selectivity of new glycine uptake inhibitors in native preparations.

NEUROCHEMICAL AND BEHAVIORAL PROFILING OF THE SELECTIVE GLYT1 INHIBITORS (±)-ALX-5407 AND LY2365109 INDICATE A PREFERENTIAL ACTION IN THE BRAIN STEM AND CEREBELLAR VS PREFRONTAL CORTICAL BRAIN AREAS

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Selective inhibitors of the glycine transporter(GlyT1) have been implicated in CNS disorders related to a hypoglutamatergic function such as schizophrenia. Elevation of synaptic levels of the NMDA co-agonist, glycine, could lead to antipsychotic effects including improved cognitive function. In vivo profiling of the selective GlyT1 inihibitors (±)-ALX5407 and LY2365109 (GlyT1 IC50's of 7 nM and 16 nM, respectively with >1,000 –fold selectivity vs GlyT2 in vitro) revealed enhanced CSF levels of glycine along with potentiation of NMDA-induced increases in extracellular levels of neurotransmitters in the PFC. However, higher doses clearly indicated inhibitory effects on motor performance (ataxia) and also respiration, suggesting significant involvement of cerebellar and brain stem areas. A dual probe in vivo microdialysis study in the rat showed that (±)-ALX5407 HCl (10 mg/kg, PO) transiently elevated PFC levels (+ 50%) of glycine (duration 4 hrs) while levels in the cerebellum(+150%) were maximally elevated for at least 9 hrs. A similar

profile was noted for LY2365109 (3 mg/kg, PO) when dialysate glycine levels were measured in the PFC and the brain stem from the same animal. Interestingly, in a similar dual probe experiment, a high dose of glycine (600 mg/kg, SC) elevated dialysate PFC glycine levels by +300 % and brain stem glycine levels by +900 % at 1 hour post treatment, but with no observable effect at 2 hours. Also, no overt behavioral changes were noted in these animals. In support of these observations, Western analyses (immuno-blotting) with both PAN-GlyT1 and GlyT1a antibodies showed a high abundance of GlyT1 and GlyT1a immuno-staining in brain stem/cerebellar vs the frontal cortical/hippocampal brain areas in tissue samples from all species studied (mouse, rat, primate and human). Finally, the inhibitory effects of (±)-ALX5407 (3 mg/kg, SC) on cerebellar levels of cGMP post mortem in the mouse, as well as the overt behavioral signs in rats, could be reversed by the glycine receptor antagonist strychnine. Taken together, these results suggest that the adverse events observed with higher doses of GlyT1 inhibitors are due to a preferential and sustained inhibition of GlyT1 sites in the caudal areas of the brain, possibly the GlyT1b sites based on KO data. This preferential inhibition results in activation of strychnine-sensitive glycine receptors that are inhibitory on both motor activity and critical brain stem functions such as respiration.

ASENAPINE: PRECLINICAL EVIDENCE FOR CLINICAL EFFECTS IN SCHIZOPHRENIA AND COGNITIVE DYSFUNCTION

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Asenapine, a novel psychopharmacologic agent being developed for the treatment of schizophrenia and bipolar disorder, was evaluated in rat behavioral tests predictive of antipsychotic activity (conditioned avoidance response [CAR]) and extrapyramidal symptoms (catalepsy). We also measured the effects of asenapine on (1) dopamine (DA) output in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) using in vivo microdialysis in freely moving rats; (2) DA output in the shell and core subregions of the NAc using in vivo voltammetry in anesthetized rats; (3) firing rate and burst firing in DA neurons in the ventral tegmental area (VTA) using in vivo single-cell recording in anesthetized rats; and 4) N-methyl-D-aspartate (NMDA)-induced currents in pyramidal neurons of the mPFC using in vitro electrophysiologic intracellular recording technique. Asenapine 0.05–0.2 mg/kg s.c. induced dose-dependent suppression of CAR (at 0.2 mg/kg, 91.5±7.5%) but did not induce catalepsy at any time interval studied (30–120 min). Similar to clozapine but not haloperidol, asenapine 0.05–0.2 mg/kg s.c. increased DA efflux in both the mPFC (maximal effect, 219.2±15.1% of control) and the NAc (235.5±21.1%) in a dose-related manner. Also, in similarity to clozapine, low-dose asenapine (0.01 mg/kg i.v.) increased DA to a greater extent in the shell than in the core region of the NAc, whereas the ratio changed at a higher dose (0.05 mg/kg i.v.). Asenapine (0.001–0.2 mg/kg i.v.) increased both firing rate and burst firing in VTA neurons in a dose-related manner. Like clozapine (100 nM) but at a considerably lower concentration (5 nM), asenapine potentiated NMDA-induced responses in pyramidal cells of the mPFC (156±19% of control). These preclinical data suggest that asenapine may exhibit highly potent antipsychotic activity with a low risk of inducing extrapyramidal symptoms. Its ability to increase both dopaminergic and glutamatergic activity in rat mPFC suggests that asenapine may have an advantageous effect not only on positive symptoms in patients with schizophrenia but also on negative and cognitive symptoms. This work was supported by the Swedish Research Council (grant no 4747), the Karolinska Institutet, Organon Laboratories Ltd and Pfizer Inc.

THE GLYT1 INHIBITOR SSR504734 IS AS EFFECTIVE AS HALOPERIDOL IN COUNTERACTING THE CEREBRAL METABOLIC EFFECTS OF SUBACUTE PHENCYCLIDINE ADMINISTRATION IN THE RAT

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Due to its still largely unknown etiology, there is no comprehensive disease model of schizophrenia that can be used as a predictive tool for testing the potential clinical utility of novel antipsychotic principles not validated in patients. We have shown previously in the rat that subacute phencyclidine (PCP) administration produces a specific pattern of changes in local cerebral glucose metabolism that presumably reflects mechanisms underlying schizophrenia-like behaviors observed in humans but not readily detectable in rodents. In the present study we addressed the question whether these changes can be alleviated by the typical antipsychotic haloperidol or by the glycine transporter 1 (GlyT1) inhibitor SSR504734. Three groups of male Long Evans rats were treated with 15 mg/kg/day PCP i.p. by means of implanted osmotic minipumps for 14 days; the control group received saline via the same route. On the last day of the study PCP-treated animals were administered either no additional drug, 0.5 mg/kg haloperidol i.p., or 10 mg/kg SSR504734 i.p. Cerebral metabolic rate of glucose was determined 80 min later in freely moving animals with the [14C]deoxyglucose technique of Sokoloff in 60 predefined brain regions. Statistical assessment was carried out by one-way analysis of variance and post hoc multiple comparisons employing the Holm-Sidak procedure. PCP treatment resulted in metabolic activation of limbic areas (accumbens nucleus, cingulate cortex, olfactory tubercle, amygdala), the extrapyramidal system (striatum, globus pallidus, substantia nigra), and regions of the neocortex (somatosensory, retrosplenial, parietal, auditory, visual). This metabolic activation was completely offset by both treatments in all affected regions except in the olfactory tubercle and—in the case of haloperidol—in the core of the accumbens nucleus. However, haloperidol also induced significant metabolic suppression in 14 regions, 11 of which were not affected by PCP alone, while this phenomenon was observed only in three regions after SSR504734 treatment. These findings indicate that the inhibition of GlyT1 is as effective as the antagonism of the D2 dopamine receptor in alleviating local brain hyperactivity in the PCP model of schizophrenia and suggest that GlyT1 inhibitors may be less prone to unwanted CNS effects than haloperidol. The data lend further support to the construct validity of employing local brain metabolism as an endpoint in animal models of psychiatric disorders.

TIME DEPENDENT DECREASES IN CENTRAL ALPHA 7 NICOTINIC-ACETYLCHOLINE RECEPTORS ASSOCIATED WITH HALOPERIDOL AND RISPERIDONE TREATMENT IN RATS

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Several post mortem studies indicate that alpha 7 nicotinic-acetylcholine receptors (nAChRs) are decreased in the brains of schizophrenic patients. Such receptor deficits may contribute to abnormalities of smooth pursuit eye movements, as well as deficits in sensory gating, sustained attention, and cognitive performance often observed in schizophrenia. However, the extent to which antipsychotic drugs contribute to alpha 7 nAChRs alterations is unknown given that the brains of antipsychotic-naïve schizophrenia patients have rarely been analyzed. This may be an especially important consideration since many schizophrenia patients are treated with antipsychotic drugs for decades. In the present study in rats, the effects of chronic oral treatment with a representative first generation antipsychotic, haloperidol, and a representative second generation antipsychotic, risperidone, on the levels of alpha 7 nAChRs in several (memory-related) brain regions were investigated. Rats were treated with haloperidol (2.0 mg/kg/day) or risperidone (2.5 mg/kg/day) orally in drinking water for periods of 15 or 90 days and then sacrificed. The brains were subsequently removed, dissected, and ELISAs for alpha 7 nAChRs were performed on lysates from the basal forebrain, hippocampus, cortex, and prefrontal cortex. The results indicated that while neither antipsychotic drug significantly affected the levels of alpha 7 nAChRs when administered for 15 days in any of the brain regions analyzed, both antipsychotics were associated with significant receptor decreases in the basal forebrain and prefrontal cortex when administered for 90 days (i.e., by as much as 22% in the case of haloperidol and 15% in the case of risperidone). These data are in general agreement with previous experiments in our laboratory using quantitative receptor autoradiography, and suggest that that haloperidol and risperidone administration may be associated with time dependent decreases in an important neurobiological substrate of memory (i.e., brain alpha 7 nAChRs). Supported by NIMH (MH 066233)

CHARACTERISATION OF ORG 25935: A SELECTIVE GLYT-1 GLYCINE UPTAKE INHIBITOR

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Facilitation of central NMDA receptor function through elevation of the obligatory co-agonist glycine may address glutamatergic hypofunction thought to underlie some of the symptoms of schizophrenia. Selective inhibition of the GlyT-1 isoforms of the glycine transporter may achieve this end in a non-excitotoxic manner. Org 25935 displays high selectivity for hGlyT-1 isoforms (pIC_{50} 6.7 – 7.3) and lacks activity at hGlyT-2 (pIC_{50} <4) in addition to other Na^+/Cl^- dependent carriers. There is no significant interaction with either strychnine-sensitive or strychnine-insensitive glycine receptors and the compound lacks affinity at a wide range of biological receptor targets. [^{3}H]–Org 25935 binds to cells expressing cloned GlyT-1 and to rat brain sections in a saturable and reversible manner (K_D 34nM). Autoradiographic visualisation of binding in rat brain indicates high levels of [^{3}H]–Org 25935 binding in several areas including thalamus, habenula, paraventricular nucleus, hypothalamus, amygdala, cerebellum and brain stem nuclei. Mapping c-fos mRNA expression levels as a marker for neuronal activation following acute administration of Org 25935 (3 and 10mg.kg^{-1}) demonstrates a robust c-fos induction within the striatum, nucleus accumbens, amygdala, habenula and paraventricular nucleus (145%, 160%, 226%, 167% and 352% respectively of basal levels after 10mg.kg^{-1}). In some brain regions, such as the paraventricular nucleus and habenula, there is good correlation between high levels of [^{3}H]-Org 25935 binding and c-fos activation. However, in brain regions such as the striatum and nucleus accumbens robust c-fos activation is observed in the absence of significant [^{3}H]-Org 25935 binding, illustrating the central effects of Org 25935 on extended neuronal network activity. Microdialysis studies have demonstrated increases in glycine in several brain regions including striatum, hippocampus and frontal cortex of freely moving rats after intra-peritoneal administration (183%, 167% and 171% respectively of basal levels after 6mg.kg^{-1}). Glycine increases measured after oral administration of Org 25935 were sustained after several days of daily dosing (130-136% of basal level after 3mg.kg^{-1}) but other measured amino acids were not altered significantly after single or repeated administration. The characteristics displayed by Org 25935 indicate potential for application in the treatment of schizophrenia.

SUPERSENSITIVITY TO AMPHETAMINE IN PROTEIN KINASE-C INTERACTING PROTEIN (PKCI)/ HINT1 KNOCKOUT MICE

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PKCI/HINT1 is a member of the histidine triad protein family denoted by a HIT (HisXHisXHis, X is a hydrophobic amino acid) sequence motif. Its amino acid sequence is conserved in a broad range of organisms. Although PKCI/HINT1 protein is widely expressed in the mammalian brain including both mesocorticolimbic and mesostriatal regions, its physiological function in CNS remains unknown. Recent microarray studies reported decreased mRNA expression of PKCI/HINT1 in the frontal cortex of individuals with schizophrenia, suggesting the possible involvement of this protein in the pathophysiology of this disease. In view of the documented link between dopamine (DA) transmission and schizophrenia, the present study used behavioral and neurochemical approaches to examine the influence of constitutive PKCI/HINT1 deletion upon: (i) basal and amphetamine-evoked locomotor activity; (ii) DA dynamics in the dorsal striatum and (iii) post-synaptic DA receptor function. PKCI/HINT1-/- (KO) mice displayed lower levels of spontaneous locomotion relative to wildtype (WT) controls. Acute amphetamine administration significantly increased locomotor activity in WT mice, however, the effect that was enhanced in KO mice. No alteration in the locomotor response to morphine or bicuculline was seen. Quantitative microdialysis studies revealed no alteration in basal DA dynamics in the striatum or nucleus accumbens of KO mice. The ability of acute amphetamine to increase DA levels was unaltered indicating that function in presynaptic DA neurotransmission in these regions do not underlie the behavioral phenotype of KO mice. In contrast, however, to WT mice, systemic administration of the direct-acting DA receptor agonist apomorphine

(10mg/kg) significantly increased locomotor activity in KO mice suggesting that post-synaptic DA function is altered in these animals. These results demonstrate an important role of PKCI/HINT1in modulating basal locomotor activity and the behavioral response to amphetamine. Furthermore they indicate that the absence of this protein may be associated with dysregulation of post-synaptic DA transmission.

11. Neuroimaging, Structural

DYSMORPHOLOGY OF FACE AND BRAIN IN MALE SCHIZOPHRENIA VIA MRI IMAGING AND 3D MORPHOMETRICS – TOTAL SHAPE AND DIRECTIONAL ASYMMETRY

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Dysmorphology of brain and craniofacies have been reported in schizophrenia. In contrast to previous studies, we present a preliminary report on brain and craniofacial dysmorphology interrogated in a single dataset using a consistent analytical methodology. 3D landmarks were extracted from MRI data of patients with DSM-IV schizophrenia and controls. 37 landmarks were selected to index the brain and 9 landmarks to index the face. Comparisons were made between patients and controls for face and brain landmarks separately. Age matched groups were assembled. The sample for the analysis of face was 37 patients (mean age 39.6, SD 7.8) and 36 controls (mean age 42.8, SD 7.3) and for the analysis of brain was 41 patients (mean age 40.6, SD 7.8) and 33 controls (mean age 43.2, SD 7.7). Geometric morphometrics applied to 3D data allows patient-control differences to be tested with robust statistical analysis and visualised with dynamic 3D graphics. Overall differences in facial shape were tested by Goodall's F test [permutation version] and, where significant, statistical models of shape discrimination were produced by logistic regression and visualised by multivariate regression of shape PCs onto predicted group membership and warping mean facial landmarks along discriminant axes. Directional asymmetry was analysed by comparing the landmark configurations with their mirrored forms. Directional asymmetry was tested for significance and, where significant, visualised. The magnitude of directional asymmetry was calculated as the squared Procrustes distance (SPD) between the means of the original landmark configuration and its mirrored form. Mean shape was found to differ significantly between patients and controls for the 9 face landmarks. The visualisation of the shape discriminant model shows that the schizophrenia face is laterally narrowed, midsagittally lengthened and anterio-posteriorly shortened. Mean shape did not differ between patients and controls for the 37 brain landmarks. Directional asymmetry was found to be significant for the face landmarks for the schizophrenia group ($p<0.0001$, SPD=0.000147) but not the control group (NS, SPD=0.000005). For the 37 brain landmarks directional asymmetry was significant for both the patient group ($p<0.001$, SPD=0.000327) and the control group ($p<0.05$, SPD=0.000129). The findings are interpreted with reference to cerebro-craniofacial developmental biology.

THE CORPUS CALLOSUM KEEPS ON GROWING IN PRETERM ADOLESCENTS

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Introduction: The corpus callosum (cc) is the major fibre tract connecting left and right hemispheres. Abnormalities of the cc have been reported in schizophrenia. Individuals born very preterm (before 33 weeks' gestation) are at risk of damage to developing white matter, including the cc, and may be at increased risk of developing psychosis. White matter continues to grow into adulthood. However, little is known about the growth and maturation of the corpus callosum in VPT individuals. Methods: Seventy-two VPT individuals and 34 Term-born controls underwent structural MRI scans at two timepoints: adolescence (14-15 years) and young adulthood (18-19 years). Cross-sectional area of the cc was determined using Analyze. A rectangular boundary was drawn around the cc in the mid-sagittal plane, which was used to sub-divide it into 4 segments: anterior, mid-anterior; mid-posterior; posterior. Results: In adolescence, the VPT group had significantly smaller total cc than the Term group ($t=3.15$; $df=104$; $p=0.002$). RMANOVA revealed a main effect of timepoint ($F(1,104)=9.14$; $p=0.003$), cc segment ($F(1,104)=16.34$; $p<0.001$) and group ($F(1,104)=4.34$; $p=0.04$). Total cc cross-sectional area increased between adolescence and adulthood, by 3.3% ($t=-1.96$; $df=33$; $p=0.058$) in the Term group, and by 13.4% ($t=-4.94$; $df=71$; $p<0.001$) in the VPT group. This attenuated the size difference between VPT and Term groups, so that by adulthood there was no significant difference in total cc size ($t=1.23$; df=1-4; $p=0.22$). There were gender differences in the maturation of cc segments. VPT males showed significant increase in all 4 segments, whereas Term males showed no significant increase in any segment. Both VPT and Term females showed significant growth only in the mid-anterior segment. Conclusions: VPT adolescents start off with a smaller corpus callosum than Term adolescents. However, VPT individuals, particularly males, show much more growth of the cc during adolescence. This period of 'catch-up' growth may indicate delayed white matter maturation or enhanced neuroplasticity in VPT individuals. Since the VPT brain is still actively growing even late in adolescence, perhaps developmental interventions could be useful during this period. Maybe it is not too late to teach adolescent brains new tricks!

BRAIN VOLUME CHANGES IN FIRST EPISODE PSYCHOSIS IN ADOLESCENT PATIENTS DURING A 2 YEAR PERIOD

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Brain volume reduction larger than expected have been reported in patients with early onset schizophrenia. Our goal was to study the progress over time of brain changes in adolescents with a first episode psychosis. Twenty-three patients (6 females) and 37 controls (14 females) with a mean age of 15 years were included. All patients were treated with second generation antipsychotics. Two MRI from all subjects were obtained; at inclusion, and after a 2 yr period. Image segmentation into grey (GM), white matter (WM) and cerebro spinal fluid (CSF) was made using SPM2 routines, and a Talairach-based segmentation was used for volumetric measurements of whole brain and frontal, parietal, temporal, and occipital lobes. Differences between patients and controls were assessed at initial and follow-up scans by ANOVA, including age and sex as covariates in the model. To verify the existence of longitudinal changes, volume data for each ROI and tissue type were analyzed using a repeated model ANCOVA, with time as the repeated factor, and group as the between-subject factor. Age and sex were included as covariates. At the initial scan, patients showed significant increase of CSF in the frontal ($p< 0.0017$) and parietal lobes ($p< 0.023$), when compared to controls, and lower GM volume in the frontal lobe ($p< 0.008$). Control subjects showed the overall pattern of longitudinal changes expected for their

age range (12-18 yr at initial scan): increase of WM and a slight decrease of GM and CSF. For patienets a significant longitudinal effect of CSF increase was observed in the frontal ($p< 0.012$) and parietal lobes ($p< 0.028$). A significant longitudinal effect was also observed in WM of the occipital lobe ($p< 0.033$). However, the longitudinal effect in patients was not of the same magnitude as in controls, and volumetric differences between the two groups after the 2 year period did not increase. Our findings seem to suggest that in adolescents with a first psychotic episode, volumetric abnormalities are not progressive.

CANNABIS USE AND GRAY MATTER REGIONAL ALTERATIONS IN FIRST EPISODE SCHIZOPHRENIA-A VOXEL BASED MORPHOMETRIC APPROACH

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The role of cannabis on the brain of patients with schizophrenia is unclear at this time. Cannabinoid receptors (CB1) have been localized to prefrontal cortex, temporal and cerebellar regions. On this basis, we explored gray matter alterations in these regions in patients with neuroleptic naïve first episode schizophrenia (FES) with cannabis use to those who did not use cannabis. A series of 39 FES, 24 without cannabis use and 15 with cannabis use, and 42 healthy controls were recruited under the Conte Center for the Neuroscience of Mental Disorders (CCNMD; MH 45156) study. We defined cannabis use as those subjects who had smoked cannabis at least 10 times or more in their life. Voxel based morphometry was done on structural MRI scans obtained using GE 1.5 T scanner using statistical parametric mapping (SPM5) software. ANCOVA was used to analyze the effect of cannabis on FES group using age and gender as covariates. The threshold p value was set to <0.001 and a voxel threshold=30. FES patients with cannabis use showed a decrease in gray matter bilaterally in the insula and precuneus, right posterior cingulate and a trend in the left middle temporal and inferior frontal gyrus as compared to their cannabis naïve counterparts. The healthy controls showed increased matter in the insular area when compared with the FES with cannabis use. There was no increase in gray matter in the FES as compared to the control group. Increased gray matter in FES patients who did not use cannabis compared to FES who used cannabis suggests the possibility of gray matter reductions in the latter group. These observations suggest that co-morbid cannabis use can amplify schizophrenia related structural abnormality. Larger, prospective long-term follow-up studies are required to further evaluate the impact of cannabis and schizophrenia. Acknowledgements: This work was supported by funds received from NIMH grants MH45156, and the NIH/NCRR/GCRC grant #M01 RR00056.

HIPPOCAMPAL VOLUME CHANGES IN SCHIZOPHRENIA AFTER SWITCHING FROM TYPICAL ANTIPSYCHOTICS TO OLANZAPINE PREDICT THERAPEUTIC RESPONSE

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a) Our research group has demonstrated previously that chronic schizophrenia patients switched from typical antipsychotic drugs to olanzapine exhibited normalization of hypertrophy of the thalamus, globus pallidus and putamen, although no change was observed in the caudate nucleus. The purpose of the present study was to determine whether the switch to olanzapine is associated with changes in volume of the hippocampus, measured by MRI. b) 10 chronic schizophrenia patients and 20 healthy control subjects were recruited. At the baseline MRI scan and clinical evaluation, patients had been treated with various typical antipsychotics for a continuous period of at least 1 year. They were switched to olanzapine and rescanned approximately 1 year later. Coronal IR sequence MRI scans (4 mm slice thickness, 1mm interslice gap, 18 slices total) were acquired on a Siemens Vision 1.5T MRI scanner. Clinical status was assessed with ESRS and PANSS scales. c) Schizophrenia patients were symptomatic but stable at baseline, and there was no significant improvement in PANSS scores after the switch. For volumetric data, the ANOVA indicated no significant main effect of diagnosis (schizophrenia vs controls) nor of time (baseline vs follow-up scan). There was, however, a significant main effect of side (left vs right hippocampus) and a significant interaction between side and diagnosis. Posthoc tests indicated that the left hippocampus was smaller than the right for all subjects ($p<0.0001$) and the left hippocampus of schizophrenia patients was significantly smaller than in controls ($p<0.05$). Inspection of the data revealed considerable individual variability in symptom change. Interestingly, there was a clear association between individual hippocampal volume change and change in symptoms over time. All who had worsening of their PANSS scores showed a reduction in hippocampal volume. In contrast, all but one subject who showed improvement in their PANSS scores showed a concomitant increase in bilateral hippocampal volume. Regression analysis revealed a significant positive correlation ($r = 0.84$, $p<0.005$) between change in symptoms and change in volume. d) These data indicate no significant group effect of switching from typical antipsychotic drugs to olanzapine on bilateral hippocampal volume. Nevertheless, the association at an individual level between increases in hippocampal volume and symptom improvement after switching to olanzapine are worthy of further study.

ALTERED BRAIN GROWTH AND STRUCTURE IN CHILDREN AND ADOLESCENTS AT GENETIC RISK FOR SCHIZOPHRENIA

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Adolescence is a critical period for the maturation of the frontolimbic and fronto-striate circuits critical for higher-order cognition, and also coincides with the emergence of the prodromal signs of schizophrenia, possibly indicating an association between these two processes. We studied cortical development and structural alterations during this critical period in 10 healthy control (HC) subjects and 14 individuals at genetic risk for schizophrenia (GHR) (with a first degree relative with schizophrenia) between the ages of 9 and 18 using magnetic resonance imaging (MRI). Images were acquired on a 3T GE scanner with an 8 channel head coil and included a high resolution T1 and PD/T2 sequences. The analyses revealed no group differences in age, gender, or ethnicity, with marginally significant differences in education ($p<.08$) and parental education ($p<.06$). Significant differences emerged in the presence of early prodromal symptoms of schizophrenia as assessed using the Scale of Prodromal Symptoms ($p<.001$). Analysis of the MRI images evaluated (a) whether

the groups differed in their cortical growth patterns during this period, and (b) whether the groups showed volumetric differences in selected regions of the neural circuitry of interest, including the prefrontal cortex, anterior cingulate gyrus (ACG), hippocampus (HIP), and basal ganglia (BG), when controlled for age. All measures were corrected for intracranial volume (ICV)that was stable with age and showed no group differences. Analyses of the growth trends for the two groups across the ages of 9 and 18 revealed a significant Group*Age interaction (p<.04) indicating that total gray matter declined more rapidly during this period for the GHR group. Growth trends also significantly differed in BG regions, in the putamen and the globus pallidus, where the GHR group showed volume increases while the HC group showed volume reduction with age. Analyses of cortical and subcortical structures revealed significantly smaller ACG (p<.005), HIP (p<.004), and BG (putamen p<.02, globus pallidus p<.05) volumes in the GHR group. These findings indicate that genetic risk for schizophrenia is associated with significant structural alterations in critical nodes of the fronto-limbic and fronto-striate circuitry present as early as adolescence, which may represent vulnerability markers for illness onset. Longitudinal assessments will further inform about their predictive value for illness onset in high-risk populations.

ASSESSING EVIDENCE FOR NEURODEVELOPMENTAL COMPONENTS IN SCHIZOPHRENIA USING A MEASURE OF CORTICAL FOLDING: AN AUTOMATED - GYRIFICATION INDEX STUDY

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The Automated-Gyrification Index (A-GI) methodology makes it possible to examine the gyrification index (GI) of large cohorts [1, 2]. Here, this methodology is applied to the study of co-morbidity (CM) of Mental Retardation (MR) and Schizophrenia (SCZ) [3, 4]. The cohort consists of 4 groups: SCZ, MR, controls (CTL) and the CM group. The scan sequence and demographics for this cohort can be found in [4]. A-GI is an image processing tool developed in the Imaging Laboratory (Sackler Institute of Psychobiological Research) at the Division of Psychiatry, Edinburgh University. We applied A-GI to both prefrontal lobes, since prefrontal GI in schizophrenia have reported differences in gyral complexity with comparison to controls [2, 5, 6]. The data was analyzed by ANCOVA. Subjects with MR had the lowest GI values; the control group had the highest values, while the SCZ and CM groups were intermediate. These results are represented in table 1 (*statistically significant). No significant difference was found between the SCZ and CM groups, suggesting that - regardless of MR – lower GI is connected with SCZ. This is in keeping with the previous findings of a neurodevelopmental component to SCZ and CM [3]. Table 1 also indicates the general separation of the control and MR groups from the SCZ and CM groups. It was also noted that across all 4 groups a significant negative correlation between age and GI exists. This suggests that GI may not be a fixed measure as previously thought, and that it is vulnerable to other factors such as age-related changes in cortical depth and curvature. A post-hoc analysis demonstrated that although all 4 groups reflected a similar pattern of prefrontal lobe volume spatial differences, it did not account for the differences found in A-GI. 1. Zilles et al: Anat Embryol. 1988; 179(2):173-9. 2. Harris et al: Biol Psychiatry. 2004; 1; 56(3):182-9. 3. Sanderson et al: Lancet. 1999; 27; 354(9193):1867-71. 4. Moorhead et al: Neuroimage. 2004; 22(1):188-202. 5. Vogeley et al: Am J Psychiatry. 2001; 158: 494 - 6. 6. Kulynych et al: Biological Psychiatry. 1997; 41(10): 995 - 999.

Table 1

	CTL/SCZ	CTL/CM	CTL/MR	MR/CM	MR/SCZ	CM/SCZ
Left p value	0.017*	0.009*	<0.001*	0.152	0.098	0.813
Right p value	0.010*	0.011*	<0.001*	0.045*	0.044*	0.988

BRAIN VOLUMES IN RELATIVES OF PATIENTS WITH SCHIZOPHRENIA: A META-ANALYSIS

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Objective: Schizophrenia is a disorder characterized by brain volume reductions particularly in the medial temporal lobe. The extent to which brain abnormalities are related to a vulnerability to schizophrenia can be addressed by examining first-degree relatives. This is the first meta-analysis which integrates all MRI studies, examining global brain volumes and medial temporal lobe volumes, in first-degree relatives of patients with schizophrenia as compared to patients and healthy subjects. Method: A systematic search in the MEDLINE database was conducted to identify MRI studies in relatives of patients with schizophrenia as compared to healthy subjects. Studies had to report sufficient data for computation of the effect size. For each study Cohen's d, was calculated. All analyses were carried out in the random effects model. Results: Twenty-three studies were identified as suitable for analyses. The analyses included 1,065 independent first-degree relatives of patients, 679 patients with schizophrenia, and 1,100 comparison subjects. Comparing relatives of patients with schizophrenia to healthy subjects hippocampal volume (d=0.31, 95% CI=0.13-0.49) and gray matter volume (d=0.18, 95% CI=0.01-0.35) were found reduced in relatives. Third ventricle volume was increased (d=0.21, 95% CI=0.03-0.40). The hippocampal volume showed a further reduction in patients as compared to their relatives (d=0.46, 95% CI=0.19-0.72). Conclusions: This meta-analysis found that brain volume reductions are present in first degree relatives of patients with schizophrenia and that the hippocampus is most affected. Nevertheless, the volume reductions found in first-degree relatives are not as extensive as in patients.

STRUCTURAL BRAIN CHANGES IN TWIN PAIRS DISCORDANT FOR SCHIZOPHRENIA: A 5-YEAR FOLLOW-UP MRI STUDY

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Sibling and twin studies have revealed that genetic factors play an important role in the risk to develop schizophrenia, and are related to the brain abnormalities found in these patients (Boos, in press). Whether the progressive brain changes in schizophrenia are mediated by genetic or disease-related factors is inconclusive. A study in probands and their healthy siblings suggested that disease related (possibly non-genetic) factors may be involved in the progressive changes in total brain volume (TBV) and gray matter volume in schizophrenia (Brans, submitted). However, this setup may

have underestimated genetic influences. To draw more final conclusions, two 1.5 T MRI brain scans were obtained from monozygotic (MZ) and dizygotic (DZ) twins discordant for schizophrenia (23 MZ and 23 DZ subjects) and matched healthy comparison twin pairs (29 MZ and 27 DZ subjects) with a scan interval of 5 years. Compared to the baseline sample (Hulshoff Pol, 2004) 91% participated at follow-up. Quantitative assessments of intracranial, total brain, gray and white matter of the cerebrum, lateral and third ventricles volumes were performed. Disease and familial related effects for progressive TBV changes in schizophrenia were analyzed using structural equation modeling with Mx software. Multivariate genetic model fitting was applied to schizophrenia liability and brain volumes, correcting for age at baseline, gender and intracranial volume. A high heritability for the stable trait of TBV was found (within subject test-retest corr. = 0.86; MZ corr. = 0.81; DZ corr. = 0.27). Schizophrenia liability was associated with a smaller TBV (within-subject cross-trait corr. = -0.26; cross-trait/cross-twin MZ corr. = -0.21; DZ corr. = -0.11). Over time, a decrease of TBV was found, which was moderately correlated within twin pairs irrespective of disease (MZ corr. = 0.43 and DZ corr. = 0.34). The decrease in TBV became more pronounced with higher schizophrenia liability due to genetic or common environmental factors (cross–member cross–trait MZ corr. = -0.18 and DZ corr. = -0.18). Other brain volumes are currently being analyzed. These preliminary findings suggest that the progressive total brain volume changes in schizophrenia may be mediated (in part) by genes. This research was supported by Grant No. 908-02-123 (HEH) from the Netherlands Organization for Health Research and Development ZonMw.

CORTICAL SURFACE MORPHOLOGY IN SCHIZOPHRENIA

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The purpose of this study is to perform a detailed analysis of the cortical surface in subjects with an established diagnosis of schizophrenia. 84 patients with schizophrenia and 71 normal controls are compared using a novel surface morphology algorithm. The cortical surface of each subject (schizophrenia patient or normal control) was warped onto the cortical surface of a reference subject using a high-dimensional non-rigid warping based on fluid dynamics. The cortical surface from each subject was warped to be exactly the same size and shape of the cortical surface of the reference subject allowing precise identification of corresponding points on the cortical surface of the subject and of the reference brain. The warped cortical surfaces were then unwarped into the original coordinate space by reversing the high-dimensional warp. The labels identifying the corresponding points on the cortical surface of each subject and of the reference subject were maintained. Signed Euclidean distances between points on the cortical surface of each subject and the corresponding points on the reference brain were obtained. The signed Euclidean distances were compared statistically between the patients with schizophrenia and normal controls using linear regression at each point on the surface and covarying for age and sex. The statistical maps obtained revealed that the main differences in cortical surface morphology between patients with schizophrenia and normal controls are located in the dorsolateral prefrontal cortex, the parietal region and the superior temporal gyrus in the right hemisphere. In the left hemisphere differences in cortical morphology were smaller, but they followed a similar distribution with involvement of the supramarginal gyrus and the superior temporal gyrus. Although these results are preliminary, we conclude that patients with schizophrenia have smaller parietal and temporal regions when compared with normal control subjects. Regional volumes will be calculated to discern whether this pattern is due to loss of white matter, gray matter or both.

BRAIN MORPHOLOGICAL CHANGES 6 YEARS AFTER THE ONSET OF PSYCHOSIS

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It remains unclear whether brain changes observed in patients with psychosis remain stable or progress over the illness course. Unfortunately existing studies have used relatively small samples and have investigated patients at various stages of their illness, with few at illness onset. We investigated changes in brain volume 6 years after the first episode of psychosis. We evaluated brain volumes (grey and white matter, cerebro-spinal fluid [CSF]) at the first psychotic episode and 6 years later, using a Dual Echo sequence acquired with a 1.5T scanner. Brain volumes were measured with a voxel-based semi-automated method (Sbamm program). We evaluated 44 patients (14 females; mean age 27 SD 9; 21 schizophrenia) and compared them with 44 healthy controls (20 females; mean age 31 SD 9). Mean length of follow up was 6.4 (SD 1.5) years. Patients and controls showed similar reductions of grey matter, and increases of white matter and CSF over time. There was a trend for patients with a diagnosis of schizophrenia to show a larger increase in CSF volume than healthy controls (p=0.07). Patients who had more severe symptoms at baseline lost significantly more grey matter over time (p=0.026). Brain changes occur at a similar rate in patients and controls. However, there may be differences in progression in patients with different clinical characteristics. Changes may reflect abnormalities of synaptic plasticity, apoptosis, or an interaction of abnormal neurodevelopmental processes with environmental insults.

NEUROLOGICAL ABNORMALITIES IN FIRST EPISODE PSYCHOSIS: THEIR CLINICAL AND NEUROANATOMICAL CORRELATES

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Approximately 60% of subjects with schizophrenia present with minor neurological signs. These are sometimes termed “soft” signs, and include abnormalities in sensory and motor performance, which are indicative of non-specific cerebral dysfunction and are also present in healthy individuals, though at significantly lower scores. To date there is still a lack of consensus on the neurodysfunction underlying neurological soft signs (NSS), and it remains unclear whether part or all of the NSS excess in schizophrenia

could be an effect of antipsychotic medication. Our group has investigated a very large sample of 310 patients at their first psychotic episode, and 240 healthy controls. We have found that already at their first episode, patients with any psychosis show higher scores of NSS than healthy individuals, independently from antipsychotic use. In patients with psychosis, higher scores of NSS are associated with a reduction of grey matter volume of subcortical structures (putamen, globus pallidus and thalamus). Signs of sensory integration deficits are additionally associated with volume reductions of cortical association areas (precentral, superior and middle temporal, and lingual gyri). These brain changes are independent of the effects of antipsychotic exposure. In fact, use of antipsychotics is associated with enlargement, rather than reduction, of subcortical structures (basal ganglia and thalami). In healthy individuals, NSS are associated with a reduction of similar cortical areas. However, differently from patients with psychosis, NSS in healthy individuals are not associated with basal ganglia reductions. This work further supports the notion that NSS reflect abnormalities in specific brain areas. Studying their anatomical substrate can provide important information on the pathogenic processes that underlie schizophrenia and other neurodevelopmental disorders illnesses in which these signs are present in excess.

CEREBRAL MORPHOLOGICAL CORRELATES OF NEUROLOGICAL SOFT SIGNS IN FIRST-EPISODE SCHIZOPHRENIA

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Background: A subtle impairment of motor coordination functions is frequently found in patients with manifest schizophrenia. Clinically these deficits present as neurological soft signs (NSS). Their morphological cerebral correlates have rarely been investigated in a comprehensive way. Methods: Optimized voxel-based morphometry (VBM) was used to investigate gray matter (GM) density and its putative association with NSS in 42 patients with first-episode schizophrenia (all treated with atypical neuroleptics) and 22 healthy controls matched for age and gender. VBM analysis comprised (a) structural comparison of the two aforementioned groups and (b) correlation between NSS-scores and GM density in both patients and healthy controls. Results: As expected, NSS scores were significantly ($p < 0.05$) higher in patients when compared to healthy controls. In relation to healthy comparison subjects, loss of GM density was pronounced in the temporal lobe (both neocortical fields and substructures of the medial temporal lobe). In patients with schizophrenia, higher rates of NSS were related to a reduced GM density in the pre- and postcentral gyrus, the cerebellum and in subcortical regions (caudate nucleus and thalamus). Conclusion: Our findings of a reduced GM density/volume in the temporal lobe in patients with schizophrenia are in line with the findings of previous studies investigating structural and functional changes in this disorder. NSS are associated with morphological alterations in distinct cerebral areas which might support the hypothesized model of a disrupted cortico-cerebellar-thalamic-cortical circuit in schizophrenia.

DIFFUSION TENSOR IMAGING IN FIRST EPISODE NEUROLEPTIC NAïVE SCHIZOPHRENIC PATIENTS: RELATION BETWEEN PSYCHOPATHOLOGY AND FRACTIONAL ANISOTROPY IN SUPERIOR TEMPORAL GYRUS

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The aim of the present study was to investigate the relationship between white matter changes in the superior temporal gyrus and psychopathology in 22 first episode neuroleptic naïve schizophrenic patients. Gray matter volume changes in superior temporal gyrus (STG) have frequently been associated with psychopathology in schizophrenic patients. Functional studies with fMRI, psychophysiology, SPECT and PET have indicated that the STG is involved in a complex neocortical network that modulates speech and language. Disturbances in this network involving STG have been associated with positive symptoms, e.g. auditory hallucinations, delusions and formal thought disorders, which are typical symptoms in schizophrenia. Few studies have investigated white matter changes in STG and the results of the studies performed have been inconsistent most likely due to differences in the samples with respect to e.g. diagnoses and history of previous antipsychotic treatment. In the present study white matter changes were measured with diffusion tensor imaging (DTI) and psychopathology was measured with PANSS. We hypothesized that a reduction in the fractional anisotropy (FA) would be associated with an increased severity of positive psychotic symptoms. Twenty-two first-episode neuroleptic naïve schizophrenic patients (16 male, 6 female, age 28.4 +/-5.3, 21 right-handed, 1 left-handed) underwent diffusion weighted scans of the whole cerebrum. Symptom severity was measured with PANSS (P-positive: 19.7 +/-3.8, P-negative: 21.3 +/-6.4, P-general: 38.8 +/-7.2, P-total: 79.8 +/-12.3). Scans were acquired on a 3 Tesla Siemens TRIO scanner using an echo-planar imaging sequence with six diffusion directions (TE 94 ms, TR 8900 ms, maximum strength of diffusion gradients=40 mT/m, b=700 s mm-2, 60 slices, 2 x 2 x 2mm voxels, no gaps, NEX=12, 84 volumes in total, 12 of which without diffusion weighting). Fractional anisotropy volumes were calculated for all subjects. Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics), part of FSL (Analysis Group, FMRIB; Oxford; UK). TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics. Statistical analysis will be constrained to the anatomical volumes of interest stated in our a priori hypothesis. Results of our study will be presented at the conference.

BRAIN ABNORMALITIES AS PREDICTORS OF TREATMENT RESPONSE TO ANTIPSYCHOTICS IN SCHIZOPHRENIA: A COHORT FOLLOW- UP STUDY

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Background Although it is well established that patients with schizophrenia have significantly more pronounced degrees of

brain abnormalities than controls, it is controversial whether such abnormalities are predictors of antipsychotic treatment response. Some studies showed that ventricular enlargement was related to response to conventional antipsychotics while pre-frontal atrophy was related to response to clozapine. In previous studies we found that 40 patients with schizophrenia showed to have a reduction of the cortical folding as well as an increased ventricular to brain ratio than healthy controls. The aim of the present study is the investigation of brain abnormalities in this cohort of patients in relation to treatment response to antipsychotics after a 5-year follow-up period. Methods By the time of the MRI acquisition and morphometric evaluation, 38 patients with schizophrenia were defined as Responsive (RespSZ) or Refractory (RefSZ) to antipsychotics treatment according to Kane et al criteria. Most of the patients with ResSZ received conventional antipsychotics and those with RefSZ were treated with clozapine. After 5 years patients were re-classified into 3 groups, according to their treatment response: those who responded to conventional antipsychotics remained in the RespSZ group (n=14), those who responded to clozapine remained RefSZ group (n=18) and those who showed an Incomplete Response to Clozapine (IRC) (n=6) formed a third group. The morphometric measurements of various brain areas of these 3 groups were compared with those of 15 healthy controls by ANOVA, with Bonferroni post-hoc tests for multiple comparisons. Results No group differences were found in measurements of the hippocampi, global brain volumes, planum temporale or cortical folding. However among the three patient groups, the IRC group showed to have more pronounced degrees of ventricular enlargement than controls in the following measurements: increased right (F=3.011, p= 0.04) and left ventricular volumes (F=4.3, p=0.01), increased right (F= 3.8, p=0.02) and left ventricle to brain ratios (F= 5.3, p=0.03), as well as an increase of the total ventricle to brain ratio (F=4.9, p=0.005) Conclusions When compared with healthy controls patients with IRC showed to have more pronounced degrees of ventricular enlargement than patients with RespSZ or RefSZ. Ventricular enlargement may represent a predictor of treatment response to clozapine.

BRAIN STRUCTURE AND NEUROPSYCHOLOGICAL FUNCTIONING IN FIRST EPISODE SCHIZOPHRENIA: A VOXEL BASED MORPHOMETRY STUDY

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Structural brain abnormalities and cognitive deficits have been well documented in schizophrenia. However, the relationship between morphological change and neuropsychological functioning has yet to be clarified. Despite continuing debate on a neurodevelopmental or neurodegenerative aetiology, there is growing evidence of dynamic changes in both brain structure and function over the course of the illness. A better understanding of these processes will allow greater differentiation between aetiological, illness and treatment factors. Data were examined from twenty-eight patients experiencing a first episode of schizophrenia. Brain structure was examined using a Voxel Based Morphometry (VBM) method. Neuropsychological functioning was measured using standardized tests of verbal fluency, executive function, memory (immediate & delayed), working memory and sustained attention. Meaningful associations were found between distinct areas of grey matter volume and neuropsychological performance in patients in their first episode of schizophrenia. The pattern of structure- function relationships was to a large extent consistent with findings in healthy controls, and appeared to differ from the published literature in chronic schizophrenia. The relationship between brain structure and function differs according to phase of illness in schizophrenia. This may be related to pathophysiological processes, bio-psycho-social effects of the illness or its treatment.

THE PREFRONTAL CORTES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Structural and functional neuroimaging studies implicate a number of common brain regions in schizophrenia and bipolar disorder, including prefrontal, anterior cingulate and medial temporal cortices. Of these, the prefrontal cortex may be differentially involved in the two disorders. Yet, the prefrontal cortex is not a homeogeneous structure but may be distinguished by a dorsal and ventral stream based on functional and anatomical connectivity. While there is increasing for trait-like functional abnormalities in bipolar patients in ventral prefrontal related inhibitory processes, schizophrenia is more closely associated with dorsal prefrontal based executive dysfunction. We will present data from post mortem, neuroimaging and neurocognitive studies that test the hypothesis that ventral prefrontal cortex is a core abnormality of bipolar disorder while dysfunction within the dorsal prefrontal stream is an essential feature of schizophrenia.

DENDRITIC SPINE STABILITY AND ITS MODIFICATION BY EXPERIENCE

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Changes in neuronal connections occur in various neurological processes ranging from the development of neuronal circuitry, learning and memory, to neuropsychiatric disorders. To study synaptic structural plasticity in intact animals, we developed a transcranial two-photon imaging technique to follow individual postsynaptic dendritic spines over extended periods of time in transgenic mice overexpressing Yellow Fluorescent Protein. Using this technique, we found that in young adolescent mice (1-month-old), 13-20% of spines were eliminated and 5-8% were formed over 2 weeks in visual, barrel, motor and frontal cortices, indicating a cortical-wide loss of spines during this developmental period. In adult mice (>4 months), 3-5% of spines were eliminated and formed over 2-4 weeks in various cortical regions. When imaged over 18 months, only 26% of adult spines were eliminated and 19% were formed in barrel cortex. Thus, after a concurrent reduction in the number of spines in the diverse regions of young adolescent cortex, spines become remarkably stable and a majority of them can last throughout life. While the cortical-wide spine stability in adulthood likely provides a structural basis for lifelong information storage, abnormal development of dendritic spines may play an important role in the pathogenesis of neuropsychiatric diseases. We have begun to address this issue by studying the effect of sensory experience on spine development and plasticity. During young adolescence when a substantial net loss of

spines occurs, we found that whisker trimming preferentially reduces the rate of on-going spine elimination than spine formation in the barrel cortex.. This effect of deprivation diminishes as animals mature but still persists in adulthood. In addition, restoring sensory experience following adolescent deprivation accelerates spine elimination but has no significant effect on spine formation. The rate of spine elimination also decreases after chronic blockade of NMDA receptors with the antagonist MK801 and accelerates after drug withdrawal. These studies underscore the important role of sensory experience in spine elimination over the majority of an animal's life span, particularly during adolescence.

ASSESSING SULCAL DEPTH DIFFERENCES IN SCHIZOPHRENIA

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There have been prior qualitative reports of unusual sulcal patterns in the cortical mantle in patients with schizophrenia. However, there are few quantitative studies of cortical shape such as the analysis of sulcal depth differences and the localization of these differences comparing well characterized groups of schizophrenia subjects and controls. In this study, we assessed sulcal depth differences across the entire cortical mantle using the PALS (Population-Average, Landmark- and Surface-based) atlas approach. The PALS atlas approach is a novel method in human brain-mapping specifically designed to cope with the complexity of human cortical convolutions and their normative variability across individuals. Fiducial surfaces were generated from segmentations of MR structural data in 20 schizophrenia subjects and 19 controls. We then created sulcal depth maps for each hemisphere by measuring the linear distance from each node in the fiducial surface to the nearest point on a cerebral hull surface that was wrapped around the hemisphere but did not extend into the sulci. Maps of sulcal depth were combined across individuals by registering the fiducial surfaces to the PALS atlas using six major sulci and gyri as landmarks. From the sulcal depth maps, we computed t-statistic maps, which were used to identify significant clusters of differential depth in each hemisphere, and we computed t-correlation maps to assess interhemispheric symmetry. No significant clusters were found when the t-statistic map for each hemisphere was thresholded at a cutoff level of $|t|>3$. No interhemispheric clusters were found when thresholding the t-correlation map at a level of $|t|>6$. These findings suggest that there are no dramatic differences in cortical shape between schizophrenics and controls, in contrast to studies that have shown large shape differences using the PALS atlas approach in other populations, such as William's Syndrome. Supported by MH71616

EARLY BRAIN DEVELOPMENT IN CHILDREN AT HIGH RISK FOR SCHIZOPHRENIA

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Schizophrenia is considered a disorder of cortical connectivity, as evidenced by reduced gray matter volumes on MRI, reduced spines and synaptic markers in postmortem studies, and abnormalities of white matter in DTI studies. Schizophrenia is also considered a disorder of brain development, though there is little direct evidence supporting this hypothesis. Very little is known about normal human brain development in the first years of life, a critical phase of cortical development. We have used MRI to study neonatal brain structure in 74 normal neonates using novel automatic segmentation approaches developed at UNC for neonatal images. We found a robust growth of cortical gray matter after birth compared to white matter. In the neonatal period, there is regional specificity of cortical gray matter growth, with the occipital region growing significantly faster than the prefrontal region. In this study, we performed neonatal MRIs on 19 children of mothers with schizophrenia and compared them with 19 matched controls (mean gestational age at MRI 42.7 ± 3.0 weeks), the first study of neonatal brain structure in children at high risk for schizophrenia. There were no significant differences in total intracranial volume or in lateral ventricle volumes between the high risk and control groups. Tissue segmentation revealed that the high risk children had approximately 2.6% less total gray matter ($p = 0.077$) and approximately 26% more myelinated white matter ($p = 0.083$) compared to controls. High risk children had a significant reduction (approximately 6.5%) of cortical gray matter volume in the occipital region ($p = 0.0325$); there were no differences in the prefrontal, frontal or parietal regions. We did not find enlarged lateral ventricles in the high risk children, suggesting that structural endophenotype may develop after birth. There is a suggestion that high risk children have altered patterns of white matter myelination in the neonatal period. We did detect gray matter abnormalities in this early stage of cortical development, especially in the rapidly growing occipital region. Our finding may reflect geneticallly mediated impairment of cortical synapse development that would be most apparent in this rapidly growing cortical region.

NEUREGULIN-1 HAPLOTYPE HAP_{ICE} IS ASSOCIATED WITH REDUCED HIPPOCAMPAL VOLUMES IN SCHIZOPHRENIC PATIENTS AND IN NON-AFFECTED FAMILY MEMBERS

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Background: The neuregulin-1 (NRG1) gene on chromosome 8p has been suggested as a potential susceptibility gene for schizophrenia. The exact way in which genetic variation in NRG1 might impact on this susceptibility for the disorder is a focus of current research. The present study aimed at investigating the possible relationship between a putative NRG1 at-risk haplotype (HAP_{ICE}; Steffanson et al., 2002) and hippocampal brain volumes in schizophrenic patients and their healthy biological relatives. **Methods:** We genotyped 30 schizophrenic patients and 53 non-affected family members with regard to the presence or absence of the NRG1 haplotype HAP_{ICE}. Structural magnetic resonance imaging was used to determine hippocampal brain volumes in the same subjects. Because we were interested in specific effects on the size of the hippocampus independent from total brain volumes, statistical analysis was performed on relative hippocampal volumes as expressed by the quotient of hippocampal and total brain volume. **Results:** The presence of the previously described and replicated NRG1 haplotype HAP_{ICE} was associated with significantly decreased hippocampal volumes in both schizophrenic patients and their relatives (schizophrenic patients: -12.0%; healthy relatives: -15.8%; $F=5.80$, $df=1, 78$, $p=0.018$). There was no significant NRG1 x diagnosis interaction effect for this specific haplotype ($p=0.66$). None of the three constituent markers

(which together make up the haplotype HAP_{ICE}) alone showed a significant effect on hippocampal volumes neither in the schizophrenic patients nor in their healthy family members. **Conclusions:** These findings provide first direct evidence for a link between the putative NRG1 at-risk haplotype HAP_{ICE} and hippocampal volume reductions in schizophrenic patients and non-affected relatives. Further investigations are necessary in order to elucidate the pathophysiological pathways that connect this NRG1 genetic variation with macroscopic changes of hippocampal volumes.

CORTICAL THICKNESS AND PSYCHOSIS: A FAMILY STUDY

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Background. Cortical thinning in schizophrenia has now been reported in several studies and seems to be a sensitive measure to identify small cortical lesions affecting distributed neurocircuits. However, studies investigating cortical thickness in relatives of patients with schizophrenia are scarce. This study examines whether decreased cortical thickness is an indicator of genetic liability for the disorder. Methods. T1-weighted MRI scans were acquired on a 3 Tesla scanner from patients with schizophrenia, their healthy siblings and controls. BrainVoyager QX was used to measure cortical thickness using the Laplace method in a preliminary study sample of 10 patients with schizophrenia, 10 non-psychotic siblings of these patients and 10 control subjects. Group analyses were performed in surface space after cortex based alignment of segmented cortices. Results. Preliminary whole brain analyses showed decreases in cortical thickness in the frontal lobe and occipital lobe but primarily in the inferior temporal lobe and inferior parietal lobe in patients compared to controls. Relatives showed cortical thinning in the posterior temporal lobe and in some regions of the frontal lobe compared to controls. When patients were compared with relatives, it was found that patients have less cortical thickness in the frontal lobe, occipital lobe, inferior parietal lobe and the temporal lobe. The results did however not reach the level of statistical significance after multiple comparison correction, which is probably due to lack of power in this preliminary sample. To increase statistical power a detailed patches of interest analysis was performed. Results revealed a trend towards decreases in cortical thickness in the right Collateral Sulcus in patients compared to controls. In the relatives, a trend towards cortical thinning in the right Cuneus and in the right transverse Occipital Sulcus was found. When patients were compared with relatives, patients appeared to have less cortical thickness in the right Collateral Sulcus and in the left Inferior Occipital Gyrus. Some increases in cortical thickness were found in the left Postcentral Gyrus in both patients and relatives compared to controls ($p<0,05$). Conclusion. Alterations in cortical thickness may be associated with the genetic liability for schizophrenia. More robust results from whole brain analyses and patches of interest analyses on a three times larger study sample will be presented.

THALAMIC SHAPE ABNORMALITIES IN SIBLINGS AT RISK FOR SCHIZOPHRENIA

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Abnormalities of thalamic structure are a reported characteristic of schizophrenia. However, the potential influence of genetic and/or environmental factors on such abnormalities remains unknown. The non-psychotic siblings of schizophrenia patients represent a valuable group for studying the relationship of genetic factors to the abnormalities of brain structure found in schizophrenia. In this study, we used high-resolution magnetic resonance imaging in conjunction with large-deformation high-dimensional brain mapping to quantify the volume and shape of the thalamus in 4 groups of age-matched (mean age 21 yrs) subjects: schizophrenia probands (n=34), the unaffected siblings of the probands (n=30), healthy controls (n=45), and the siblings of the controls (n=42). Thalamic volume did not differ across groups in either the left or right hemisphere ($F(3,144)<1.3$, $p>0.3$, using a linear model that included gender, total cerebral volume, and age as covariates). For shape analysis, we first reduced the dimensionality of the thalamic surfaces by principal components analysis (keeping the first 15 principal components of the shape covariance, accounting for 88% of total shape variance across all 4 groups). A canonical discriminant function, derived using just the schizophrenia probands and control subjects, was then applied to all 4 groups to generate a (univariate) shape "score" for the left and right thalamus of every subject. For both hemispheres the resulting scores between probands, proband-siblings, and controls were all significantly different from each other ($p<0.02$, t-tests), and the scores for the proband-siblings were intermediate between the other two groups. The scores between control subjects and their siblings were not significantly different ($p>0.3$). The results indicate that thalamic shape abnormalities are present in relatively young schizophrenia subjects and in their non-psychotic siblings. This finding extends our previous finding of shape abnormalities in an older cohort (mean age 38 yrs) of schizophrenia subjects (Csernansky et al., Am J Psychiatry, 161:896-902, 2004). The presence of thalamic shape abnormalities in the siblings of schizophrenia subjects suggests that genetic influences are involved in their development. Support: MH071616 and MH056584

INCREASED PREFRONTAL GYRIFICATION IN A LARGE HIGH RISK COHORT CHARACTERIZES THOSE WHO DEVELOP SCHIZOPHRENIA AND REFLECTS ABNORMAL PREFRONTAL DEVELOPMENT

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In our cohort considered at high risk (HR) of developing schizophrenia, we previously found a significant difference in the extent of right prefrontal cortical folding between those who subsequently developed schizophrenia and a matched group who remained well. This study aimed to determine if this pre-existing difference distinguished the 17 individuals who developed schizophrenia from the 128 individuals in the HR cohort who remained well and also to explore possible underlying differences in prefrontal volumes of grey matter, white matter and CSF. Prefrontal cortical folding was measured bilaterally by an automated version of the Gyrification Index (A-GI), a ratio reflecting extent of folding. The software also provided information on volumes of white matter, grey matter and CSF in native space. Multivariate logistic regression assessed the probability that prefrontal A-GI predicts diagnostic outcome in the HR cohort and subsequently assessed the effect on A-GI of regional CSF, grey and white matter. HR individuals who subsequently developed schizophrenia were distinguished from the remaining

cohort by increased right prefrontal GI. Mean volume of right prefrontal grey matter also differed between groups, but mean white matter volume did not. Post-hoc correlations of age with right prefrontal grey and white matter further distinguished the two groups and a linear regression analysis showed a significant interaction between age and diagnosis on the mean volume of right prefrontal white matter. Increased right prefrontal GI is a premorbid structural feature of those HR who develop schizophrenia and indicates abnormal right prefrontal development.

Partial correlations (controlling for sex) between age and A-GI, grey matter, white matter and CSF volumes in the prefrontal lobe of each group with p-values of significant correlations

Right Prefrontal Correlation	HR who remained well(n=128)	HR who developed illness (n=17)
Age with A-GI	r = -.074	r = .147
Age with mean grey matter volume	**r = -.191 p = .031**	r = .205
Age with mean white matter volume	**r = -.222 p = .012**	**r = .584 p = .018**
Age with mean CSF volume	**r = -.204 p = .022**	r = -.200

COMPARISONS OF CRANIOFACIAL DYSMORPHOLOGY IN SCHIZOPHRENIA AND BIPOLAR DISORDER USING 3D GEOMETRIC MORPHOMETRICS

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Craniofacial dysmorphology has been proposed as a marker of cerebro-craniofacial dysmorphogenesis in psychotic illness. We have previously reported craniofacial dysmorphology in schizophrenia patients using geometric morphometrics to analyse shape differences. Here we extend these analyses, in an interim study, by comparing craniofacial dysmorphologies in schizophrenia and bipolar disorder. Since we previously found schizophrenia dysmorphology to be more pronounced in females than in males, we restrict the present analysis to females. The schizophrenia sample was 32 patients with DSM-IV schizophrenia or schizoaffective disorder (mean age 49.4, SD 10.3) and 34 controls (mean age 45.8, SD 7.5). The bipolar disorder sample was 14 patients with DSM-IV bipolar disorder (mean age 44.7, SD 16.3) and 75 controls (mean age 38.0, SD 9.7). Geometric morphometrics applied to 3D data allows patient-control differences to be tested with robust statistical analysis and visualised with dynamic 3D graphics. Principal component [PC] analysis was used to reduce the dimensionality of the shape space and analyses were carried out on PCs with eigenvalues greater than the mean. Overall differences in facial shape were tested by Goodall's F test [permutation version] and, where significant, statistical models of shape discrimination were produced by logistic regression and visualised by multivariate regression of shape PCs onto predicted group membership and warping mean facial landmarks along discriminant axes. Goodall's F test found shape differed between patients and controls for schizophrenia ($p < 0.005$) and, for bipolar, a trend towards shape difference was found ($p = 0.08$). Hotelling's test also indicated significant shape difference for schizophrenia patients and controls [$T^2 = 116.4$, $p < .0001$] and a trend towards a difference for bipolar patients and controls [$T^2 = 28.1$, $p = 0.07$]. The schizophrenia face was characterised by receding midface, small nose, horizontally narrow mouth, wide lateral margins and reduced facial height. The bipolar face was characterised by receding midface, small nose, vertically narrow mouth, wide lateral margins and reduced facial height. The findings are interpreted with reference to cerebro-craniofacial developmental biology. These studies were supported by the Stanley Medical Research Institute.

LONGITUDINAL STUDY OF MRI BRAIN MORPHOLOGY IN SCHIZOPHRENIA INVOLVING MULTIPLE WITHIN-SUBJECT ASSESSMENTS

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Background: There is now increasingly convergent evidence for progressive frontotemporal brain volume reductions among schizophrenia patients. However, most studies to-date have been limited by small sample sizes, relatively short durations of follow-up, and extrapolating lifetime trajectories for brain volume changes based on assessments at two time-points. Methods: A total of 495 high-resolution MRI brain scans were obtained from 139 schizophrenia patients and 40 healthy volunteer subjects in the ongoing Iowa Longitudinal Study of Recent-Onset Psychoses. All subjects had at least two MRIs each. Three-quarters of the sample (137 subjects) had at least 3 scans (or up to 5 scans). Mean duration between first and last scans was 6.7 years. Mean age at first scan was 27.5 years. Using repeated measures mixed models analyses, within-subject brain volume changes among schizophrenia patients were compared against healthy volunteers. Results: There were significant diagnostic group-by-age interaction effects on total cerebral gray matter (GM), frontal and parietal lobar GM volumes. Schizophrenia patients had greater GM volume reductions compared to healthy volunteers; with reciprocal enlargements in CSF volumes. No statistically significant diagnostic group-by-age interaction effects were found with white matter volume measures or with lateral ventricles. Conclusions: Findings from this large longitudinal study, where study participants have undergone multiple MRI brain morphometric assessments over an average period of almost 7 years, provide additional compelling evidence in support for ongoing brain volume changes during the lifelong course of schizophrenia.

Regions of Interest	B-coefficient (cc/year)		Group*Age Interaction $F_{1,314}$ (p)
	Patients	Controls	
Total cerebral GM	-4.62	-2.94	5.13 (.02)
Lateral ventricles	0.14	0.00	0.65 (.42)
Frontal GM	-2.19	-1.35	5.69 (.02)
Frontal CSF	1.63	0.33	9.26 (.002)
Temporal GM	-0.68	-0.52	1.81 (.18)
Temporal CSF	0.34	0.02	8.80 (.003)
Parietal GM	-1.08	-0.68	4.91 (.03)
Parietal CSF	0.44	0.08	4.77 (.03)

WHITE MATTER INSIGHTS INTO SCHIZOPHRENIA: A PRELIMINARY STUDY

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Lack of insight into illness poses problems for the treatment of schizophrenia. Despite these problems, the neural substrates of insight are

poorly understood. MRI studies have focused on the role of the dorsolateral prefrontal cortex and orbitofrontal cortex in insight, but other studies have also found that insight is negatively correlated with gray matter concentration in the left and right posterior cingulate, as well as bilateral inferior temporal regions. This distributed set of sites suggests that disruption in a neural circuit may account for poor insight in schizophrenia. Thus far, however, no studies have examined insight from a neural circuitry perspective. To this end, we employed diffusion tensor imaging (DTI) to examine correlations between insight and white matter integrity on a whole brain basis. Nineteen patients with schizophrenia or schizoaffective disorder (6 women) were assessed for insight using the Scale to assess Unawareness of Mental Disorder (SUMD;Amador and Strauss, 1991). DTI was acquired using a double echo spin echo sequence (TR=6000ms, TE=100ms, matrix=128x128, FOV=320mm, 19 5mm slices, no gap, NEX=7, b=1000 s/mm^2). Diffusion was acquired using 8 non-collinear diffusion weighted gradients (Jones et al., 1999). Images were placed into standard space using previously published methods and were masked for white matter. Correlations between FA and the sum of scores on the first three (current) SUMD items (related to overall awareness of illness and effects of treatment) were computed on a voxelwise basis, with age as a covariate. A false discovery rate correction was applied (p=.005, q=.1) along with an extent threshold of 50 voxels. The clusters identified from this analysis were used as seeds for tractography, which was evaluated using DTIStudio. SUMD scores were negatively correlated with FA in the superior temporal white matter, along with the white matter of the posterior cingulate. Tractography using the former location demonstrated pathways including the parietal cortex. Tractography using the latter location demonstrated pathways including the inferior longitudinal fasciculus and the uncinate fasciculus. To our knowledge, this study is the first to show correlations between FA and insight in patients with schizophrenia. The results suggest that disruptions in a circuit involving fronto-temporal and temporo-limbic regions are associated with poor insight. Supported by NIMH grant R01MH064783.

AFFECTIVE SYMPTOMATOLOGY IN FEMALE PATIENTS WITH SCHIZOPHRENIA IS CORRELATED TO TEMPORAL LOBE VOLUME

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Much investigation has been done regarding hippocampal volume in relation to major depressive disorder and animal models of depression support the involvement of this structure in such. Depressive symptoms are often a feature of patients with schizophrenia and previous studies have indicated that female patients with schizophrenia experience more mood symptoms compared to male patients with schizophrenia. This study was designed to evaluate the neurobiology of mood symptoms in subjects with schizophrenia. Using a retrospective analysis of patients from our data base at the Mental Health Clinical Research Center at the University of Iowa, we examined the relationship of regional brain volume to self reports of affective symptoms in patients with schizophrenia. Our overall sample consisted of 171 men and 71 women who did not differ in age or education. There was a significant difference in self reports of dysphoric mood measures from the Comprehensive Assessment of Symptoms and History (CASH) as well as the Hamilton depression scale, the women having higher scores than men (p's <0.03). Both of these measures of mood were significantly correlated to whole temporal volume in the women (p's <0.045) but not to the volume of the frontal, parietal, or occipital lobes. Both the right and the left temporal lobes show association to the mood symptoms and this appears to involve both gray and white matter, but not CSF volume. Surprisingly, there was no relationship of the hippocampal volume to these mood symptoms. Further analysis of more defined structures is underway. There was no correlation of mood symptoms in men to any regional brain volume including the hippocampus.

STRUCURAL ABNORMALITIES OF THE RIGHT INFERIOR COLLICULUS IN SCHIZOPHRENIA: EVIDENCE FOR INVOLVEMENT OF LOW SENSORY AREA RELATED TO EARLY STAGE OF AUDITORY PROCESSING

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The ample reciprocal networks between higher cortical brain regions and lower subcortical brain areas and their interactive effects suggest a need for investigation of structural integrity of the subcortical areas related with early sensory processing in schizophrenia. We investigated morphologies of the inferior colliculus and the superior colliculus, which are related with the early stage processing of the visual and auditory stimuli, in patients with schizophrenia (N = 28) compared to healthy control subjects (N = 34), using high-resolution magnetic resonance imaging (MRI).In the comparison of regional volumes, most of the structures of the patient group were smaller than those of the normal group. However only right inferior colliculus showed significant difference (F=5.95, df=1, p= .018) compared with control subjects. Our findings of reduced inferior colliculus volume suggest the possibility that structural abnormality of the inferior colliculus in patients with schizophrenia may be involved in both auditory cognitive dysfunction and symptomatic expression of the schizophrenia.

LOCALIZED GRAY MATTER DEFICITS IN ADOLESCENTS WITH FIRST-EPISODE PSYCHOSIS

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We recently reported gray matter reduction in the frontal lobe in adolescents with a first-episode of psychosis using region-of-interest analysis (Moreno et al 2005). In order to confirm and better localize this gray matter deficit, we processed the same sample of magnetic resonance images (MRI) using voxel-based morphometry (VBM). The sample included 23 patients (6 females) and 37 controls (14 females). The mean age for both groups was 15 years. VBM as implemented in SPM2 (Wellcome Department of Cognitive Neurology, London, UK) was utilized to produce the statistical parametric maps, using an optimized protocol (Ashburner and Friston, 2000; Good et al 2001). An ANCOVA statistical model was used to test for regionally specific gray matter volume differences between the patients and controls. Age, gender and wholebrain gray matter volume entered the analysis as covariates. Statistical parametric maps of gray matter volume were generated using a statistical threshold of

p<0.001 uncorrected for multiple comparisons and with a cluster extent threshold of 100 voxels. This extent threshold was chosen to exclude minimal clusters and is in line with accepted criteria within the field (Farrow et al 2005). Patients showed a large area of smaller gray matter volume in the right frontal lobe. The peak voxel of the largest cluster was located in the middle frontal gyrus (Talairach coordinates 26, 32, 44, $t_{(52)}$=4.42, clustersize: 6375 voxels, voxel resolution 1mm^3, clustersize corrected p< 0.001). There were no areas where patients had significantly increased gray matter volume. First, the results of the current VBM-study confirm our previous findings of gray matter deficits using region-of-interest volumetry. Second, the current study extends the previous findings by localizing the greatest gray matter deficit at the middle frontal gyrus. To assess whether these gray matter changes predate symptom onset and/or are progressive are important goals for future studies. Ashburner and Friston, Neuroimage, 11, 805-821. Farrow et al., Biological Psychiatry, 58, 713-723. Good et al., Neuroimage, 14, 21-36. Moreno et al., JAACAP, 44, 1151-1157.

GREY MATTER REDUCTIONS OVER 9 YEARS IN SUBJECTS AT HIGH RISK OF SCHIZOPHRENIA

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The aim of this study [1] was to see if structural MR images collected over 9 years from 2 scanners could distinguish between control subjects and people at high risk (HR) of schizophrenia. We used voxel based morphometry to perform this analysis. T1 data were acquired on a 1T Siemens machine in the first 5 years of the study and a 1.5T GE machine in the following 4 years. Each of 146 HR and 33 control subjects were scanned up to 5 times, approximately 18 months apart. All 495 images were processed using a grey matter optimised protocol, and then smoothed at 12 mm FWHM. The resulting grey matter segments were then entered into a random effects analysis, supported by SPM99 [2]. Each subject group was proportionally similar on each scanner. A confound was included to account for any scanner difference. Two contrasts were constructed to examine grey matter loss over time (p-corrected < 0.05). The first examined loss that was greater in those subjects at high risk of schizophrenia (n=392) than in control subjects (n=103). Reductions were seen in the right hemisphere in the inferior frontal gyrus, pars opercularis, insula and precentral gyrus. Reductions were seen in the left hemisphere at the apex of the sylvian fissure, the superior temporal gyrus and insula. The second contrast examined loss that was greater in control subjects than in those subjects at high risk of schizophrenia and found widespread reductions in temporal and frontal lobes. The pars opercularis and sylvian fissure areas are involved in language function and deficits here may be related to the language function deficits in schizophrenia and HR subjects. The absence of normal pruning in the HR group in the temporal and frontal lobes may account for additional positive symptoms. However, on detailed examination of the changes over the 9 year period it can be seen that there are non-linear patterns of change over the 9 years, and the statistical contrast used does not distinguish between e.g. (losses in A) - (losses in B) and (losses in A) + (increases in B). Contrasting two groups spread equally over two scanners does to some extent 'naturally' account for scanner differences but, the effect of including scans from two scanners is still likely to confound the results and these effects need to be examined in more detail before a final conclusion can be drawn. [1] Johnstone et al., Br J Psychiatry. 2005 Jan;186:18-25. [2] Ashburner et al., Neuroimage. 2000 11:805-821

DEVELOPMENT OF A RELIABLE METHOD FOR PARCELLATION OF THE FRONTAL POLE

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Precise delineation of the FP (BA 10) from the posterior structures of the prefrontal cortex(PFC) has not been achieved on MR images due to lack of a natural sulcal demarcation that separates these areas. Hence, a landmark-based definition of the posterior boundary of the FP is of paramount importance to study this important frontal subregion in various neuropsychiatric conditions. In our recent MRI-based parcellation study of the PFC, we have suggested that the coronal plane containing the anterior termination of the olfactory sulcus (ATOS) could be employed as a landmark for designating the posterior boundary of the FP(John et al., 2006, in press). This proposal has been made on the basis of previous cytoarchitectonic studies that have studied BA 10 (Ongur et al., 2003). We report the inter-rater reliability of estimating the FP gray matter volumes utilizing the above landmark-based definition of the FP. Using high resolution MPRAGE MR scans, independent raters produced two sets of manual segmentations of the FP of both hemispheres in five subjects. These scans were initially rotated into AC-PC coordinates, and interpolated into 0.5×0.5×0.5 mm isotropic voxels using trilinear interpolation. Manual outlining of FP was carried out on successive coronal sections starting from the section anterior to that containing the ATOS, which was defined as the posterior boundary of the FP. Image pre-processing and manual segmentation were carried out using Analyze 7.0 (Robb et al., 1989). The inter-rater reliability of gray matter volumes generated by manual segmentation of the FP by the two independent raters was estimated by calculating the intra-class R coefficient (ICC). FP gray matter volumes obtained using the above method by the two independent raters yielded an average right FP gray matter volume 4770.50 mm3 and left FP gray matter volume of 5586.50 mm3. The ICC of the FP gray matter volume estimates between the two raters was 0.91. We report a reliable method for parcellating the FP utilizing a landmark-based definition of its posterior boundary based on the cytoarchitectonic features of sub-divisions of the anterior prefrontal cortex. The high inter-rater reliability (ICC = 0.91) of gray matter volumes generated using this method supports its potential utility in conducting non-biased comparisons of groups of subjects with and without neuropsychiatric disorders.

SCHIZOPHRENIA AS A PROGRESSIVE BRAIN DISORDER

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Brain imaging studies have consistently demonstrated brain abnormalities in schizophrenia patients. These changes are largely confined to decreases in gray matter volumes and enlargement of the lateral and third ventricles. To date schizophrenia has been considered to result from abnormalities in neurodevelopment, with brain changes to be static. However, schizophrenia has long been viewed as a progressive or degenerative, not a developmental, disorder. Indeed, Kraepelin considered the progressive clinical deterioration to be the hallmark of the disorder, naming it dementia praecox to reflect this particular aspect. Lately, others have reemphasized the importance of the decline in functioning as a clue to schizophrenia pathogenesis, suggesting that brain abnormalities in schizophrenia

could be expected to reflect this clinical progression. Indeed, we and others have reported brain abnormalities to increase over time in schizophrenia. Interestingly, not all patients show changes in brain volumes over time: we demonstrated that the changes are particularly pronounced in those with a poor prognosis in the first years of illness. The gray matter brain loss that occurs in the first year of illness is clinically highly relevant since we found it to predict the level of functioning in these patients at two and five years of follow-up. In another cohort of around 200 subjects we found that the progressive changes are most pronounced in the frontotemporal areas as postulated by Kraepelin over a hundred years ago. The density loss in the frontal lobe was related to the number of hospitalizations, which may be a proxy for the number of psychotic relapses experienced by these patients and again suggest that the tissue loss may be related to the course of illness. Interestingly, the progression in these frontal brain changes appeared to be attenuated by treatment with clozapine and olanzapine, but not by typical antipsychotics. More recently we have demonstrated that patients who (ab)use cannabis show larger gray matter brain loss over a five year follow-up period than those who refrain from cannabis use in a cohort of around 60 first-episode patients that were followed for five years. Thus, not only are brain changes progressive in schizophrenia, they are clinically relevant since they are related to outcome, psychotic relapses, and the presence or absence of drug abuse and may be reversed by some of the atypical antipsychotics, such as olanzapine and clozapine.

DIFFUSION TENSOR IMAGING OF FRONTO-PARIETAL CONNECTIONS IN PATIENTS AT ULTRA-HIGH RISK FOR SCHIZOPHRENIA

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It has been hypothesized that the clinical and cognitive symptoms of schizophrenia may result from a 'disconnection syndrome' in which communication between brain regions is disrupted. One cortical circuit commonly investigated in schizophrenia is the frontal-parietal loop. Patients with schizophrenia exhibit structural alterations in frontal and parietal lobes, and cognitive tasks that rely on these regions, such as working memory, have been shown to be impaired. Our laboratory has previously employed diffusion tensor imaging (DTI) to show that patients in the first episode (FE) of schizophrenia show decreases in fractional anisotropy (FA), an index of white matter organization, in the superior longitudinal fasciculus (SLF), a major white matter tract connecting the frontal and parietal lobes. However, it is not known whether these changes are present prior to the onset of schizophrenia. To address this we have performed DTI scans on subjects clinically determined to be at ultra-high risk (UHR) for developing schizophrenia, and age-matched controls and compared this to our data in FE patients. The analysis of DTI data is methodologically difficult due to the challenges of aligning internal tracts using software designed for whole brain registration. Therefore, we have employed a rigorous registration method designed to ensure that patients and controls are compared only in regions where both groups contain data, and that the center of each subjects' tracts are aligned. To achieve this we used Track-Based Spatial Statistics (TBSS; FMRIB Software Library) to create a mean group FA 'skeleton' representing the center of all white matter tracts common to the entire group, and projected each subjects' data onto this skeleton. Statistics were applied to anatomically defined regions of interest in the right and left SLF. In the comparison of FE patients, UHR patients, and control subjects, there were significant group differences in FA. Control subjects had higher FA than both FE and UHR patient groups on the right, while on the left controls were higher than UHR patients, who were higher than FE patients. This result extends previous structural and functional findings in frontal and parietal lobes in schizophrenia by indicating that it is not only discrete cortical regions, but the entire fronto-parietal circuitry that is disrupted in schizophrenia, and that this disruption may be present prior to the onset of the illness.

GENOTYPE, SCHIZOPHRENIA AND THE THALAMUS

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Genetic polymorphisms have been shown to influence the structure and function of the CNS. In this study, we compared the effects of minor vs ancestral alleles in genes associated with neuronal survival on longitudinal changes in thalamic volume:BDNF-rs6265, ADCYAP-rs2856966, CNP-rs2070106, DAPK-rs4877365, DAPK1-rs4878104, DBN1-rs2544809, EGFR-rs11543848, FGF-rs1048201, GSK3B-rs334558, IL3-rs40401 and, COMT-rs4680. High-resolution MR scans were collected from 62 schizophrenia subjects (mean age 37.2+/-12.9 years) and 63 control subjects (mean age 36.0+/-14.5 years) on two occasions approximately two years apart. The average between-scan interval was 2.2 years, ranging 1.4 – 4.8 years. Computerized algorithms were used to map and register the surfaces of the left and right thalami from all scans. Thalamic volumes were computed as the volume enclosed by these surfaces. The thalamic surfaces were further divided into regions corresponding to thalamic nuclei. The regions defined were: the sensory-motor thalamic zone, the associative thalamic zone and the remainder thalamic zone. Surface zone deformation with respect to the controls was then computed. For each structural measurement at all time points, we computed a slope value for each subject based on a method proposed by Laired and Ware (1982). These slope values are summarized in the Table. ANOVA was used to look for genotype effects on dependent variables (volume or surface zone deformation) with age and gender as covariates. We observed significant genotype effects for rs4877365, rs11543848 and rs4878104, and genotype by group interactions for rs2856966, rs4878104 and rs2070106 (see Table). These results indicate that genes associated with neuronal survival may influence the rate of change in thalamic structure in schizophrenia subjects. Supported by MH071616 and MH056584.

Structure and Genotype

Genotype	mean (SD)	slope volume whole brain (mm3/yr)	slope volume intercranial space (mm3/yr)	slope volume thalamus left (mm3/yr)	slope volume thalamus right (mm3/yr)	slope sensory-motor nuclei left (mm/yr)	slope sensory-motor nuclei right (mm/yr)	slope associative nuclei left (mm/yr)	slope associative nuclei right (mm/yr)	slope remainder nuclei left (mm/yr)	slope remainder nuclei right (mm/yr)
	Schizophrenia Probands	-32.5 (229)	-13.1 (259)	0.5 (9)	8.23 (74)	-0.0010 (0.004)	0.0013 (0.021)	0.0005 (0.005)	0.0056 (0.044)	-0.0019 (0.007)	0.0073 (0.054)
	Controls	32.0 (191)	12.9 (181)	-0.5 (11)	-8.10 (54)	0.0011 (0.004)	-0.0013 (0.013)	-0.0005 (0.005)	-0.0055 (0.033)	-0.0018 (0.006)	-0.0072 (0.058)
rs4877365 1				genotype effect: F = 5.1, p=0.024							
rs11543848 1										genotype effect: F = 4.3, p= 0.042	
rs4878104 1				genotype effect: F = 5.3, p=0.023							
rs2856966 2							genotype*group effect: F = 4.1, p = 0.032				
rs4878104 3					genotype*group effect: F = 3.97, p = 0.0494						
rs2070106 4										genotype*group effect: F = 4.03, p = 0.047	

1. more positive in subjects having the minor allele 2. post-hoc, schizophrenia proband - more positive rates of change for minor allele carriers, and more negative for non-carriers; control - more negative rates of change for minor allele carriers, and more positive for non-carriers 3. post-hoc, schizophrenia proband - more positive rates of change for minor allele carriers, and more negative for non-carriers; control - more negative rates of change for minor allele carriers 4. post-hoc, schizophrenia proband - more positive rates of change for minor allele carriers; control - no difference for both carriers and non-carriers

GRAY MATTER CORRELATES OF NEUROLOGICAL SOFT SIGNS IN MALES WITH FIRST-EPISODE SCHIZOPHRENIA

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In schizophrenia higher rate of minor neurological soft signs (NSS) can be found. They reflect higher order integration and coordination of sensory-motor acts. They are thought to arise from a subtle brain dysfunction, although their exact origin remains unclear. Some evidence point to morphological abnormalities of basal ganglia, cerebellum and some neocortical areas including prerontal and temporal cortex. Only limited data on the relationship between brain structure and neurological soft sign in a diagnostically homogenous group of patients at the beginning of the illness are available. **Objectives:** to investigate the regional gray matter correlates of NSS in males with first-episode schizophrenia (n=37). **Methods:** Neurological evaluation scale was used to assess the severity of four clusters of NSS (sensory integration, motor coordination, sequencing of motor acts and primary signs) and patients were classified into groups with expressed (E) or non-expressed (NE) individual cluster signs. T1 MR images of the whole head were processed according to the voxel-based morphometry protocol – we compared gray matter concentration in E and NE groups of corresponding NSS clusters. Cluster level of statistical significance corrected for multiple comparisons was used for inference. **Results:** All patients were treated with atypical antipsychotics. 20 patients (54%) had abnormalities in sensory integration, 11 (30%) in motor coordination, 24 (65%) in motor sequencing and 23 (62%) in primary signs. Patients with expressed motor sequencing signs had significantly smaller gray matter concentration in caudate nucleus on both sides. No other differences between groups were identified. **Discussion:** Our data further support the role of basal ganglia in the pathogenesis of schizophrenia. They are in accordance with the proposed abnormality in fronto-subcortical coordination and the relations of NSS to cognitive dysfunction and particular outcomes of the disease. In contrast to other published evidence we found no cortical or cerebellar structures to be related to the severity of minor neurological abnormalities. This may reflect the different diagnostic populations studied in previous reports. **Conclusion:** the study shows an association between sensory-motor processing abnormalities and shrinkage of basal ganglia gray matter in a homogenous group of first-episode schizophrenia patients. Supported by the Ministry of Education of the Czech Republic, Project No. MSM0021622404.

AN MRI STUDY OF THE BASAL GANGLIA IN FIRST-EPISODE SCHIZOPHRENIA

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Introduction: The basal ganglia play an important role in motor, sensory, and cognitive processes. Some MRI studies suggest abnormalities of the basal ganglia in first-episode schizophrenia. Previous studies have examined the basal ganglia by nuclei (caudate, putamen, globus pallidus, and nucleus accumbens) as opposed to using a unified basal ganglia complex that incorporates anterior/posterior and dorsal/ventral divisions. We conducted a MRI study to examine the dorsal-ventral basal ganglia and subcommissural limbic forebrain in first-episode schizophrenia. Methods: Ten treatment-naïve first-episode subjects with schizophrenia (n=8 males, 2 females, mean age=19.9, SD=5.2) and ten healthy volunteers (n=8 males, 2 females, mean age=20.0, SD=2.4) participated in this study. We used high-resolution 3-D SPGR MRI sequences to measure the dorsal-ventral basal ganglia and subcommissural limbic forebrain in the left and right hemispheres. Results: A repeated measures ANOVA was used to investigate the effects of group (subjects with schizophrenia, healthy volunteers), side (right, left), and group by side interaction. The analysis revealed a significant effect of side for both the dorsal-ventral basal ganglia (p=0.001) and the subcommissural limbic forebrain (p=0.04). However, the repeated measures ANOVA did not reveal a significant effect of group or group by side interaction for either region of interest. Conclusions: Preliminary findings from this study suggest that volumes of the dorsal-ventral striatum and subcommissural limbic forebrain are unaltered in treatment-naïve subjects with schizophrenia. Further investigation of other regions of interest in the unified basal ganglia complex is currently under way.

A VOLUMETRIC MAGNETIC RESONANCE IMAGING STUDY OF CAUDATE NUCLEI IN FIRST-EPISODE AND CHRONIC PATIENTS WITH SCHIZOPHRENIA

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Disruption of caudate volume has been hypothesized to play a key role in the pathophysiology of schizophrenia. Previous evidence suggests that whole caudate volumes may be smaller or unaltered in neuroleptic naïve and minimally exposed first episode psychosis (FEP) patients and in chronic patients on atypical antipsychotics. More recent research however, has found larger grey matter caudate volumes in FEP and chronic patients, both on atypical antipsychotics. Thus, more study is necessary with improved methodologies to determine the effects of illness vs. medication on subcortical structures. The intent of this study was to determine the direction and degree of caudate volume alteration in FEP patients and chronic patients with schizophrenia. To investigate this change in caudate structure, 57 participants were used; 16 FEP patients (illness duration: 3.5 months, σ=2.1 months) minimally exposed to atypical antipsychotics (15.8 days, σ=22.8 days) and 17 matched controls; 10 chronic patients (illness duration: 11.5 years, σ=6.7 years) on atypical antipsychotics (chlorpromazine equivalents: 465.0 mg/day, σ=298.4 mg/day) and 14 matched controls. Structural magnetic resonance images were acquired using a Siemens Sonata 1.5 T scanner at baseline. Patients were scanned as follows: FEP patients during an antipsychotic-free washout period and chronic patients while receiving chronic atypical antipsychotic medication. The caudate was demarcated manually in 0.5 mm coronal slices using Display software and whole caudate volumes were obtained. Results showed significantly larger caudate volumes in FEP patients than in matched healthy controls. In contrast, caudate volumes did not differ significantly between chronic patients and matched healthy controls. Our findings indicate that acute exposure to atypical antipsychotics may cause caudate hypertrophy in minimally exposed FEP patients. Conversely, chronic administration of atypical antipsychotics may not demonstrate this hypertrophy and yield unaltered caudate volumes in chronic patients compared to their controls. Funding for this project is provided in part by the University of Alberta Hospital Foundation.

INTERHEMISPHERIC CONNECTIVITY AND SCHIZOPHRENIA- DIFFUSION TENSOR IMAGING STUDY

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A reduction in interhemispheric brain connectivity in schizophrenia is thought to contribute to the etiology of the disease, though until recently it has been difficult to assess this connectivity in vivo. DTI (Diffusion Tensor Imaging) measures the diffusion of water in the brain and can be used to describe the coherence and integrity of white matter tracts in the corpus callosum, thereby providing information concerning loss of interhemispheric connectivity. Previous DTI studies in schizophrenia inconsistently report decreased fractional anisotropy (FA), a measure of anisotropic diffusion, within different portions of the corpus callosum, however none of these studies have used precise, anatomical subdivisions. To investigate separate parts of the callosal fibers, DTI and structural MRI scans were obtained from 32 schizophrenic subjects and 42 controls. Corpus Callosum cross sectional area and its probabilistic subdivision was determined automatically from the structural MRI scans using a model based deformable contour segmentation. The subdivision employs a previously generated subdivision probability atlas, based on the distance to trans-callosal DTI fibers associated with an anatomical lobe subdivision. The structural scan was then co-registered with the DTI scan and the anatomical corpus callosum subdivisions were propagated to the associated FA map. Results revealed decreased FA within the parts of the corpus interconnecting anterior (P=0.03) and posterior (P=0.008) frontal regions in the schizophrenia group compared with the control group, but no significant changes within the callosal fibers interconnecting parietal (P=0.12) and temporo-occipital (P=0.07) brain regions. This study provides quantitative evidence for a reduction of interhemispheric brain connectivity in schizophrenia, and further points to frontal connections as possibly disrupted in schizophrenia.

THE RELATIONSHIP BETWEEN THIRD VENTRICLE VOLUME AND URINE SPECIFIC GRAVITY IN PATIENTS WITH SCHIZOPHRENIA AND PRIMARY POLYDIPSIA

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Polydipsia is relatively common in patients with schizophrenia. Several etiologies have been postulated as the cause of the polydipsia, including a structural defect in the thirst controlling centers of the hypothalamus and adjacent third ventricle. The enlargement of the third ventricle has been postulated to be correlated with primary polydipsia but never directly tested before. The authors investigated the relationship between the volume of the third ventricle and primary polydipsia as measured by urine specific gravity less than 1.011 in 26 patients with schizophrenia and 22 healthy controls. Patients with schizophrenia showed a significant enlargement of the third ventricle volume relative to comparison subjects (F=4.38, DF=3, 44, P=0.0422). No significant differences between the two groups were found for total CSF volume or total ventricle volume. Moreover, there was a significant negative correlation between the third ventricle: total CSF ratio and USG (r=-0.46864, p=0.0181). These findings support the hypothesis that the third ventricle volume is inversely correlated with the development of primary polydipsia. The enlargement of the third ventricle is considered to be a proxy measure of structural abnormality (decreased volume) of the tissues in the hypothalamus that surround the third ventricle and are postulated to be the brain regions in control of serum osmolarity.

WHITE MATTER DEVELOPMENT DURING LATE ADOLESCENCE IN HEALTHY MALES: A CROSS-SECTIONAL DIFFUSION TENSOR IMAGING STUDY

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Background: Previous MRI studies of healthy children have reported age-related white matter (WM) changes in language and motor areas of the brain. The authors investigated WM development in healthy adolescent males through age-associated changes in fractional anisotropy(FA), radial and axial diffusivity. Methods: Twenty-four healthy adolescent males (mean age = 16.6, SD = 2.5 years) were divided into two groups with an age split of 16.9 years and underwent a whole-brain voxelwise analysis. Results: At a threshold of $p < 0.001$ and extent threshold of 100 contiguous voxels, several clusters with increased FA and axial diffusivity and no differences in radial diffusivity were observed in older adolescents compared to the younger adolescents in the left and right arcuate fasciculus, bilateral posterior internal capsule/thalamic radiation, bilateral prefrontal gyrus, right superior temporal gyrus, and posterior corpus callosum. Increased FA and axial diffusivity of several clusters along the arcuate fasciculus significantly correlated with a test of language and semantic memory. Conclusions: These results suggest ongoing maturational changes especially in the arcuate fasiculus during late adolescence. Increased FA and axial diffusivity with no changes in radial diffusivity may reflect a developmental pattern of reduced tortuousity toward more straightened fibers and/or increased axonal fiber organization during late adolescence.

REDUCED FRONTAL MYELIN-ASSOCIATED WATER FRACTIONS IN FIRST-EPISODE PSYCHOSIS

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Introduction: Abnormalities of frontal lobe white matter have been implicated in the emergence of psychotic symptoms.. Some studies of white matter volumes have reported loss of frontal white matter volume in schizophrenia-related psychosis. Assessments of white matter anisotropy suggest there may be disruptions of white matter integrity in multiple regions, however it is not clear which compartments of frontal white matter are affected in psychosis. Using a more tissue-specific novel technique based on T2 relaxation decay curves, we assessed the myelin integrity of white matter in a cohort of first-episode psychosis (FEP) patients. Methods: MRIs were obtained on a GE Signa 1.5T System. T2 relaxation measures were acquired using a 48-echo CPMG protocol on a single 10 mm axial slice. This maximized the visualization of interhemispheric white matter and

medial nuclei in order to assess myelin water fractions (MWF). Regions of interest were manually selected for left and right genu, minor forceps, anterior/posterior internal capsule, splenium and major forceps. Subjects: 58 FEP patients (age range: 13.6-49.9 years) and 39 healthy volunteers (age range: 15.8-55.9 years) were included in this preliminary study. First-episode psychosis patients' diagnoses at entry included schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder and PNOS. Analyses: An Omnibus ANOVA model with diagnosis, gender and age was applied. Bonferroni corrections were not applied to this preliminary data. Exploratory correlations between age and regional MWF were performed. Results: Both left and right minor forceps had reduced MWFs compared to healthy volunteers ($p < .05$). MWF was also reduced in the right anterior internal capsule in FEP compared to healthy volunteers ($p = .03$). Main effects of gender were observed in the right genu ($p = .01$), the left genu ($p = .001$), the left minor forceps ($p = .001$), the right splenium ($p = .04$), and the left splenium ($p = .001$). No significant correlations between age and MWFs were seen for any region of interest. Conclusions: The assessment of myelin integrity using a novel 48-echo T2 relaxation protocols suggests that the frontal white matter abnormalities in patients with FEP may be related to either loss or disruption of myelin. The current results indicate that frontal regions are particularly affected in patients with psychosis.

IMPAIRED ACTIVITIES OF DAILY LIVING IN SCHIZOPHRENIA: CORRELATION WITH REDUCED CORTICAL GREY MATTER VOLUME

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Schizophrenia is often associated with impaired ability to perform everyday purposeful tasks which may impact community survival. The Instrumental Activities of Daily Living (IADL) scale measures the ability of an individual to perform such tasks. We investigated the relationship between IADL rating and brain structure in a prospectively acquired cohort of people with schizophrenia. 19 subjects satisfying a diagnosis of DSM IV schizophrenia were recruited (7 female, mean age 33.5 years ± 7). Illness duration was 7.5 years ± 4.5. Scores on the Scales for Assessment of Positive and Negative Symptoms indicated primarily negative symptomatology (SAPS mean score 20, SANS mean score 33). Of the 19 subjects, 14 were receiving atypical and 5 typical antipsychotic medication. 11 subjects lived in supported accommodation and 8 were living independently. The IADL questionnaire was completed as part of clinical and neuropsychological tests and was rated subjectively. Reliability was confirmed through collateral history from records and carers. A 3D, T1-weighted, whole-head, structural MRI dataset was acquired for each subject at 3T (Intera, PMS). Total cortical grey matter volume was estimated using voxel based morphometry. The analysis protocol included modulation with Jacobian determinants for the effects of spatial normalisation in SPM2. Subjects scored a mean of 12.5 (s.d. ± 2.3) out of 16 on the IADL. Their mean grey matter volume was 474.48ml (s.d. ± 49.39). Bivariate non-parametric correlation revealed a positive trend between grey matter volume and IADL score ($r=0.442$, $p=0.06$). Hence, poor performance of IADL was associated with relatively reduced total cortical grey matter volume. Total CSF and white matter volumes were not correlated with IADL score. To place our finding in context, mean grey matter volume in our laboratory database of 33 healthy volunteers was 589 ml. Hence our patient sample exhibited cortical grey matter volume well below the 'normal' range. The cause of reduced grey matter in schizophrenia is not known. Our data suggest that while the group of schizophrenia patients exhibits a deficit in total grey matter volume this is most pronounced in those who are instrumentally impaired. People with schizophrenia who have less cortical grey matter are less able to perform everyday purposeful tasks; this suggests a possible application: in the future prediction of community survival. This work was funded by the MRC [UK].

LENGTH OF PRODROME AND DUP PRIOR TO FIRST EPISODE PSYCHOSIS: CORRELATES WITH BRAIN VOLUME CHANGES AT 6-YEAR FOLLOW-UP

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Length of prodrome and duration of untreated psychosis (DUP) have been shown to have structural brain correlates at time of first episode psychosis (FEP). Together, prodrome and DUP comprise the duration of untreated illness (DUI).This study examined whether prodrome, DUP, and DUI were related to global brain volume changes over six-year follow-up. 45 subjects from an original cohort of 90 FEP patients, who were scanned six years previously, were re-scanned using high resolution Magnetic Resonance Imaging. Changes in tissue volumes between baseline and follow-up were calculated and corrected for whole brain volume. Prodrome was defined as the period from first definite change in behavioural, psychological or emotional functioning to date of psychosis onset. DUP was defined as the period between date of psychosis onset and date of first treatment. Mean follow-up interval was 6.4 (± 1.4) years, and did not differ significantly between male (n=30) and female (n=15) subjects. Longer prodrome was associated with significant white matter (WM) volume increase over the follow-up period ($p=0.008$), and with significant cerebral spinal fluid (CSF) volume decrease ($p=0.041$). Longer DUP was significantly associated with WM volume decrease ($p=0.018$). Longer prodrome correlated significantly with shorter DUP ($p=0.002$). Neither prodrome length nor DUP differed significantly by gender. In males, longer prodrome was correlated with significant WM volume increase ($p=0.005$) and significant CSF volume decrease ($p=0.031$); and with gray matter volume increase at trend level (0.094). Non-significant correlations in the same direction were observed in females. In males, but not in females, longer DUP was associated with significant WM volume decrease ($p=0.041$). There were no significant correlations between DUI and global volumes. WM volume increase over six-year follow-up is associated with both longer prodrome and shorter DUP, but not with DUI. Prodromal illness is, by definition, subthreshold in severity to the psychotic symptoms experienced during DUP. The findings suggest that the severity of untreated illness in its elementary stages, rather than the duration alone, is related to structural changes over time. Thus length of prodrome and DUP may differentially determine later pathological processes. Alternatively, predisposing factors may exist that give rise

both to a less severe onset of illness and to less marked brain changes.

BRAIN STRUCTURE AND OUTCOME IN SCHIZOPHRENIA WITHIN THE NORTHERN FINLAND 1966 BIRTH COHORT

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Background: Schizophrenia patients with poor outcome are suggested to have increased brain structural abnormalities, but the results are inconsistent (Staal et al. 1999, DeLisi et al. 2004). Objectives: Our aim was to define differences in volumes of gray and white matter and intracranial cerebrospinal fluid (CSF) between schizophrenia subjects with good and poor clinical and social outcome in an unselected, population based cohort. Methods: Subjects with psychosis from the Northern Finland 1966 Birth Cohort were invited to MRI scans of the brain and psychiatric assessments, conducted in 1999-2001. Volumes of gray and white matter and cerebrospinal fluid (CSF) were measured. Interviews and case registers were used to rate measures of outcome including psychiatric hospitalizations, positive and negative symptoms (PANSS), use of antipsychotic medication, educational level, social and occupational functioning (SOFAS), and occupational status. Both MRI-data and measures of outcomes were available for 51 (30 men, 21 women) subjects with DSM-III-R schizophrenia. Results: Cases with over median time spent in psychiatric hospital (poor outcome) had less gray matter (the proportion of gray matter of intracranial volume, i.e. white, gray and CSF) compared to cases with under median time spent in hospital (43.8% vs. 45.4%, $p<0.05$). Also, those with under median score on SOFAS (poor outcome) had less gray matter compared to those with good outcome (over median on SOFAS) (43.8% vs. 45.2%, $p<0.05$). Poor outcome cases (over median score on positive PANSS items, under median SOFAS) had also increased proportion of CSF volume. When adjusted for family history of psychosis, obstetric complications, and sex, these differences remained statistically significant. Conclusions: In this representative sample of relatively young individuals decreased volume of gray matter and excessive volume of CSF were associated with poor outcome in schizophrenia. References: DeLisi LE, Sakuma M, Maurizio AM et al. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. Psychiatry Res 2004 Jan 15;130(1):57-70. Staal WG, Hulshoff HE and Kahn RS. Outcome of schizophrenia in relation ti brain abnormalities. Schizh Bull 1999;25(2):337-348.

COGNITIVE IMPAIRMENT AND SCHIZOPHRENIA – A CLINICAL, IMAGING AND GENETIC STUDY

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Low IQ is a risk factor for schizophrenia and some people with learning disability may have severe early onset schizophrenia or an associated intermediate phenotype. We are engaged in five-year longitudinal study of young people aged 13-22 years receiving special educational support, largely for cognitive difficulties, to test the hypothesis that within the young mildly learning disabled population (IQ approx 50-80) are individuals whose educational difficulties are the result of cognitive impairments due to an extended phenotype of or the premorbid phase of psychotic illness. One hundred and sixty-seven subjects with and without the schizoytypal cognitions predictive of schizophrenia in the Edinburgh High Risk Study (EHRS) have been serially examined with 80 controls, using clinical and structural Magnetic Resonance Imaging (MRI) methods over a four year period. Cytogenetic and molecular genetic studies have been conducted. Widespread psychopathological features and MRI anomalies have been demonstrated and schizophrenia is indeed developing in subjects from the predicted groups. Voxel-based morphometry analyses demonstrate significant relationships between psychopathology and brain structure similar to those which occur in developing schizophrenia in the EHRS and in schizophrenia generally. The inter-relationships between these and other clinical and imaging features and genetic findings are therefore illuminating the mechanisms underlying the development of psychotic illnesses.

THE VENTRAL AND DORSAL STRIATUM IN SCHIZOPHRENIA: AN MRI STUDY

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Background: The ventromedial striatum (VMS), or limbic striatum, is believed important both for reward-guided behaviors and for psychosis. We, thus, hypothesized its volume may be reduced in schizophrenia. Methods: We measured the VMS and dorsal striatum, using 1.5 Tesla MRI scans in 20 right-handed male, chronic, medicated schizophrenics, and in 20 NCLs. We used 1.5 mm SPGR images for absolute volume ROI measurements and, to correct for head size and calculate relative volumes, we used 3mm spin echo double axial images co-registered to 1.5 mm SPGR images for whole brain measurements. All SPGR scans were realigned and resampled yielding isotropic voxels. The VMS was defined as striatal tissue inferior to an oblique line formed by the connection between defined points at the inferior-lateral border of the putamen and the medial border of the caudate. Results: We found no group differences in relative left or right VMS (ps>0.30) volumes. However, we found a near significant region by diagnosis interaction for relative dorsal striatal volumes ($F=3.75$, $df=1,38$, $p=0.06$) with schizophrenics showing larger relative putamen volume (0.61 vs. 0.57 %, $p=0.075$) but unchanged relative caudate volume (0.498 vs. 0.495 %, $p=0.88$) compared with NCLs. Correlations between striatal subregion volumes and measures of clinical and cognitive functioning will also be presented. Conclusions: VMS volume did not differ between groups, but we found larger putamen, but not caudate, relative volume in schizophrenics. Given the increase in striatal volume attributed to neuroleptic treatment, our findings suggest caudate, but not putamen, is intrinsically decreased in volume in schizophrenia, and through its anatomic linkage to prefrontal cortex may contribute to schizophrenic cognitive deficits.

PREFRONTAL CORTICAL PYRAMIDAL NEURONS IN SCHIZOPHRENIA: MORPHOLOGICAL ALTERATIONS AND MOLECULAR MECHANISMS

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Dysfunction of the dorsolateral prefrontal cortex (DLPFC) is thought to underlie certain critical cognitive deficits in schizophre-

nia. This dysfunction is associated with structural abnormalities in pyramidal neurons, the major source of excitatory projections from the DLPFC. For example, in subjects with schizophrenia, DLPFC pyramidal neurons have smaller cell bodies and a reduced density of dendritic spines, the major site of excitatory inputs to pyramidal neurons. In addition, these alterations appear to be specific to, or at least more prominent in, pyramidal neurons located in deep layer 3 than in other cortical layers. A number of both intra- and extracellular signaling pathways have been shown to regulate spine dynamics. For example, members of the RhoGTPase family (e.g., Cdc42, Rac1 and RhoA) are critical regulators of spine structure, and the spine-specific proteins, Duo and drebrin, are essential for spine maintenance and spine formation, respectively. In the DLPFC of subjects with schizophrenia, expression of the mRNAs for Cdc42 and Duo were significantly reduced. In addition, the expression level of these transcripts was significantly correlated with spine density. In contrast, the expression levels of these RNAs were not altered in monkeys chronically exposed to typical or atypical antipsychotics. Together, these observations provide a structural basis for deficient excitatory transmission in the DLPFC in schizophrenia and suggest potential molecular mechanisms that might contribute to this disturbance.

WHITE MATTER ABNORMALITIES IN FIRST EPISODE AND CHRONIC SCHIZOPHRENIA USING DIFFUSION TENSOR IMAGING IN THE MIND CLINICAL IMAGING CONSORTIUM STUDY

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Diffusion tensor imaging (DTI) is a magnetic resonance imaging method that measures the spatial profile of the self diffusion of water molecules in tissue. DTI has been shown to be sensitive to white matter pathologies including the status of myelin. White matter abnormalities have been detected in schizophrenia using DTI, typically in the form of reduced diffusion anisotropy compared with matched control subjects. The exact neurobiological meaning of reduced anisotropy in white matter is unclear. The majority of published studies have included relatively small number of subjects, often on the order of 20 in each group. In order to examine relationships between DTI measures of white matter and other important measures such as cognition and gene polymorphisms, a larger number of subjects will be required. One approach to increasing the number of subjects in a clinical study is to use multiple acquisition sites. While solving the problem of number of subjects, this introduces other methodological issues related to site differences, including scanning equipment and subject demographics. The MIND Institute has established a collaborative multi-site consortium to address these issues. The MIND Consortium obtained baseline structural MRI scans on a total of 313 subjects from four participating sites, including 45 first-episode patients, 108 chronic schizophrenia patients, and 160 matched controls. The MRI scans, included a DTI sequence, were collected using either a 1.5T Siemens scanner (Iowa, New Mexico, MGH) or a 3.0T Siemens Trio scanner (Minnesota). The anatomical MRI data were processed to allow identification of the brain compartment and also segmentation into CSF, gray and white matter. DTI data were processed using GTRACT software to provide both scalar and vector measures of the diffusion tensor data (Cheng et al., Neuroimage. 2006 Jul 1;31(3):1075-85. DTI data and the anatomical data were co-registered to allow identification of the white matter compartment. Results will be presented examining between group comparisons of DTI regional measures and relationships with cognition and clinical variables. Support: This work was supported by the MIND Clinical Imaging Consortium.

COMPARISON OF IN VIVO MAGNETIC RESONANCE METHODS FOR EXAMINING WHITE MATTER ABNORMALITIES IN SCHIZOPHRENIA

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Multiple neuroimaging studies have found evidence of white matter abnormalities in patients with schizophrenia. Postmortem gene expression studies have also found evidence of altered expression of myelin related genes. To date, three imaging methods have been used to examine white matter composition in schizophrenia. The most common imaging method for examining white matter has been diffusion tensor imaging (DTI). DTI measures the self diffusion of water molecules in tissue and provides a measure of tissue microstructure organization based on the spatial diffusion profile in the tissue. Scalar measures providing metrics of the degree of diffusion anisotropy can then be computed from the diffusion tensor. Magnetization Transfer Imaging (MTI) is another commonly used method for assessing white matter in disorders such as multiple sclerosis. MTI provides a measure of the protons that are bound to large molecules such as myelin and has been used as a measure for myelin damage. T2 Relaxography (T2R) measures the water trapped in the myelin sheath through the use of a multi echo data collection from which the spectrum of T2 relaxation is estimated. A short T2 component between 20-50msec is thought to reflect the myelin water signal. While differences between patients with schizophrenia and controls have been observed with all three imaging methods, to date no study has directly compared the three methods in the same subjects. We are conducting a neuroimaging study of first episode and chronic schizophrenia patients and matched controls in which the three modalities (DTI, MTI, T2R) are being collected in the subjects. T2R data will be collected using a novel multi echo, multi slice, linear combination method which allows multiple slices to be collected instead of the standard one slice method. Processed data from each subject for each of the three modalities will be registered together using a rigid body registration. The subjects will then be non-linearly registered to a common brain template to allow voxelwise analyses to be performed. We will present the results of analyses in which we will compare the regional distribution of abnormalities detected by the three methods as well as quantify the effect sizes observed with each of the methods. Supported by R01 MH060662.

DERMATOGLYPHIC ABNORMALITIES AND HIPPOCAMPAL VOLUMES ARE ASSOCIATED IN SUBJECTS AT HIGH GENETIC RISK OF SCHIZOPHRENIA

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We have previously found that subjects at high genetic risk of schizophrenia have significantly less complex dermatoglyphic patterns

than healthy controls (1). To further our understanding of the aetiology of schizophrenia, we sought to investigate the relationships between abnormalities of brain structure and dermatoglyphics in the same high risk (HR) population. We acquired T1 MR images and dermatoglyphic data (from which a measure of pattern complexity was calculated: whorls - arches) from 114 HR subjects – 78 without psychotic symptoms (HRwell), 21 with symptoms (HR+) and 15 who were subsequently diagnosed with schizophrenia (HRill) - and 30 controls. VBM was performed using the SPM99 toolbox [http://www.fil.ion.ucl.ac.uk/spm/software/spm99/], based on the grey-matter optimised protocol developed by Good (2). Multiple regressions were performed in SPM with middle temporal lobe small volume corrections and dermatoglyphic complexity scores. Where significant overall correlations were found, the corresponding maximum peak voxels were extracted into SPSS to test for subject-group by complexity-score interactions. In the HR population as a whole, we found a correlation of complexity with grey matter density (GMD) in the hippocampus (pcor = 0.035, r = 0.304 (p = 0.001)). Hippocampal volume has previously been positively correlated with finger ridge asymmetry in twins discordant for schizophrenia suggesting a trait effect (3). We also found correlations with thalamus (pcor = 0.031, r = -0.334 (p < 0.005)) and inferior temporal gyrus GMD (pcor = 0.021, r = -0.403 (p < 0.005)). These findings are consistent with regional pathologies reported in previous imaging studies and further support the view that they represent a neurodevelopmental trait effect. In addition, the association of structural and dermatoglyphic abnormalities support the hypothesis that they reflect a partially overlapping genetic vulnerability to schizophrenia. (1) Langsley et al, Schiz Res 74:122-124, 2005 (2) Good et al, NeuroImage 14:21-36, 2001 (3) van Oel et al, Schiz Res 52:181-193, 2001. GKSL, DEJ, AMM and SML are all supported by the Sackler Foundation

DIFFUSION ANISOTROPY CHANGES IN SCHIZOPHRENIA

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Schizophrenia has been shown to involve a number of brain regions. A number of studies have shown changes in the structure and function of grey matter regions. More recently diffusion tensor imaging (DTI) has been used to study white matter in more detail. The purpose of this study was to evaluate gross white matter changes in schizophrenia using DTI. For this study, 22 male patients (mean age 28.5) with schizophrenia and 28 male control subjects (mean age 29.9) were recruited into an imaging study for evaluation of brain morphology. Informed consent was obtained from all subjects in accordance with the local Institutional Review Board. The subjects underwent a multi-modality imaging study to obtain anatomical T1 and T2 images using a 1.5 T scanner. DTI data was acquired on a 3T scanner using six directions of diffusion encoding and a b-value of 1000. The anatomical images were processed using a standard image analysis pipeline including AC-PC alignment, tissue classification, and automated extraction of the brain. The DTI images were analyzed in a standard manner that included motion and eddy current correction, spatial filtering with a median filter, generation of diffusion tensor, and generation of fractional anisotropy images. The DTI data was co-registered with the AC-PC aligned T1 weighted images using a rigid registration and a mutual information registration metric. This was used as an initialization for a non-linear B-Spline registration to correct for susceptibility distortion in the images. After the images were non-linearly aligned, a Talairach based parcellation of cerebral white matter was performed and the average anisotropy was measured within these regions. The results showed a trend towards reduced FA in the right (p=0.05) and left hemispheres (p=0.08) after controlling for age. Significant reductions were found in the parietal lobe (left: p=0.004; right: p=0.003). The temporal lobe (left: p=0.14; right: p<0.05) and occipital lobe (left and left: p=0.14) also showed trends toward reduced fractional anisotropy. Other studies have shown similar reductions in the FA within the temporal and parietal lobes. While the findings suggest an overall reduction in white matter organization, the deficits appear to be greater in the right hemisphere as compared to the left hemisphere. Diffusion tensor tractography holds the possibility to explore these differences in a tract by tract basis not possible with regional measurements.

BASAL GANGLIA SHAPE ABNORMALITIES IN SIBLINGS AT RISK FOR SCHIZOPHRENIA

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Increases in the volume of basal ganglia structures have been reported in schizophrenia, and generally attributed to the effects of antipsychotic drug treatment. Recently, we have found that shape abnormalities accompany such changes in basal ganglia volume. We are particularly interested in whether abnormalities of basal ganglia structure are present in the siblings of schizophrenia subjects, since genetic influence rather than antipsychotic drug treatment would be the presumed causative factors in such subjects. In this study, we used large-deformation high-dimensional brain mapping to quantify the volumes and shapes of the caudate, putamen, and globus pallidus in 4 groups of age-matched (mean age 21 yrs) subjects: schizophrenic probands (N=37; mean duration of illness: 3.4 yrs; most were receiving atypical antipsychotic drugs), their non-psychotic siblings (N=31), healthy controls (N=45) and their siblings (N=42). The volumes of the various basal ganglia structures did not differ significantly across the four subject groups. For shape analysis, we used principal components (PC) analysis to reduce the dimensionality of the 3D surfaces to 15 PCs for each subject in each structure. MANOVA applied to the resulting PCs (using all subject groups) showed a significant shape difference for all basal ganglia structures, except for the right globus pallidus. Canonical discriminant functions, derived using just the probands and controls, were then applied to all groups to generate a (univariate) shape "score" for each subject in each structure. Based on these shape scores, proband-siblings were significantly different from probands in the caudate bilaterally (L: p=0.03; R: p=0.005, t-tests) and right putamen (p=0.04) with the scores intermediate between the proband and control groups in the caudate and right putamen. Proband-siblings were significantly different from controls in all basal ganglia structures. These data suggest that abnormalities of basal ganglia structures occur in the non-psychotic siblings of schizophrenia subjects as well as schizophrenia subjects themselves. The presence of structural abnormalities of the basal ganglia in such relatives suggests that genetic factors may be involved in the development of such abnormalities in schizophrenia patients. Support: MH071616 and MH056584

CEREBRAL CONNECTIVITY, SCHIZOPHRENIA AND GENETIC LIABILITY: A DIFFUSION TENSOR IMAGING STUDY

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Schizophrenia is thought to have its base in cerebral vulnerability such as altered cortical connectivity, which is supported by functional MRI-based findings. Of late, studies using diffusion tensor imaging (DTI) have supported the dysconnectivity theory by showing microstructural white matter changes in neural circuits, specifically in fronto-temporal, fronto-parietal, and fronto-thalamic connections. However, the concept of DTI white matter alteration as a structural endophenotype has yet to be addressed. Diffusion weighted images as well as T1-weighted anatomy volumes were acquired on a 3 Tesla MRI scanner from 30 patients with schizophrenia, 30 non-psychotic siblings of these patients and 30 healthy controls. Measures of fractional anisotropy (FA) as indicators of white matter tract integrity were computed using Trackmark and BrainVoyagerQX software (BrainInnovation, Maastricht, The Netherlands). Parametric images of the average FA of the different groups were acquired after transformation to Talairach space. Differences between groups were assessed with voxelwise analysis of variance and t test comparisons, and confirmed in region of interest analyses. Preliminary analyses in a subgroup (n=10 per group) show microstructural (DTI) white matter changes in psychotic patients and, to a lesser extent, in their healthy siblings when compared to controls. This suggests that altered cerebral connectivity may be an endophenotypic marker of schizophrenia liability.

REGULATORY MECHANISMS OF CYTOSKELETAL DYNAMICS IN DENDRITES

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Pathological findings indicate a correlation between schizophrenia and morphological in dendritic spine spines, small protrusions occurring at ~90% of excitatory synapses. Dendritic spines are rapidly motile, identifying them as primary sites of anatomical plasticity in brain circuits. Spine motility is driven by a specialized spine cytoskeleton of actin filaments whose dynamics are regulated by synaptic transmission via activation of postsynaptic glutamate receptors. The endpoint of this process depends on actin-binding proteins. One of these, profilin, accumulates in dendritic spines when NMDA receptors are activated, a process that has been shown to accompany fear-conditioned learning and which is required for spines to remain anatomically stable. Recently we have shown that NMDAR receptor stimulation leads profilin to accumulate in the nucleus of neurons where it has been shown to regulate the activity of a specific gene transcription factor. These two sites of action, at the synapse and nucleus, suggest a novel pathway by which profilin may link anatomical plasticity at synapses to gene expression thought to be essential for long-term memory. Other experiments implicate the balanced activity of two actin binding proteins, α-actinin and drebrin that regulate the cytoplasmic arrangement of actin filaments, as essential for the correct maturation of adult dendritic spines. These molecular events provide new insights into processes that regulate the stability of synaptic circuits in the brain.

REGION-SPECIFIC ORBITOFRONTAL VOLUME DEFICIT IN SCHIZOPHRENIA AND ORBITOFRONTAL VOLUMETRIC ASSOCIATION WITH IOWA GAMBLING TASK IN HEALTHY POPULATION

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The gross social deficits associated with large orbitofrontal pathological lesions are well known. However more subtle associations between volumetric measures of Orbitofrontal Cortex (OFC) and social behavior have not been well characterized. To investigate this association and its pathology we compared chronically treated schizophrenia patients with healthy control (HC) subjects on a novel, reliable parcellation of subregions of OFC and their associations with behavior, especially the Iowa Gambling Task (IGT), and with schizophrenic psychopathology. Twenty-four patients with schizophrenia and 25 age-matched, HC subjects underwent high-resolution MRI. Three subregions of OFC were manually delineated according to anatomical boundaries: Gyrus Rectus (GR); Middle Orbital Gyri (MidOG); and Lateral Orbital Gyrus (LatOG). Both patients and controls underwent cognitive/behavioral evaluations using the IGT, Wisconsin Card Sorting Test (WCST), and Trail Making Test (TMT). A bilaterally smaller MidOG volume was observed in patients with schizophrenia, compared with HC ($F_{1,47}$=17.4, P=.0001, 11% difference), whereas GR and LatOG did not differ although GR showed a rightward asymmetry in both groups ($F_{1,47}$=19.2, P<.0001). In the schizophrenia group, a smaller left MidOG was associated with a longer duration of the illness (P=.002), and a smaller right MidOG with worse positive formal thought disorder (P=.001) in the Scale for the Assessment of Positive Symptoms (SAPS). The schizophrenia group showed poorer performance in the IGT compared to the HC group, but no association with OFC volume. However, within the HC group, right hemisphere larger MiOG volume was associated with better performance in the IGT (P=.001 - .006) and left hemisphere larger volume with the TMT (P=.003). The present study, applying a new anatomical parcellation method, demonstrated a bilateral, subregion-specific OFC gray matter volume deficit in patients with schizophrenia. Furthermore, this volume deficit was associated with duration of illness and with formal thought disorder. In HC, this is, to our knowledge, the first report of a quantitative association between OFC volume and IGT performance within non-psychiatric population.

REGIONAL CHANGE IN BRAIN MORPHOMETRY IN SCHIZOPHRENIA ASSOCIATED WITH ANTIPSYCHOTIC TREATMENT

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The purpose of this pilot study was to: determine if regional brain volume change occurs in schizophrenia during very short periods of withdrawal from/stable treatment with antipsychotics, and; to

compare results of region-of -interest (ROI) and voxel-based morphometry (VBM) image analysis. In two small groups of psychiatric inpatients with schizophrenia, MRI was obtained before and after antipsychotic withdrawal, and at two time points during chronic stable antipsychotic treatment. Regional brain volumes were measured using ROI methods. Regions of grey matter volume change were identified with VBM. In the medication withdrawal group, using ROI methods, no effect of treatment state or antipsychotic type on any regional brain volume, and a positive correlation between both total grey matter and temporal grey matter volume change and emerging psychopathology, were seen. VBM showed no effect of treatment state or antipsychotic type on grey matter volume in any region, corrected with the false-discovery rate (FDR). Uncorrected, an interaction between treatment status and medication type in right middle frontal, right medial frontal, right and left superior frontal, right cingulate, and right superior temporal gyrii as well as in the right and left hippocampal gyrii was observed. In the chronic stable treatment group, ROI analysis showed an interaction of treatment and antipsychotic type in right caudate, left hippocampus, and total cerebrospinal fluid volume. VBM showed no effect of treatment state or antipsychotic type on grey matter volume in any region, FDR-corrected. Uncorrected, VBM in the chronic stable treatment group showed an interaction between time and antipsychotic type in left superior temporal lobe. With two caveats—our small sample size and previously demonstrated instability of volume measurements over time measured with MRI, even in large samples of in schizophrenia patients—our data suggests that treatment state and emergent symptoms were associated with regional volume change in over very short time periods. Longitudinal regional brain volume change in schizophrenia patients are likely physiologic and therefore potentially reversible. The results of ROI and VBM analysis do not always correspond well, although correction with the false-discovery rate appears to improve the correlation between these two commonly-used methods.

DIFFUSION TENSOR IMAGING (DTI) INVESTIGATION OF ILLNESS PROGRESSION IN A LONGITUDINAL SAMPLE OF PATIENTS WITH SCHIZOPHRENIA AT THE EXTREMES OF THE OUTCOME SPECTRUM

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The burgeoning literature on MRI in schizophrenia has in recent years accumulated considerable evidence for disturbed connectivity among a range of cortical and subcortical structures. Consequently, interconnecting white matter tracts are now the focus of systematic and multimodal scientific scrutiny. The DTI, a promising new technique of white matter assessment, has already produced data, implicating internal capsule, corpus callosum, and several association fiber tracts in schizophrenia pathophysiology. Published DTI investigations documenting pathological changes in regional anisotropy have analyzed both first-episode and chronic schizophrenia patients, yet longitudinal follow-up in schizophrenia patients is yet to be reported. This would be all the more important since there have been repeated suggestions of differential anisotropy changes with aging in normal subjects and schizophrenics. Moreover, there appears to be a relationship between white matter deficits associated with illness progression and symptomatic severity of its course. We are currently in process of analyzing morphometric and DTI data from a longitudinal cohort of normal subjects and schizophrenia patients with good and poor clinical outcomes, scanned with an identical scanner and imaging sequences twice 5 years apart. Baseline DT images were obtained on 104 schizophrenia patients (51 good-outcome, 53 poor-outcome) and 41 normal subjects. The follow-up group consisted of 21 normal and 39 schizophrenia subjects, the latter including 22 patients with poor outcomes and 17 patients with good outcomes. There were no significant sex, age, or good-to-poor outcome proportion differences between the groups within the baseline or follow-up samples. Pilot analyses in a subsample of the longitudinal cohort (23 patients and 8 normals) show that all patients with schizophrenia regardless of outcome displayed significantly greater decreases in anisotropy over time than normal controls in the orbitofrontal, anterior cingulate, and left temporal (Brodmann area 20) white matter. These preliminary results suggest more rapid anisotropy decreases in several frontotemporal white matter regions in schizophrenia patients in comparison to normal controls. More detailed analyses of the longitudinal anisotropy changes within a range of projection, commissural, and association tracts, as well as tractography results (tract length and coursing angles) for selected fiber tracts will be presented at the symposium.

DIFFERENT EFFECT OF CHILDHOOD TRAUMA ON HIPPOCAMPAL VOLUME IN HEALTHY SUBJECTS AND IN PATIENTS WITH FIRST EPISODE PSYCHOSIS

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Background: Smaller hippocampal volume has been largely reported in patients with chronic schizophrenia, while findings in first-episode psychosis are inconsistent. Severe stress during childhood has also been associated with smaller hippocampal volume. However, prior studies on hippocampal volume in psychosis have neither reported nor controlled for a history of childhood trauma. This study investigates the effect of childhood stressful events on hippocampal volume in first episode-psychosis patients. Methods: We recruited 41 healthy controls and 61 patients with first-episode of psychosis as part of the large Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study. We collected information on physical abuse from parents, sexual abuse and family arrangements before age 17, using the Childhood Experience of Care and Abuse (CECA) questionnaire. Hippocampal and whole brain volumes were measured using coronal MRI scans. We tested the effect of different stressful childhood events on hippocampal and whole brain volume. Results: No effect of childhood stressful event was found on whole brain volume. Unexpectedly, the presence of a stressful childhood event was associated with a larger hippocampal volume in female healthy subjects (4.5±0.2 vs 3.7±0.3 cm3; p=0.03); however there was no effect of childhood trauma on hippocampal volume in female psychotic patients. When looking at all the female subjects with a history of childhood trauma, we found that controls had a 9% larger mean hippocampal volume compared to patients (p=0.08). In particular, control females with history of physical abuse had a 13% larger mean hippocampal volume than female patients with the same history

(p=0.098); control females with a history of sexual abuse had a 9% larger mean hippocampal volume than female patients with the same history (p= 0.33); and control females with a history of more than one family arrangement had an 11% larger mean hippocampal volume than female patients with the same history (p=0.04). We did not find any difference when comparing male subjects. Conclusions: We found an enlargement of the hippocampus in female healthy subjects with a history of childhood trauma, but not in psychotic patients with a history of childhood trauma. We hypothesize that the different biological effect of stressful childhood events on the hippocampus can have a role in the development of psychosis and possibly in other psychiatric disorders.

INCREASED GYRIFICATION IN WELL RELATIVES WITHIN FAMILIES AFFECTED BY BOTH BIPOLAR DISORDER AND SCHIZOPHRENIA: AN AUTOMATED GYRIFICATION INDEX STUDY

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Bipolar disorder and schizophrenia are highly heritable conditions that are associated with structural brain abnormalities [1]. Structural imaging studies have indicated that psychosis patients, and to some extent their unaffected relatives, have subtle deficits in several brain regions, including Pre-Frontal Lobes (PFL) [2]. We applied our Automated Gyrification Index tool (A-GI) [3,4], developed at the Sackler Institute of Psychobiology, Division of Psychiatry, Edinburgh University, to an investigation of PFL cortical folding in well relatives from mixed families affected by both schizophrenia and bipolar disorder (n=24), families affected by schizophrenia alone (n=23), families affected by bipolar disorder (n=21) alone and controls with no family history of psychosis (n=47). A-GI was applied to the PFL anterior to the genu of the corpus callosum in 1mm coronal slices (nominally 40 slices per brain). Our analysis demonstrates right-side PFL increased gyrification of well relatives in the mixed affected families when comparisons are made with the relatives of the schizophrenia alone and bipolar alone and control families. Post-hoc analysis reveals that the increased gyrification in the relatives from mixed affected families is most prominent in the posterior aspect of the right PFL. On the left PFL no significant differences were found between the relatives from the mixed families, the relatives in families affected by schizophrenia alone, bipolar disorder alone and the controls from unaffected families. A comparison between relatives and bipolar patients in the mixed families demonstrates significant reductions in GI for patients on the right PFL. Both age and gender were employed as covariates. Table 1 gives the PFL left and right estimates of marginal means and their std. errors. Data collection is ongoing, including genetics associated with psychosis and additional results will be available at presentation. The increased gyrification on the right side of the mixed affected families implies a possible structural correlate of susceptibility genes prevalent in families affected by both schizophrenia and bipolar disorder. 1 McIntosh Am J Med Genet B 5;141,76-83 2 Job Schizophr Res. 1;64,1-13. 3 Moorhead Neuroimage. 15;31,1560-6. 4 Zilles Anat. Embryol. 179,173–9.

Table 1 Gyrification Index (std. Error)

	Mixed Relatives	Mixed Patients	Bipolar Relatives	Schizophrenia Relatives	Controls
Right A-GI	2.35 (0.019)	2.28 (0.022)	2.27 (0.020)	2.29 (0.019)	2.29 (0.013)
Left A-GI	2.26 (0.018)	2.22 (0.021)	2.25 (0.019)	2.26 (0.019)	2.24 (0.013)

BRAIN MORPHOMETRY IN FIRST EPISODE AND CHRONIC SCHIZOPHRENIA USING COMPUTER AUTOMATED QUANTIFICATION OF CORTICAL THICKNESS AND SUBCORTICAL VOLUMES IN THE MIND CLINICAL IMAGING CONSORTIUM STUDY

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Schizophrenia exhibits heterogeneous clinical and cognitive symptoms that likely reflect diverse etiobiologies. Use of automated, quantitative morphometric image analysis software permits the detection of changes in brain morphometry while facilitating analysis of large numbers of subjects. Correlating distinct structural changes with clinical and cognitive features of illness may facilitate biological subtyping of schizophrenia. Attempts to further associate such subtypes with genetic variation could contribute to an understanding of pathophysiology and improved treatment selection. These studies require large sample sizes such as afforded by a multi-site design to enhance statistical power, yet multi-site imaging studies pose methodological and technical challenges. Herein the first analysis of clinical morphometry data in the MIND Institute multi-site study on schizophrenia is presented. Baseline structural MRI scans were obtained on a total of 313 subjects from four sites, including 45 first-episode patients, 108 chronic schizophrenia patients, and 160 matched controls. High resolution MRI scans were collected using either a 1.5T Siemens scanner (Iowa, New Mexico, MGH) or a 3.0T Siemens Trio scanner (Minnesota). Structural data were analyzed using FreeSurfer, an automated set of software tools for study of cortical and subcortical anatomy (Fischl and Dale, 2000) using the data available from 288 subjects. Cortical surface models of the gray-white and pial surfaces were generated and the distance between these surfaces was used to compute cortical thickness. A surface-based averaging technique that aligned the main cortical folds across individuals allowed between-group comparisons (for example schizophrenia vs. controls) while essential variables (age, gender, subject education) were modeled for contribution to effect. FreeSurfer subcortical segmentation provided volumetric data for right and left thalamus, caudate, putamen, pallidum, hippocampus, and amygdala. Within site and across site comparisons for subcortical structures were examined. Correlations between structural measures and several clinical and cognitive measures were examined. Results support the feasibility of clinical neuroimaging studies on this scale, particularly given ease of use of automated tools. This study also forms the foundation for studies

designed to examine the contribution of genetic variation to the schizophrenia phenotype.

DIFFUSION TENSOR MRI IN SUBJECTS AT HIGH RISK OF SCHIZOPHRENIA

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Diffusion tensor (DT-) MRI is a useful tool to investigate possible anatomical connectivity disorders in schizophrenia. Previous studies have investigated changes in fractional anisotropy (FA), which is thought to be a marker of white matter fibre integrity. We have previously found a significant decrease of FA in frontotemporal and frontoparietal white matter tracts (arcuate and uncinate fasciculi) in patients with schizophrenia [1]. In the present study we investigated whether significant changes of white matter FA are also found in the brains of relatives of individuals with schizophrenia who are at high risk for genetic reasons. We compared white matter FA of 22 high risk subjects and 20 subjects with schizophrenia with a control group of 41 subjects. All participants underwent DT-MRI by acquiring a baseline (b = 0 s/mm2) axial diffusion-weighted (DW) scan and 51 DW scans at b = 1000 s/mm2 with diffusion gradients in non-collinear directions. All DW volumes were registered to the baseline volume and the diffusion tensor was estimated in each voxel. FA maps were then computed for each subject. All the baseline volumes were registered using non-linear registration with SPM5 to the MNI T2-weighted MRI template and the transformation matrices applied to the FA maps. These were then smoothed applying a 12 mm FWHM isotropic Gaussian filter. The small volume correction tool of SPM5 was used to define a priori the hypothesised volumes for the uncinate and the arcuate fasciculi using 10.0 mm radius spheres centred at the coordinates selected from the Tailarich atlas [1]. We found significantly reduced FA in patients with schizophrenia compared to controls within the small volume correction over the right uncinate fasciculus (p=0.012) and the right arcuate fasciculus (p=0.013). No significant changes in FA were found in the small-volume corrections on the left side. No significant differences in FA were found when the high risk subjects were compared to the controls. This study replicated previous findings showing decreased FA in white matter fibres connecting the frontal and temporal lobes of schizophrenia patients. This difference in FA is not present in white matter of individuals at high risk of schizophrenia for genetic reasons. This suggests that white matter abnormalities in schizophrenia are state rather than trait effects. [1] Burns et al. Br. J. Psychiatry (2003),182,439-443

SIGNALING MECHANISMS CONTROLLING DENDRITIC SPINE MORPHOLOGY IN THE STRIATUM

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Schizophrenia is a major neuropsychiatric disorder of largely unknown etiology. An emerging view suggests that schizophrenia results from subtle, but abnormal, neuronal development and this may result from aberrant expression or localization of proteins that influence neuronal migration, synaptogenesis, or synaptic structure. Dendritic spines are specialized protrusions from neuronal dendrites that receive the majority of excitatory input in the central nervous system. Recent studies have found that spines are highly dynamic, changing size and shape during development as well as in the adult brain. The principle cytoskeletal component of dendritic spines is F-actin, and the ability of spines to change shape has been attributed to the rapid regulation of the assembly and disassembly of the actin cytoskeleton. Spinophilin and its homolog, neurabin, are actin-binding proteins that regulate dendritic spine function and morphology. Several recent studies have found that spinophilin interacts with the third intracellular loop of several GPCRs, including D2- (D2-R) and a2-adrenergic (a2-AR) receptors and plays a role in their desensitization. Spinophilin and neurabin also contain a common central PDZ domain, and a C-terminal coiled-coil domain. In recent studies, we have found that the rho GEF, Lfc, interacts with the coiled-coil domain of spinophilin and neurabin. This interaction between Lfc and neurabin/spinophilin plays an important role in Rho-dependent organization of F-actin in spines and this is important for spine maturation. The role of Lfc/Rho in the regulation of spine morphogenesis, as well as the role of other regulators of F-actin in dendritic spines will be discussed.

ALTERED ORBITOFRONTAL SULCO-GYRAL PATTERN IN SCHIZOPHRENIA

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Orbitofrontal alteration in schizophrenia has not been well characterized, likely due to marked anatomical variability. To investigate the presence of such alterations, we evaluated the sulco-gyral pattern (gyrification) of this “H-shaped” sulcus. Fifty patients with schizophrenia (100 hemispheres) and 50 age- and gender-matched controls (100 hemispheres) were evaluated using 3-D high-spatial resolution MRI. Based on a previous study by Chiavaras and Petrides (2000), the sulco-gyral pattern of the “H-shaped” sulcus, which forms the boundaries of major orbitofrontal gyri, was visually classified into three types (Type I, II, and III, in order of frequency) within each hemisphere. Chi-square analysis was performed to compare the sulco-gyral pattern, and categorical regression was applied to investigate clinical/cognitive associations. Controls manifested almost the identical orbitofrontal sulco-gyral pattern reported by Chiavaras and Petrides (P=.90-.95), where the distribution was significantly different between left and right hemispheres (Type I: right>left, Type II, III: left>right, χ^2=6.41, P=0.041). For schizophrenics, the distribution was quite different (χ^2=11.90, P=0.003) from controls, especially in the right hemisphere (χ^2=13.67, P=0.001). Moreover, the asymmetry observed in controls was not present in schizophrenia (χ^2=0.13, P=0.94). Specifically, the most frequent Type I expression was decreased and the rarest Type III expression was increased in schizophrenia, relative to controls. Furthermore, patients with Type III expression in any hemisphere evinced poorer socioeconomic status, poorer cognitive function, and more severe symptoms, compared to patients without Type III expression. In contrast, patients with Type I in any hemisphere showed better cognitive function and milder symptoms compared to patients without Type I. The present study provides evidence of altered orbitofrontal sulco-gyral pattern in schizophrenia, possibly related to a susceptibility to schizophrenia, as sulco-gyral patterns are strongly influenced by processes during neurodevelop-

ment. The observed contrasting association of Type III expression with poorer outcome, and that of Type I expression with better outcome, further suggests clinical heterogeneity, and possible differences in treatment-responsiveness in schizophrenia. Such altered sulco-gyral pattern may reflect a morphological trait marker, which is unlikely due to secondary effects of illness such as medication.

EFFECT OF ANTIPSYCHOTIC MEDICATION ON HIPPOCAMPUS IN FIRST EPISODE PSYCHOSIS: IS THIS GENDER SPECIFIC?

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Background: brain abnormalities have been found in patients at their first episode of psychosis. It remains unclear whether antipsychotic medications induce changes at this stage and whether such effects are drug-type dependent. To address this question we studied, in a sample of first episode psychosis, the volume of hippocampus which is a highly neuroplastic structure, susceptible to a wide variety of insults and reported as reduced in chronic schizophrenia. Methods: we compared 78 patients at their first episode of a functional psychosis (mean age: 27 years, SD=7; 41% female; 40 schizophrenia/schizophreniform disorders, 29 affective psychosis and 9 other psychosis, DSM-IV criteria) with 78 sex and age matched controls. Hippocampal volumes were traced using 1.5 mm coronal, 1.5T, high resolution MRI images. Subjects were divided in three groups depending on current treatment: typical antipsychotics; atypical antipsychotics; drug-free. Results: there was no difference in hippocampal volumes between patients and controls. However, female patients had smaller hippocampal volumes than female controls, while the opposite was true in males (two-way ANOVA; total volume: F=5.43, p=.02; left-side: F=3.66, p=.05; right-side: F=5.51, p=.05). Results were not influenced by diagnosis or duration of illness. We did not find any correlation between cumulative dose of antipsychotic received at the moment of the MRI and hippocampal volumes. Female patients taking atypicals, but not typicals, had a statistically significant smaller hippocampal volume than drug-free patients and controls (one-way ANOVA; total volume: atypicals vs drug free, p=.02; atypicals vs controls=.01, p=.01/right side: atypicals vs drug free, p=.05; atypicals vs controls=.01/ left side: atypicals vs drug free, p=.02; atypicals vs controls=.02). In males we did not find a statistically significant drug effect on hippocampal volumes. Conclusions: Our data suggest a specific effect of atypical antipsychotics in female patients. This could be due to an influence on hormonal systems (such as the hypothalamic-pituitary-adrenal axis) that have been shown to influence brain volumes systems. This result should be further investigated in longitudinal studies.

NEGATIVE SYMPTOMS AND FRONTAL BRAIN TISSUE VOLUMES IN SCHIZOPHRENIA – A MAGNETIC RESONANCE IMAGING STUDY

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Numerous magnetic resonance imaging (MRI) studies have shown smaller brain tissue volumes among patients with schizophrenia compared with controls. The relationship between variation in brain morphology and symptom severity is less conclusive. In this study, we assessed correlations between negative symptoms and frontal brain tissue volumes among 39 patients (14 women and 25 men) with schizophrenia (n=33) or schizoaffective disorder (n=6) recruited as part of the Human Brain Informatics (HUBIN) study at Karolinska Institutet in Stockholm, Sweden. Mean age was 41.2 years (SD 7.8), age at onset of illness 24.7 years (SD 4.9) and duration of illness 16.5 years (SD 8.6). All but three patients received antipsychotic medication at the time of investigation. Frontal lobe grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes were measured from segmented MR-images using a 1,5 T GE scanner and BRAINS software tools. In addition, to closely investigate frontal GM, parcellated volumes of nine cortical regions in each hemisphere (cingulate gyrus and sulcus, superior frontal gyrus and sulcus, middle frontal gyrus and sulcus, inferior frontal gyrus, straight gyrus and subcallosal gyrus) were measured using FreeSurfer. Negative symptoms were assessed using SANS (Scale for the Assessment of Negative Symptoms). SANS composite score (sum of all 25 items, max score 125), SANS total score (sum of subscores, max score 25), and five subscores (affective blunting, alogia, apathy, anhedonia and attention, max score 5 each) were used to correlate negative symptoms with brain tissue volumes controlling for age and intracranial volume. Frontal WM volume correlated with SANS composite score (r=0.327, p=0.048), and trend level correlated with SANS total score (r=0.285, p=0.087) and the anhedonia subscore (r=0.290, p=0.082). Frontal GM volume trend level correlated with the attention subscore (r=0.306, p=0.066). Volume of left cingulate gyrus correlated with the alogia subscore (r=0.481, p=0.002). Trend level correlations were found between right frontal superior gyrus and the attention subscore (r=0.274, p=0.092), right frontal middle gyrus and the alogia subscore (r=0.279, p=0.086), and between SANS total score and left frontal superior sulcus (r=0.312, p=0.053) and left frontal medial sulcus (r=-0.279, p=0.085). The results indicate that presence of negative symptoms may be associated with variations in frontal lobe tissue volumes.

COMPARISON OF THALAMIC SHAPE AND VOLUME BETWEEN SCHIZOPHRENIA SUBJECTS AND CONTROLS

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Individuals with schizophrenia have reduced thalamic volumes when compared to controls. Some studies suggest that the anterior and posterior regions of the thalamus are disproportionately affected. To extend these findings, surface mapping was used to identify regions on the thalamic surface that corresponded to groups of thalamic nuclei. The following three zones were studied in 52 schizophrenic subjects and 65 controls: specific, associative, and remainder. The group of nuclei in the specific thalamic zone receives sensory and motor input and projects to their respective cortical regions. The group of nuclei in the associative thalamic zone receives sensory input and projects to the temporo-parietal-occipital, prefrontal, and limbic association cortex. The group of nuclei in the remainder zone includes regions on the surface of the thalamus that were not otherwise included. Using high-resolution magnetic resonance imaging and large-deformation high-dimensional brain mapping, 3D surfaces and quantified deformations of the three zones were generated. A significant decrease in thalamic volume ($p < 0.016$) was found in schizophrenic subjects compared to controls. There was also an overall significant group effect ($F = 6.37$, $p = 0.013$) on three surface zones, and the group x zone interaction was at the trend level ($F =$

2.24, p = 0.087). Post hoc analyses show that there were significant inward deformations in two of the three zones - specific ($p < 0.02$) and associative ($p < 0.02$). The remainder thalamic zone trended towards significance ($p < 0.08$). These findings suggest that the specific and associative zones form a substantial portion of the total observed shape deformity of the thalamus. Supported by: R01-MH056584, P50 MH071616 56429

THE NEUROBIOLOGY OF INSIGHT IN SCHIZOPHRENIA: RELATIONSHIP OF AWARENESS TO FRONTAL AND PARIETAL BRAIN REGIONS

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BACKGROUND: A frequent and important phenomenon associated with schizophrenia is poor insight, or a lack of awareness of the presence and pathological nature of symptoms. The neurobiology of insight is not well understood. A few studies have found abnormalities in certain regions of the frontal lobe associated with insight. However, no study has evaluated all regions of the frontal lobe in relation to insight. In addition, 'neglect' is a form of anosognosia similar to poor insight. Neglect has been localized to the parietal lobe yet no study has investigated whether parietal morphology may be involved in lack of insight in schizophrenia. This study was designed to evaluate the neurobiology of insight by measuring functionally distinct sub-regions of the frontal and parietal lobe, and correlating them with ratings of insight. METHODS: MRI scans were obtained from nineteen patients diagnosed with schizophrenia that had an evaluation of insight with the SUMD (Scale to assess Unawareness of Mental Disorder). Analysis of the MRI scans was carried out using an integration of BRAINS2 and FreeSurfer software. FreeSurfer automatically parcellates the cortex into functionally distinct regions. Data were analyzed by examining the Spearman partial correlations between SUMD scores and individual brain sub-regions within the frontal and parietal lobes. RESULTS: There was no relationship between global measures of brain regions and insight (frontal and parietal lobe volumes). There was a significant correlation to insight with bilateral Middle Frontal Gyrus (MFG) ($r = -0.54004$, $p = 0.0252$). Smaller MFG was associated with greater unawareness. Examination of either side separately did not show a significant correlation, although the right-sided correlation was stronger than the left. DISCUSSION: Our findings strengthen the idea that the dorsolateral prefrontal cortex (DLPFC) is involved in insight with schizophrenia since MFG contributes a large portion of DLPFC. Moreover, these findings are localized to this region, as no global or other regional measure showed relationship to degree of insight. This is consistent with the findings of the aforementioned studies as well as with the fact that the DLPFC has been associated with higher-order cognitive function.

A LARGE SCALE (N=400) INVESTIGATION OF GRAY MATTER DIFFERENCES IN SCHIZOPHRENIA USING OPTIMIZED VOXEL-BASED MORPHOMETRY

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Background: Many studies have employed voxel-based morphometry of MRI images as an automated method of investigating cortical gray matter differences in schizophrenia. However, results from these studies frequently disagree, likely due to different methodological or statistical approaches. Objective: To use voxel-based morphometry to investigate gray matter differences in schizophrenia on a sample significantly larger than any published to date, and to increase statistical power sufficiently to reveal differences not apparent in smaller analyses. Methods: Magnetic resonance whole brain SPGR structural images were acquired from four geographic sites, all using the same model GE 1.5T scanner and same version software, and combined to form a sample of 200 patients with schizophrenia and 200 healthy controls, matched for age, gender and scan location. Gray matter concentration was assessed and compared using optimized voxel-based morphometry. Results: Compared to the healthy controls, patients with schizophrenia showed significant decrease in gray matter concentration in multiple cortical and subcortical regions, some previously unreported. Overall, our results found lower concentrations of gray matter in all of the regions identified in prior studies reviewed, most of which had reported individually only a portion of affected areas. Conclusions: Gray matter differences in schizophrenia are most comprehensively elucidated using a large, diverse and representative sample. Methodologic issues inherent in comparing subject scans across different geographic sites will also be discussed.

EVALUATION OF CEREBELLAR FOLIATION IN SCHIZOPHRENIA

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The cerebellum and its circuit with the cerebral cortex have been shown in numerous structural and functional imaging studies to be affected by schizophrenia. To extend our understanding of cerebellar development we have begun to focus on the finer details of its structure and function, with a goal of more completely understanding its development and how it may be affected in schizophrenia. The development of the cerebellum's fine structure through fissuration and foliation occurs over an extended timeline. The primary fissure appears late in the first trimester, branching of the folia continues through postnatal period, and maturation of the cerebellum likely continues into adolescence. Since the cerebellum is connected through various loops with most regions of the cerebral cortex, neurodevelopmental anomalies, regardless of their etiology, may impact or directly involve changes in cerebellar foliation. Therefore, we hypothesize that the foliation and functional localization in the cerebellum is altered in patients with schizophrenia. Subjects for this study include 10 healthy, normal control subjects and 10 subjects diagnosed with schizophrenia. Multi-modal, high-resolution structural scans were acquired for each subject. These were processed using our typical workup. In this process the T1 image is ACPC aligned and resampled to 0.5 mm isotropic resolution. The T2 image is coregistered to the T1 image, and is also resample to 0.5 mm isotropic resolution. A continuous-classified image was created. Folia were defined on the midline slice according to the nomenclature of Larsell and Jansen. Landmarks were placed at the peak and base of white matter on each folium on the midline, on each sagittal slice every 5 mm from midline, as well as at all branching and ending points of the folia. Additional foliations not represented on the mid-sagittal slice were identified as sub-foliations of main folia. These were most numerous on the caudal edge of Lobe VI and in crus I and crus II of Lobe VIIa. Reconstruction of folia centers from landmarks was accomplished through use of VTK. Measures for the folia

include the number of branches, folia and subfolia as well as the core size of each folia. The highest variability in folia core size and branching were found in Lobes VI and VII. Pending final analysis, the measures appear to trend toward less folia branching in the patient group, with a simpler foliation pattern.

DELINEATING THE SUPERIOR TEMPORAL GYRUS USING DYNAMIC PROGRAMMING IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Dynamic programming (DP) can be utilized to delineate regions of interest (ROI) on triangulated cortical surfaces such as the planum temporale (PT) and cingulate cortex (Ratnanather et al, 2003, 2004). Of particular interest is the superior temporal gyrus (STG) which has been implicated in schizophrenia (SZ) [Barta et al. 1990, DeLisi et al. 1994] and bipolar disorder (BPD) [Frazier et al. 2005, Bruno et al. 2006]. Because the STG contains Heschl's gyrus and PT, structures that are essential to auditory and speech processing, delineating an ROI that contains all three of these structures will allow more complete and more robust analyses of the underlying causes of auditory hallucination in SZ. More importantly, DP allows for two critical components of cortical analysis: namely, a 3D representation of the grey-white matter surface and a cortical representation that shows the position, variation, and density of the neocortical cells which are currently viewed as grey matter on MRI. In this study, triangulated surfaces were generated from MR subvolumes of masked ROIs of the STG from 20 SZ, 20 BPD and 20 age- and gender-matched controls. Using the curvature of the triangulated surface, the boundary of the STG surface was generated via DP tracking of sulcal, gyral, and geodesic curves on the surface. DP was initiated by careful placement of several landmarks. The posterior landmark of the STG boundary begins at the intersection of the angular gyrus (AG) and the STG at the most posterior extent of the lateral fissure (LF). The anterior landmark of the STG boundary is located at the superior portion of the temporal pole at the ascending ramus of the LF. The inferior extent of the STG boundary follows from the posterior landmark along the superior temporal sulcus (STS) all the way to the anterior landmark. The superior extent of the STG boundary follows from the anterior landmark along the LF to the posterior landmark. Surface areas were then calculated by summing the areas of all the triangles that comprised the triangulated surfaces of the STG. For all subjects, the left STG is significantly smaller than the right STG ($p<0.001$). Moreover, males had significantly larger STGs than females ($p<0.0001$), and BPD had significantly smaller left STG than right STG compared to SZ and controls ($p<0.0015$). Analysis of surface area can then be correlated with volume and thickness obtained by Labeled Cortical Depth Maps. Supported by: RO1-MH064838, P41-RR15241

CORTICAL GYRATION IN FIRST DEGREE RELATIVES OF SCHIZOPHRENIA PATIENTS

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Background: Genetic factors have been known to enhance the risk for schizophrenia. Neurobiological antecedents of such increased risk may be elucidated by examining adolescent first degree relatives of schizophrenia patients before they manifest the illness. Cortical gyration indices provide evidence of subtle structural changes. We examined cortical surface area, curvature and thickness in first degree relatives of schizophrenia patients and healthy subjects. **Methods**: A well characterized cohort of first degree relatives (HR, offspring & siblings, n=31) of schizophrenia patients and matched healthy control subjects (HS, n=33) underwent structural MRI. Using BRAINS2, lobewise cortical surface areas, thickness and curvatures were obtained. We used multivariate ANCOVA by including age and gender as covariates to examine the differences between the groups. **Results**: Parietal lobes bilaterally showed decreased gyral surface area (right, HS=108.82±14.77 cm^2, HR=99.47±14.02 cm^2, $F(1,64)=6.10$, $p=0.016$, left, HS=104.82±14.28 cm^2, HR=95.90±14.91 cm^2, $F(1,64)=5.01$, $p=0.027$) and increased sulcal curvature (right, HS=0.085±0.017 mm^{-1}, HR=0.094±0.014 mm^{-1}, $F(1, 64)=5.14$, $p=0.024$; left, HS=0.083±0.016 mm^{-1}, HR=0.094±0.017 mm^{-1}, $F(1,64)=5.76$, $p=0.02$) in HR subjects relative to HS. Left temporal gyral curvature was decreased in HR subjects (HS=0.077±0.009 mm^{-1}, HR=0.074±0.005 mm^{-1}, $F(1,64)=3.96$, $p=0.051$). We observed a significant risk status and gender interaction at the frontal sulcal curvature (Right, $F(1,64)=5.82$, $p=0.019$, Left, $F(1,64)=4.24$, $p=0.044$) and right occipital sulcal curvature ($F(1,64)=4.37$, $p=0.041$). In HR males, the curvature was decreased and in HR females it was increased. Such interaction effects were not observed in the parieto-temporal regions. Total brain surface area (HS, 1758.31 cm^2; HR, 1729.88 cm^2; $F(1,64)=0.4$, $p=0.5$) and cortical thickness in any lobe were not altered. **Discussion**: Our observations suggest that the first degree relatives of schizophrenia patients manifest differences in the parieto-temporal regions before the onset of the illness. This region is part of the heteromodal association area implicated in the integration of multimodal sensory inputs. Gender and risk status interaction at the frontal and occipital regions suggest that gender may have a pathoplastic effect in first degree relatives. Our findings provide preliminary clues to subtle brain alterations before the onset of the illness in those at risk for schizophrenia.

DIFFUSION MRI TRACTOGRAPHY IN FIRST-EPISODE SCHIZOPHRENIA

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Background. Schizophrenia may be a disorder of brain connectivity and attention has been mainly focused on the cortical synaptic circuitry and much less so on the white matter connecting pathways. Using diffusion tensor imaging (DTI) data, probabilistic tractography is able to obtain a connectivity index along white matter pathways reflecting fibre organisation. DTI tractography is also able to investigate tract-specific fractional anisotropy (FA), a measure that reflects the directional coherence of the fibre tracts. We present here a DTI tractography study of the corpus callosum and the uncinate fasciculus in first- episode schizophrenia. We aim to test the hypothesis that, when compared to healthy controls, abnormal connectivity is already present early in the disease. Methods. Eighteen patients with first-episode psychosis and 21 healthy subjects took part in the study. A probabilistic tractography algorithm (PICo) was used to

study fractional anisotropy (FA). In the analysis of the corpus callosum, seed regions were placed in the genu and splenium to track fibre tracts traversing these regions, and a multi-threshold approach to study the probability of connection was used. To isolate the uncinate fasciculus a region of interest (ROI) was placed on the anterior aspect of the uncinate fasciculus and a second ROI more inferiorly on T1 weighted images normalised to a standard space. The regions were then transformed into the diffusion tensor data space where probabilistic tractography (PICo algorithm) was used to estimate the probability of connection between the two ROI. For the analysis of the corpus callosum we used multiple linear regressions with age, gender and tract volume as covariates to explore group differences. Results. FA was reduced in tracts crossing the genu, and to a lesser degree the splenium, in patients compared with controls. There were no clinical correlations with tract coherence suggesting that these abnormalities may precede the onset of symptoms. A preliminary analysis of the uncinate fasciculus data revealed an asymmetric distribution in connectivity values and FA in both groups. Conclusions. Decreased FA may be due to axonal abnormalities including less coherent fibre alignment or abnormal myelination. The significance of the connectivity abnormalities described here may be secondary to cortical changes and/or to primary white matter pathology.

CORTICAL THINNING OF THE CINGULATE GYRUS IN SCHIZOPHRENIA

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Neuroimaging studies have shown reductions in gray matter volume of the cingulate gyrus in schizophrenia. Variation in cortical thickness measuring the depth of the gray matter ribbon may reflect neuronal organization in schizophrenia. MRI scans from 64 normal controls and 49 schizophrenic patients were analyzed in this study. A 3D region of interest encompassing the cingulate cortex was masked in each hemisphere in each subject. Bayesian segmentation with an expectation-maximization algorithm to fit the compartmental statistics was used to label voxels in the subvolume as gray matter (GM), white matter (WM), or cerebrospinal fluid. Surfaces were generated at the GM/WM interface using a topology-correction method and a connectivity-consistent isosurface algorithm. Cortical thickness maps indexed over the cingulate surface were estimated using the Local Labeled Cortical Depth Map algorithm (LLCDM). One surface was selected as template and the Large Deformation Diffeomorphic Metric Surface Matching approach was used to deform all other surfaces to the template and transform cortical thickness maps to the template. To perform statistical analysis, the template surface was partitioned into three regions (anterior, middle, and posterior) via the basis function of the Laplace-Beltrami operator. We performed the rank sum test on the null hypothesis that the mean thicknesses within each region are equal in the control and schizophrenic populations. The alternative is that the mean thickness is greater in the control than in schizophrenia. The p-values listed in the table suggest that the cortical thickness is reduced in both left and right cingulate cortex in the schizophrenic group. Supported by NIH P50MH071616, R01MH056584 and P41RR015241

p-value	Anterior	Middle	Posterior
Left	0.0351*	0.0585	0.0184*
Right	0.0592	0.0263*	0.0053*

CANNABIS USE AND GRAY MATTER VOLUME IN SCHIZOPHRENIA: A FIVE-YEAR LONGITUDINAL MRI STUDY

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Background: Progressive gray matter volume reductions have been found in schizophrenia and greater decreases seem to be related to poorer outcome. As patients with schizophrenia and cannabis use have a worse prognosis progressive gray matter changes in these patients might be more extensive. Method: Patients with recent-onset schizophrenia (n=57) and matched healthy comparison subjects (n=31) were included in this study. For all subjects magnetic resonance imaging scans were obtained at inclusion (T0) and after five years (T5). Diagnosis was assessed at T0 and T5 with the Comprehensive Assessment of Symptoms and History and drug and alcohol use was assessed with the Composite International Diagnostic Interview. Moreover, drug use was randomly checked with urine toxicology and confirmed by relatives. Patients who fulfilled DSMIV criteria for alcohol or drug abuse/dependence or had used drugs, other than cannabis, were excluded from the study (n=6). Of the remaining group, 19 patients used cannabis regularly and 32 patients had not used any drugs during the follow-up. At T5 clinical and functional outcome were measured and cumulative amount of antipsychotic medication was calculated. At T0 and T5 total brain, gray and white matter, lateral and third ventricle volumes were measured. Percentages of volume change over time were calculated. Univariate analysis of covariance and pairwise comparisons were performed. Results: Cannabis using patients, non-using patients and healthy comparison subjects differed significantly in gray matter, lateral and third ventricle volumes. Cannabis using patients with schizophrenia showed a more rapid decrease in brain gray matter (F=8.1 df=76 p=.001) and increase in lateral (F= 3.8 df=76 p=.025) and third (F=4.04 df=76 p=.022) ventricle volumes as compared to healthy subject and non-using patients. Gray matter volume decrease occurred in all patients with schizophrenia as compared to healthy subjects, but was significantly greater in patients using cannabis (Mean Diff.=2.7 SE=1.1 p=.03). Outcome did not differ between cannabis using and non using patients with schizophrenia. Conclusion: In schizophrenia progressive gray matter volume decrease occurs during the first five years of illness. Cannabis use is associated with a more pronounced decline in gray matter brain volume in patients with schizophrenia. This decline could be explained by the comorbid cannabis abuse/dependence disorder or by the toxic effects of cannabis.

PREVALENCE OF CAVUM SEPTUM PELLUCIDUM IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS, OFFSPRING OF SCHIZOPHRENIA PATIENTS AND COMPARISON SUBJECTS

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Introduction: Septum pellucidum is a thin translucent membrane beneath the corpus callosum, medial wall of lateral ventricles and is believed to be a component of the limbic system. Although all fetuses have a cavity between the two layers known as Cavum (CSP), majority of them are believed to fuse by the first year of life. It has

been proposed that presence of CSP in adults is a midline brain developmental anomaly that is found more frequently in schizophrenia (SZ). The incidence of CSP is extremely variable (0.1%to85%) depending upon the resolution of the method. In this study, we examined the prevalence of CSP in a large number of SZ patients, offspring of SZ patients and comparison subjects. Methods: MRI scans from ongoing studies at University of Pittsburgh of first episode patients (n=89, age=23.8±7.4, M/F=61/28), genetically at risk individuals (offspring and siblings of schizophrenia patients, (65, age 15.3±3.5, M/F=32/33) and normal controls (120, age=21.8+7.8, M/F61/28) were used in this study (124 T1-weighted 1.5-mm coronal slices, with no gap, obtained with a 1.5-T GE scanner; 3D SPGR coronal, matrix=256x256x192, FOV=24cm). CSP was measured by the number of slices it appears in a 10_ACPC resampled 1mm coronal image using BRAINS2 software by one of the authors (JS), blind to group status. Test retest and inter-rater reliability (with RR) was 0.96 and 0.95 respectively on 20 scans. Results: CSP was present in 64% of the first episode patients (mean length 1.87±2.3mm), 64.6% of the at-risk individuals (1.64±1.96mm) and 64.2% of the normal controls (1.88±2.0mm). There was no statistical difference in the prevalence as well as the size of the CSP. We also did not find any influence of the sex and age in the presence or size of CSP in any of the groups. Discussion: We believe that relatively high incidence of CSP is due to the higher resolution of the MR images. The absence of CSP differences across groups is convincing since to our knowledge this is one of the largest studies examining CSP in untreated first episode psychosis and high risk populations. It is possible that previous studies that included 3 mm slices could have missed small CSP. We did not however, find any difference in the incidence of larger CSP or any difference in the mean size. Our data cast doubt on the significance of CSP as markers of neurodevelopmental pathology in schizophrenia. Supported by NIMH grants MH45156, 45203 and the NIH/NCRR/GCRC grant #M01 RR00056.

STATISTICAL ANALYSIS OF SURFACE ROUGHNESS VIA LOCAL AREA MAPS: APPLICATION TO THE CINGULATE IN HEALTHY AND SCHIZOPHRENIC SUBJECTS

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Recent attention has focussed on quantifying the structure of the gray-white matter interface. Prior algorithms for cortical analysis have avoided the variability of this interface to improve the consistency of measures of cortical thickness. However, quantifying the organization of the innermost layer of the cortical mantle, i.e., the roughness of the gray-white matter interface at the level of magnetic resonance (MR) scans, could offer a new approach for testing the hypothesis that aberrations in neurodevelopment are involved in the pathogenesis of schizophrenia (Rapoport et al., 2005). A study of semi-automated methods for analysis of the cingulate cortex suggests that it would be difficult to manually trace the gray-white boundary to assess its roughness (Ratnanather et al., 2004). We thus propose an automated method for assessing this feature of the cortical mantle. We quantified roughness using the *local area map* which is a measure of surface area per unit volume. The local area at scale σ about a point on the surface is defined by convolution of the surface area element with a 3D Gaussian kernel of size σ. By studying statistical properties of local area maps, we were able to determine whether one surface, or group of surfaces, was rougher than the other. Gray-white surfaces of the cingulate cortex were reconstructed from MR images collected from 54 schizophrenia subjects and 68 healthy controls, group matched for age, gender and parental socioeconomic status. At each scale for each surface, we computed the statistics of the local area and relative local area histograms which were analyzed via one-sided rank-sum tests. At the smallest scale, σ=0.5mm, the right anterior cingulate yielded p-values of 0.025 and 0.2 for the median and standard deviation of the local area respectively and 0.025 for the median of the magnitude of the relative local area. Corresponding values for the right posterior cingulate were p=0.025, 0.03 and 0.02. But no significant differences were observed for the left cingulate. The results suggest that at the scale mm, the right cingulate is rougher for the group with schizophrenia than for the control group. To the extent that an increase in roughness of the gray-white matter interface suggests disorganization of the innermost cortical layer, these results are consistent with the hypothesis that schizophrenia is characterized by a defect in cortical development. Supported by NIH P50MH071616, R01MH056584 and P41RR015241.

REDUCED THALAMIC VOLUME IN DRUG-NAïVE FIRST EPISODE SCHIZOPHRENIA PATIENTS: CORRELATIONS WITH COGNITIVE VARIABLES

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The thalamus has been traditionally implicated in the pathophysiology of schizophrenia. Structural studies have inconsistently shown the presence of thalamic volume differences in patients with schizophrenia. However, only a few studies have examined the relation between thalamic structure and cognitive variables in early phases of the illness. The aim of this study was to investigate thalamic volumes in first episode psychosis patients and healthy comparison subjects and to assess the relationship between thalamic volumes and key cognitive dimensions, executive functioning and sustained attention. This study used a sample of right-handed previously untreated first episode patients with non-affective psychosis (n = 61) and right-handed healthy comparison subjects (n = 40). There were no significant differences between patients and healthy comparison subjects with regard to age, gender, height, educational level, parental socioeconomic status and alcohol or cannabis consumption. Magnetic resonance imaging scans were acquired on a 1.5-T GE Signa scanner using a SPGR sequence. Thalamic volumes in the right and left hemispheres and total thalamic volume were automatically segmented and calculated using BRAINS2. All the thalamic volumes were visually revised. Analysis of covariance (ANCOVA) was used to compare thalamic volumes between patients and controls. Intracraneal volume was used as the covariate. Spearman's partial correlations with intracranial volume as the covariate were used to examine relationships among thalamus volume measures and cognitive dimensions Right, left and total thalamic volumes of the patients with non-affective psychosis were significantly smaller than those of the healthy subjects (total thalamic volumes: $F = 5.60$, $p = 0.020$; left thalamic volumes: $F = 5.92$, $p = 0.017$; right thalamic volumes: $F = 4.31$, $p =$

0.04). However, larger thalamic volumes in patients were associated with a poorer cognitive executive functioning (r=-0.300, p=0.048). Thalamic volumetric differences between patients with non-affective psychosis and healthy controls are already present at early phases of the illness. However, further investigations are warranted to fully clarify the relationship between those structural anomalies and cognitive outcomes. Funding: Instituto de Salud Carlos III, FIS 00/3095, 01/3129, PI020499, G03/32, and SENY Fundació Research Grant CI 2005-0308007, Fundación Marqués de Valdecilla A/02/07

AMYGDALA VOLUME IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

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Introduction: Structural abnormalities of the amygdala have been documented in patients with schizophrenia and bipolar disorder. In schizophrenia a reduced volume of amygdala was consistently reported. In contrast in bipolar disorder some authors observed increased volumes of the amygdala and others found decreased volumes. The aim of this study was to investigate the amygdala volume in a sample of patients with schizophrenia or bipolar disorder compared to healthy individuals. Subjects: Thirty-four patients with bipolar I disorder, twenty-eight patients with schizophrenia and thirty healthy control subjects participated in the study. MRI scanning was performed on a 1.5 Tesla Magnetom (Siemens, Erlangen). A T1-weighted, MPRAGE sequence (TE = 4.42 ms, TR = 1900 ms, TI = 700 ms, flip angle = 15°, FOV 256 x 256 mm) of 176 consecutive slices was acquired with a voxel size of 1 x 1 x 1 mm. The amygdalae volumes were manually traced blindly to diagnosis by P.M. Relative volumes of left and right amygdale were estimated in regard to total gray matter volume. Results: Left relative amygdale volume was reduced in patients with schizophrenia compared to healthy subjects. No differences of amygdalae volumes were observed between patients with bipolar disorder and control subjects or patients with schizophrenia. Conclusion: In this study we could confirm prior reports of reduced amygdale volume in schizophrenia. In contrast to previous findings we could not observe significant volumetric abnormalities of amygdale in patients with bipolar disorder.

ALTERED CORTICAL THICKNESS IN ADOLESCENTS AND YOUNG ADULTS AT GENETIC RISK FOR SCHIZOPHRENIA

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Objective: Adult first-degree relatives of persons with schizophrenia carry elevated genetic risk for the illness, and demonstrate structural brain abnormalities. Because substantially less is known about these phenotypes in adolescent subjects we sought to demonstrate that young high risk (HR) relatives of persons with schizophrenia manifest altered brain volumes. We assessed this in a novel approach to measuring cortical thickness that, to our knowledge, has not been previously used in young HR samples. Methods: Participants were 27 non-psychotic, un-medicated first-degree relatives of persons with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type and 48 un-medicated controls, recruited from the community and hospitals in metropolitan Boston (ages 13-28). MRI data was acquired on a Siemens 1.5T MR scanner. Data were analyzed using morphometric approaches combining the Cardviews and Freesurfer tools. Differences are tested with two-tailed tests. Results: The HR participants have significantly thinner cortices than controls in a number of regions typically altered in schizophrenia, even though they are not psychotic and have not received antipsychotic medications. The differences are more pronounced in the right hemisphere. These areas are located in the frontopolar and dorsolateral prefrontal cortex (DLPFC), in the orbitofrontal cortex (OFC), the insula, mainly in its anterior portion, anterior and posterior cingulate, anterior and posterior parahippocampus, temporal pole, temporal occipital, fusiform, precuneal and occipital areas. Similarly, in the left hemisphere the differences are localized in the frontopolar cortex and DLPFC, OFC, anterior insula, anterior and posterior cingulate, paracingulate, posterior parahippocampus and occipital areas. Conclusions: These data are in agreement with volumetric differences observed in these cortical areas in schizophrenia. These promising data, while preliminary, indicate altered cortical thickness in those at risk for schizophrenia, independent of psychosis. Future work can study the relationship of these measures to possible onset of schizophrenia and to susceptibility genes.

DIFFUSION TENSOR IMAGING (DTI) AND AGE AT ONSET OF PSYCHOSIS IN SCHIZOPHRENIA: A VOXELWISE CORRELATION ANALYSIS

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Background: Premorbid motor impairment has been observed to be predictive of early-onset schizophrenia (EOS)[1], however the biological mechanism underlying this association remains unknown[2]. **Methods:** Forty-two adolescents (23M, 19F) with EOS (range of age at onset of psychosis [AOP], 7 to 18 years) participated. In addition to T1, T2 and FLAIR images for clinical purposes, DTI sequence with matching FSE sections and high-resolution 3D SPGR (IR-Prep) sequence were obtained. Whole brain (DTI) images with 25 gradient directions were obtained parallel to the AC-PC. A template image was selected from all of the subjects and transferred into Talairach space using AFNI and all other images were registered to this template. The intra-subject registration was accomplished using a linear rigid-body transformation. The resultant rigid transformation matrix was stored for registering the FA maps of all subjects. Raw diffusion images were corrected for susceptibility induced spatial distortions using the T2 volume of each subject. The FA map of each subject was then transformed to the Talairach coordinates by combining all three transformations into a single operator and was applied to the original FA map. A voxelwise ANCOVA program was used to examine whether variability in AOP was related to white matter FA. **Results:** Positive correlations between FA and age at onset of psychosis were observed in the subcortical white matter in the left supplementary motor area (SMA) (Talairach coordinates: x=-24, y=-1, z=23) and the left striatal region (x=-14, y=-10, z=48) ($p < .001$, uncorrected with an extent threshold of 100 contiguous voxels), adjusting for age at time of MRI scan. Lower FA in the left SMA region was associated with worse performance on the finger-tapping test (p=0.03). **Conclusions:** These data support a hypothesis that abnormal developmental refinement of cortical-subcortical neural pathways may contribute to the attentional and

programming processes involved in motor performance (poor motor control) and adaptive behavior (onset of psychotic symptoms)[1] in early-onset schizophrenia. References: 1.Manschreck TC, Maher BA, Cadela SF (2004): Earlier Age of First Diagnosis in Schizophrenia is Related to Impaired Motor Control. *Schizophr Bull* 30(2):351-360. 2.Lim KO, Harris D, Beal M, Hoff AL, Minn K, Csernansky JG, et al (1996): Gray Matter Deficits in Young Onset Schizophrenia are Independent of Age of Onset. *Biol Psychiatry* 40(1):4-13.

INSIGHT AND PARIETAL CORTICAL VOLUME IN SCHIZOPHRENIA

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Many patients with psychotic disorders have impaired insight. We have hypothesized that impaired awareness of illness may be related to anosognosia, which is denial of motor loss primarily involving neurological lesions of parietal or fronto-parietal cortex of the non-dominant hemisphere. However, no studies have examined the relationship between volumetric alterations in the parietal cortex and impaired insight in schizophrenia. This, to our knowledge, is the first study which is being conducted to examine the association between parietal volume and insight deficits in schizophrenia. Preliminary data from this ongoing study is based on eight patients (average age = 43.6±8.8; M/F = 7/1) with DSM-IV TR diagnosed schizophrenia or schizoaffective disorder. Insight was assessed with insight-item on PANSS and structural MRI scans with 1.5 T GE system were obtained to measure parietal volume and intracranial volume. Morphometric measurements were conducted using BRAINS 2 by a trained rater blind to clinical information. A trend towards a correlation was found between insight scores (1 = good insight; 6 = poor insight) and right total parietal volume (Spearman's R = 0.55; p = 0.10). However, this trend was lost after right total parietal volume was adjusted for the intracranial volume. These preliminary findings suggest that impaired insight in schizophrenia may be related to structural changes in the right parietal cortex. This finding is in consistence with well-documented denial of motor loss in neurological lesions of the non-dominant parietal or fronto-parietal cortex. This observation, in addition to our earlier reports of associations between insight and prefrontal-sub-regions, suggests that parietal lobe may an important non-frontal component of the neural circuit mediating insight function. However, caution is required in the interpretation of these preliminary findings as they are based on a very small sample. We will be able to report more data making a more confident interpretation possible.

LONGITUDINAL DIFFUSION TENSOR IMAGING (DTI) OF WHITE MATTER CHANGES IN SCHIZOPHRENIA

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The notion that schizophrenia is a disorder of frontotemporal dysconnection was first proposed by Wernicke almost 100 years ago. Recent studies have confirmed (micro)structural abnormalities within the frontal and temporal lobes and indicate a functional dysconnectivity between these regions. Additional evidence from post-mortem and genetic studies points to white matter as a possible source of the frontotemporal deficits. In vivo assessment with DTI, a method for measuring water motion, has evidenced diffusion abnormalities in frontotemporal connections, including the uncinate fasciculus and cingulum - fiber tracts connecting anterior temporal with orbitofrontal regions and cingulate with prefrontal/temporoparietal regions, respectively. The majority of the DTI studies have focused on cross-sectional assessments of chronic patients and have not evaluated first-episode patients or followed patients over time to determine whether the abnormalities are progressive or static. We present DTI data at time of first hospitalization and at follow-up 1.5 years later from a sample of first-episode schizophrenics, first-episode patients with bipolar disorder with psychosis, and matched controls. Preliminary data from 9 first-episode schizophrenics, 12 bipolar patients with psychosis, and 11 controls show significant intergroup fractional anisotropy (FA) differences in uncinate fasciculus, with post-hoc analyses showing that first-episode schizophrenia patients had lower FA than bipolar patients with psychosis and controls. In contrast, no significant FA differences were found for the cingulum. These findings suggest altered frontotemporal connectivity through the uncinate fasciculus, which appear to be specific to first-episode schizophrenia and similar to findings in chronic schizophrenia. In contrast, no between-group abnormalities for the cingulum suggest that neocortical-limbic connectivity may be intact early in the course of the illness. The latter findings differ from those we reported for chronic schizophrenia where both the uncinate fasciculus and cingulum were abnormal. In a separate study in our laboratory on schizotypal personality disorder, we reported uncinate but not cingulate abnormalities, suggesting again the preservation of frontolimbic functions. We plan to follow first-episode patients to determine whether or not there is progression of the cingulum findings in schizophrenia. We will report both baseline and follow- up findings in this symposium.

A NEUROANATOMICAL BASIS FOR THE FREQUENCY OF DISCRETE SPONTANEOUS ACTIVITIES IN PEOPLE WITH SCHIZOPHRENIA

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Limited behavioural repertoire impacts quality of life in chronic schizophrenia; lack of purposeful movement restricts self-care and also reduces social activity. The basal ganglia play a central role in the decision of whether and when to move and also influence cognitive pattern generators in the forebrain. Whilst the caudate has been implicated in responding to stimuli associated with motivational outcomes, the putamen has been reported to be more involved with responding to initiation of movement toward goal-directed activities, especially those actions with an expected reward. We sought to identify the structural volumetric neuroanatomical correlates of the frequency with which patients with schizophrenia performed discrete motor activities. We present a methodology aimed at analysing the 'structure' of spontaneous movement through examination of the complex time-series comprising an actigraph recording. We hypothesised that anatomy may constrain function in schizophrenia, in this case the frequency of spontaneous motor behaviour. 'Actiwatches' were used to record spontaneous motor activity over a 20 hour period in sixteen male patients with schizophrenia. Time-series data were analysed for the number of 'on' and 'off' movement epochs (i.e. discrete spontaneous activities), which might indicate a degree of structure to ongoing activity. Subjects underwent a whole-brain structural MRI scan. 'Number of discrete movement epochs' was positively

correlated with the volume of specific homologous regions within bilateral rostro-ventral putamen and temporal poles. There were no significant correlations between number of discrete movement epochs and total volume of movement, age, duration of illness, chlorpromazine equivalent anti-psychotic medication dosage, SANS 'avolition' or BARS (akathisia) score. These data suggest that in people with schizophrenia the volume of bilateral putamen may influence the complexity of their behaviours, as distinct from the overall amount of behaviour. This type of measure may be of utility in situations in which behavioural change is anticipated (e.g. with behavioural or pharmacological interventions), as well as a way of further exploring human voluntary behaviour in health and disease. Our data add to the growing body of evidence that disorders of the basal ganglia may contribute to fronto-striatal neural circuit dysfunctions expressed as positive and negative symptoms of schizophrenia.

A ^{1}H-MRS AND DTI STUDY OF DEFICIT AND NONDEFICIT SCHIZOPHRENIA

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Schizophrenia (SZ) can be classified into separate syndromes: deficit and nondeficit. Primary, enduring negative symptoms are used to define the deficit form of the illness, which may have a unique etiology, biological substrate, disease course, and treatment profile. The goal of this ongoing study is to investigate a brain network putatively involved in deficit SZ through (1) neurochemical measures obtained with proton magnetic resonance spectroscopy (1H-MRS), and (2) white matter connectivity indices obtained with diffusion tensor imaging (DTI). Twenty patients with SZ (10 deficit and 10 nondeficit) and 10 normal volunteers will participate in this study. MR scans are acquired with a Philips ACS-NT 3Tesla scanner equipped with a SENSE head coil. Water-suppressed spectra are acquired with a PRESS sequence (TR =2000 ms, TE=35 ms, 1024 points, 2000 HZ, 256 averages) from 1.5 cc voxels prescribed in the dorsolateral prefrontal (DLPF) and inferior parietal (IPC) regions. Sixteen averages of unsuppressed-water spectra are collected with the same parameters. Spectra are analyzed using fully automated, standard curve fitting software, LCModel. DTI is acquired with a single-shot echo-planar imaging sequence with SENSE parallel imaging (2.2mm isotropic voxels, 212 X 212mm FOV, 60 slices for a whole brain coverage, DW encoded along 32 independent directions). Anatomical images are collected with a MPRAGE (1 mm isotropic voxels, 256 X 256mm FOV, TR/TE/TI= 8/3.8/842.5 ms, FA= 8°). Fiber tracking and anisotropy indices are assessed with DTIStudio (Jiang et al, 2006). The superior longitudinal fasciculus (SLF) is identified based on orientation maps based on established methods (Wakana et al, 2003). Fractional anisotropy (FA) and mean diffusivity (MD) are obtained from ROIs drawn in the DLPF and IPC. Preliminary MRS findings reveal elevated DLPF glutamate+glutamine (GLE) in the deficit versus nondeficit patients, suggestive of glutamatergic dysfunction. Consistent with previous studies, there is a trend for an overall NAA decrease in patients versus controls which suggests compromised neuronal function. Good reliability for fiber tracking and ROI methods has been established between raters. To our knowledge, this is the first study to compare MRS and DTI measures in deficit and nondeficit SZ. Results of this study may support efforts to develop treatment strategies for deficit and nondeficit subgroups.

INCREASED RIGHT PREFRONTAL GYRIFICATION INDEX IN ADOLESCENTS AT HIGH RISK OF SCHIZOPHRENIA THROUGH COGNITIVE IMPAIRMENT AND SCHIZOTYPAL FEATURES – BASELINE FINDINGS FROM THE EDINBURGH STUDY OF COMORBIDITY

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In the Edinburgh High Risk Study (EHRS) increased right prefrontal lobe cortical folding was identified as one of the factors predictive of the later development of schizophrenia in a genetically predisposed group.1 To confirm and extend these findings we quantified the prefrontal cortical folding in a group of adolescents at high risk of developing schizophrenia by virtue of cognitive impairment and examined it with respect to their risk for later schizophrenia. Recruitment was carried out as part of the Edinburgh Study of Comorbidity (ESC) which is a large prospective study of adolescents with cognitive impairment who are therefore at high risk of later schizophrenia. 394 adolescents receiving special educational assistance were recruited and rated using the Structured Interview for Schizotypy (SIS). A binary cut-off on the SIS was found to significantly predict the later onset of schizophrenia in the Edinburgh High Risk Study.2 This cut-off was used to divide the subjects into two groups – those with a presumed higher risk of schizophrenia (SIS+) and those with a presumed lower risk of schizophrenia (SIS-). Approximately equal numbers in each group were randomly chosen to receive a magnetic resonance imaging (MRI) scan. The SIS+ group consisted of 51 males and 23 females (mean age 15.8; mean IQ 75.1), while the SIS- group consisted of 42 males and 30 females (mean age 16.0; mean IQ 71.3). No significant differences were seen between the groups with respect to demographic variables. Prefrontal cortical folding was assessed using the gyrification index (GI) determined automatically by the new aGI tool developed in our laboratory.3 Differences between the groups were assessed using t tests. The SIS+ group had an increase in right prefrontal GI compared to the SIS- group (2.25 vs 2.20, t=1.96, p=0.05). Thus, within this group of adolescents at high risk for later schizophrenia due to cognitive impairment, those most at risk show brain structural changes at baseline consistent with findings in people with genetic risk factors who go on to develop the disorder. 1 Harris et al, Biological Psychiatry 2004; 56(3):182-9 2 Miller et al, British Journal of Psychiatry 2002; 180:179-184 3 Moorhead et al, Neuroimage 2006; (31)4:1560-6

PROGRESSIVE BRAIN STRUCTURAL CHANGES MAPPED AS PSYCHOSIS DEVELOPS IN 'AT RISK' INDIVIDUALS

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Schizophrenia, and other related psychoses are associated with brain structural abnormalities, but the timing of the development of these brain abnormalities relative to the emergence of psychotic symptoms is unknown. In this longitudinal Magnetic Resonance Imaging study, we applied Cortical Pattern Matching, in combination with Struc-

tural Image Evaluation, using Normalisation, of Atrophy (SIENA), to images of the brain from 35 people who were at ultra-high risk for developing psychosis. Compared to people who did not develop psychosis (n=23), people who converted to psychosis (n=12) during a one-year follow-up showed significantly greater brain contraction in the right prefrontal region. Brain volume loss was accelerated around the time of onset of psychosis, indicating ongoing pathological processes during the transition stage to illness. The prefrontal volume loss is in line with structural and functional abnormalities in schizophrenia, suggesting a critical role of this change in the development of psychosis.

CLINICAL AND NEUROPSYCHOLOGICAL CORRELATES OF WHITE MATTER ABNORMALITIES IN RECENT ONSET SCHIZOPHRENIA

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Objective: To investigate the clinical and neuropsychological correlates of white matter abnormalities in patients with schizophrenia studied early in the course of illness. Methods: Thirty-three (21M/12F) patients with recent onset schizophrenia and 30 (18M/12F) healthy volunteers completed structural and diffusion tensor imaging exams. Patients also received clinical and neuropsychological assessments. Fractional anisotropy maps were compared between groups in the white matter using a voxelwise analysis following inter-subject registration to Talairach space and correlated with functional indices. Results: Compared to healthy volunteers, patients demonstrated significantly ($p < .001$; cluster size $\geqq 100$) lower FA within temporal lobe white matter regions corresponding anatomically to the right and left uncinate fasciculus, left inferior fronto-occipital fasciculus and left superior longitudinal fasciculus. There were no areas of significantly higher FA in patients compared to healthy volunteers. Lower FA in the uncinate fasciculus correlated significantly with greater severity of negative symptoms (alogia and affective flattening), and worse verbal learning/memory functioning. In addition, higher FA in the inferior fronto-occipital fasciculus correlated significantly with greater severity of delusions and hallucinations. Conclusions: White matter abnormalities are evident in patients with schizophrenia early in the course of illness, appearing most robust in left temporal regions. These abnormalities have clinical and neuropsychological correlates, which may be useful in further characterizing structure-function relations in schizophrenia and constraining neurobiological models of the disorder.

REDUCED WHITE MATTER DENSITY IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS PRESENTING WITH UNFAVORABLE PREDICTORS OF OUTCOME

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Objective: To investigate the putative association between predictors of outcome and structural cerebral alterations in patients with first-episode schizophrenia. The predictors of functioning impairment were assessed using the Strauss-Carpenter-Scale (SCS), a well established instrument for this purpose. Methods Predictors of outcome were rated on the Strauss-Carpenter Scale (SCS) in 40 patients with first manifestation of schizophrenia spectrum psychosis. Additionally, each patient underwent high-resolution T1-weighted magnetic resonance imaging (MRI). Optimized voxel-based morphometry (VBM) with individual created sample-based-template was applied to investigate gray matter (GM) and white matter (WM) density and their putative association with prognostic values. Results VBM analysis revealed a low total SCS score (indicating an unfavorable course of the disease) to be significantly correlated with a reduced WM density pronounced in the right frontal and temporal lobe as well as in the right external capsule. On the other hand, no significant association was found between SCS total value and GM density. Conclusion /Prospective Our preliminary findings of a reduced WM density in patients with an unfavorable prognosis add weight to the concept of schizophrenia as a disconnectivity-syndrome. We are currently investigating the putative association between SCS subscores and GM/WM density and will be able to present these results at the congress.

ANTERIOR HIPPOCAMPAL VOLUME REDUCTION IS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN SCHIZOPHRENIC PATIENTS WITH WATER IMBALANCE

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The neuropsychological consequence of hippocampal volume reduction in schizophrenia remains poorly understood. Despite the structure's recognized role in declarative memory and associated cognitive function, there is unclear association between hippocampal volume reduction and memory or other cognitive deficit in schizophrenia. Recent work has linked volume reduction in the anterior segment of the hippocampus to neuroendocrine dysfunction and water imbalance in schizophrenia, highlighting the potential importance of this region to clinical pathophysiological features of the illness. To further investigate the functional significance of the hippocampus in schizophrenia, we evaluated neuropsychological correlates of the anterior and posterior segments of the hippocampus and other adjacent brain structures in a patient sample that included patients with water imbalance. The sample consisted of 26 patients with schizophrenia: seven polydipsic hyponatremic, ten polydipsic normonatremic, and nine nonpolydipsic normonatremic. Patients underwent structural MRI scanning on a 3.0 T scanner, and volumes of anterior hippocampus, posterior hippocampus, amygdala, whole brain tissue, and third ventricle were obtained. Patients were administered neuropsychological tests assessing IQ, auditory attention, verbal and nonverbal memory, emotional memory, and facial discrimination. Across all patients, there were consistent significant correlations between multiple cognitive measures (IQ, auditory attention, all memory tasks) and anterior hippocampal volume, ranging from a magnitude of $r = .38$ to $r = .66$ for IQ. Cognitive measures, however, were not associated with posterior hippocampal or other brain region volume. To evaluate the specificity of the cognitive impairment, partial correlations were calculated controlling for IQ, and this led to a prominent attenuation of the relationship between attention and memory variables

and anterior hippocampal volume. Reduction in anterior hippocampal volume, but not other brain region volume, was associated with diminished generalized cognitive/intellectual functioning in a sample of schizophrenic patients that included individuals with water imbalance. Thus, in addition to the neuroendocrine dysfunction ascribed to the anterior hippocampus in schizophrenia, this region and its associated circuits may also play an important role in mediating cognition in schizophrenia. Supported by NIH:R01 MH56525 (MG)

MORPHOMETRIC GROUP ANALYSIS EXPLORATION OF SCHIZOPHRENIC VERSUS CONTROLS YIELDS SENSORY REGION ATROPHY

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Background: Numerous studies identify the frontal, temporal and parietal lobes as general regions that are consistently found to have diffuse decreased measures of thickness and/or volume in schizophrenic populations. These deficits may lead to characteristic issues with emotional processing, working memory, semantic/language function and sensory processing. **Purpose:** A whole brain analysis using FreeSurfer was implemented to contrast cortical thickness between schizophrenic and non-schizophrenic subjects, allowing for intragroup analysis across the entire brain. **Methods:** A T1-weighted MRI was performed on 25 age-matched schizophrenic (n= 13) and control (n= 12) subjects. Data was collected on a Marconi 1.5T scanner and processed using FreeSurfer tools. Once preprocessing was complete, the data were averaged to represent an average cortical surface. A group analysis fit a general linear model at each surface vertex. Cortical thickness was determined in controls vs. schizophrenics, with a significance level of $p < .05$. Clusters of 45 or more significant voxels were manually extracted. **Results:** The group analysis comparing controls vs. schizophrenics yielded 20 clusters with a significant decrease in cortical thickness in schizophrenics. Of these 20 clusters, 14 fall in the frontal, parietal and temporal lobes, with 6 regions falling in the occipital lobe. Twelve of the clusters were included in the superior insula, intraparietal sulci, superior temporal sulci and calcarine sulci. **Conclusion:** Our results yielded findings similar to many published studies on regions of interest with reduced cortical thickness in schizophrenia. Also noteworthy was the finding that the majority of the areas with decreased cortical thickness all play a role in processing sensory information. Some studies have suggested that abnormalities in the processing of sensory information may be specific to schizophrenia, thus helping differentiate it from other psychoses.

SINGLE-VOXEL QUANTITATIVE PROTON MR SPECTROSCOPY IN CORPUS CALLOSUM OF PATIENTS WITH SCHIZOPHRENIA: SUGGESTS CALLOSAL DISCONNECTION

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There is increasing evidence suggesting a cortico-cortical disconnection in the pathophysiology of schizophrenia. Previous genetic and structural magnetic resonance (MR) imaging studies suggested an axonal or myelin-related pathology in schizophrenia. Corpus callosum is the major inter-hemispheric commissure which plays important roles in cognitive processes that are impaired in patients with schizophrenia. The main aim of this study was to investigate the transcallosal disconnectivity theory about the pathophysiology of schizophrenia by using proton MR spectroscopy (1H-MRS). We hypothetized that axonal or myelin-related pathology in schizophrenia might cause changes in neurometabolite concentrations which could be detected by 1H-MRS. We studied 12 first-episode and 16 chronic patients, and 28 control subjects. We measured the absolute concentrations of major neurometabolites (N-acetylaspartate, choline and creatine) and T2 relation time of tissue water (T2B) in the genu of corpus callosum by 1H-MRS. The NAA concentration was significantly lower in the first-episode as well as in chronic patients, compared to the respective controls ($P<0.01$). The NAA concentrations in the first-episode and chronic groups were strongly correlated with the Brief Psychiatry Rating Scale (BPRS) and Scale of Assessment of Negative Symptoms (SANS) scores ($P<0.01$). There was a weak relationship between the NAA concentrations of all patients and Scale of Assessment of Positive Symptoms (SAPS) ($P=0.046$). The T2B values were significantly higher in the patients, compared to the controls ($P<0.01$). The correlation of reduced NAA concentration with the severity of psychopathology indicates callosal dysfunction in schizophrenia. Prolongation of T2B suggests a myelin-related pathology in the pathophysiology of schizophrenia.

HIPPOCAMPAL VOLUME CHANGE IN SCHIZOPHRENIA: A 5-YEAR LONGITUDINAL STUDY

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Schizophrenia patients show reductions in hippocampal volume relative to healthy subjects. How these changes progress over time is still unresolved. Furthermore, it is unknown to what extent these findings are confounded by effects of medication. We earlier presented brain volume data of 159 schizophrenia patients and 158 controls across the adult age range (Hulshoff Pol, 2002, Am J Psych). A total of 96 patients and 113 controls were scanned for a second time after an average interval of 5 years. Of a subsample hippocampal volumes were obtained; at baseline hippocampal volumes are available for 96 patients (age 33.30 SD 12.20) and 116 controls (age 38.16 SD 14.48), at follow-up volumes are obtained of 62 patients (age 29.57 SD 10.15) and 54 healthy subjects (31.91)). Both baseline and follow-up volumes, as well as volume change over time were compared between the groups, corrected for age, intracranial volume at baseline (IC-0) and sex. Using linear regression it was investigated whether the age dependency of volume change over time (controlled for IC-0 and sex) differed between the groups, i.e. the interaction between age and group was tested. Furthermore, in patients the relationship between hippocampal volume change over time (controlled for age, sex and IC-0) and cumulative medication intake was investigated with Spearman Rank correlations. Both at baseline ($p=0.002$) and at follow-up patients showed a significantly smaller hippocampus volume ($p=0.003$). Change over time did not differ significantly between the groups when corrected for age ($p=0.247$). Also, the group X age interaction was not significant ($p=0.08$). Cumulative intake of typical antipsychotics (haloperidol equivalents) was negatively related to hippocampal volume change ($rho=-0.415$; $p=0.015$), i.e., patients with higher doses during the scan-interval showed larger hip-

pocampal volume decrease. In contrast, there was a trend towards a positive relationship between cumulative intake of atypical antipsychotics (haloperidol equivalents, rho=0.32; p=0.06) and more specifically olanzapine (milligram, rho=0.37; p=0.06) and hippocampal volume. These preliminary findings suggest a different neurodevelopmental trajectory of hippocampal volume change in patients and healthy subjects. Interestingly, however, the type and dose of antipsychotic medication intake appear important confounders and a possible neuroprotective effect of atypical antipsychotics, in particular olanzapine is suggested.

BRAIN-DERIVED NEUROTROPHIC FACTOR POLYMORPHISMS AND FRONTAL CORTEX MORPHOLOGY IN SCHIZOPHRENIA

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In a previous investigation a polymorphism in the brain-derived neurotrophic factor (BDNF) gene was associated with frontal lobe gray matter volume variation in patients with schizophrenia. The aim of the present study was to extend the previous investigation by analyzing associations between three BDNF polymorphisms and regional frontal cortex morphology in patients with schizophrenia and healthy control subjects. BDNF genotyping was performed using PCR and pyrosequencing techniques in 96 patients with schizophrenia or schizoaffective disorder and 104 healthy control subjects. Cortical morphology was analyzed by processing MR brain images with the FreeSurfer software package. General linear model analysis was used to study associations between BDNF gene variants and cortical thickness in patients and controls, respectively. Regional frontal cortical volumes were defined from automatic cortical parcellations and divided by intracranial volume, as measured by use of the software BRAINS. Age was used as a covariate in the analysis and the threshold for significance was set at $p<0.01$ uncorrected. For patients with schizophrenia, the BDNF -633 T/A polymorphism was associated with thickness and volume of distinct subregions of the dorsolateral prefrontal cortex of both hemispheres. Data indicated trends towards association between the BDNF Val66Met and 11757 G/C polymorphisms and the volume of specific frontal lobe regions in patients with schizophrenia. Among controls, there were no significant associations between BDNF polymorphisms and cortical thickness. There were trends towards association between BDNF gene polymorphisms and volumes of some frontal lobe regions for control subjects, although these differences did not reach statistical significance. The findings indicate that polymorphisms in the BDNF gene may be associated with variation in frontal lobe structure. Such genetic differences may contribute to the interindividual variation in frontal cortex morphology as seen in patients with schizophrenia. The study was supported by the Swedish Research Council (2003-5845 and K2004-21X15078-01A), and the Wallenberg Foundation.

EARLY PSYCHOSIS INTERVENTION PROGRAM IN VANCOUVER: NEUROIMAGING DATA FOR A LIFE HISTORY BASED STUDY

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Background: Numerous studies have now established the presence of brain abnormalities in multiple brain regions in persons with psychotic disorders. Lack of specificity of these abnormalities may be related to methodological problems including non-standardized technology platforms (scanner type, imaging software) and clinical complexity of these disorders. The current study is an expansion of work presented by Smith et al (2006) to further elucidate the nature of brain abnormalities in the context of life-history and the emergence of psychosis. Subjects: 77 First Episode psychosis subjects (mean age 21.5yrs, 49 male, 23 female), 21 of whom were drug naïve at scan time and the remainder with less than 10 weeks of lifetime exposure to antypsychotics (n=31, 74% of patients on medication by scan time) and 37 controls (mean age 24.7, 16 male, 21 female). Methods: High-resolution 3D-SPGR images were obtained on a GES 1.5 T scanner as a series of 124 contiguous 1.5mm thick axial brain slices. Skull-edited MRI volumes were used and then processed in FSL to derive total intracranial volume (ICV), total gray (GM), total white matter (WM), cortical gray matter (cGM) and lateral ventricle volumes (LV). Results: No differences between patients and healthy controls were seen for any regions of interest. There was a significant main effect of age for all volumes of interest. Only LV volume showed a significant Group by Age interaction ($F=4.86$; $df=1,103$; $p=0.0297$). Conclusions: Segmentation data of that heterogeneous sample at baseline do not show any statistical significant difference between patients and controls. Future research should be conducted both on a longitudinal perspective and on life-history approach complex regression statistical analyses.

DIFFUSION TENSOR IMAGING OF LIMBIC NETWORKS IN CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA

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Introduction: One hypothesis that unifies the diversity of symptoms associated with schizophrenia involves the disruption of neural connectivity between brain regions. As myelinated neurons provide for rapid and efficient communication between brain regions, brain white matter serves as a possible suspect in the search for underlying etiologic factors in schizophrenia. Methods: Diffusion Tensor Images (DTI) were obtained in twelve directions on 14 children and adolescents with schizophrenia, 1 patient with schizoaffective disorder, and 15 age and gender matched controls. The DTI images were acquired in twelve directions on a 3 Tesla Siemen's TRIO scanner and transformed into fractional anisotropy (FA) and average diffusivity (AD) images. Two different analyses streams were applied to the images. The first involved a 12-parameter affine transformation applied to the FA images using SPM99 to render the images into a common stereotactic space. The images were subsequently smoothed with a 5 mm FWHM Gaussian filter prior to a cluster-wise group analysis. The second analysis approach used a region of interest approach to calculate the volume and FA measures within the fornix. Results: In the voxel-based approach, children and adolescent patients with schizophrenia demonstrated a significant decrease in FA and associated increase in AD in the left posterior hippocampus ($p<0.001$, Bonferroni corrected on the cluster-level). ROI analysis of the fornix demonstrated no change in either FA or AD, but a significant decrease in volume of the fornix ($p < 0.05$). Conclusions: These findings all implicate limbic pathology in individuals with an early onset schizophrenia. This symposium will present data on white matter pathways within the limbic system and describe how aberrant patterns that develop in schizophrenia can contribute to the symptomatology.

12. Neuroimaging, Functional

NEURAL MECHANISMS OF ANTICIPATION AND RECEIPT OF REWARD: AN FMRI COMPARISON STUDY IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR MANIC DISORDER

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Knowledge about the role of dopamine in psychiatric disorders including schizophrenia and the affective disorders like bipolar mania is rapidly increasing in recent times. Transmission of reward signals is one of the best characterized functions of the dopamine system in animal studies and the findings have been confirmed in investigations with human subjects. In our functional magnetic resonance imaging (fMRI) experiment we aimed to investigate how expectation and receipt of rewards modulate brain activation in schizophrenic compared to bipolar manic patients. We used a simple gambling game with monetary reward. We compared 12 patients (mean age 39 y) with a current episode of schizoaffective disorder or schizophrenia with 12 patients with a current manic episode (mean age 34 y) and 12 healthy subjects (mean age 37 y). All patients took neuroleptic i.e. dopamine antagonistic, medication. Images were taken on a 3T Siemens Trio Scanner (TR=1.5, TE=35 msec). Subjects were instructed to react with a certain button press to two different stimuli to have a 60% chance to win a previously announced amount of money ($1.25 or $0.40). In 40% of the trials subjects were not rewarded with the announced amount of money despite pressing the correct button. In the control trials no money was announced, subjects only had to press an arbitrary button and could not win any money. Rewards were displayed after each button press. Data were analysed event related using SPM2 (Wellcome Institute, London). Analyses of data from medicated schizophrenic patients and healthy controls revealed differential activation of dopaminergic brain areas upon expectation (ventral tegmentum) and receipt vs. omission (nucleus accumbens) of rewards. In manic patients we did not find similar brain activation and the nucleus accumbens activation upon receipt vs. omission of rewards was significantly lower in the manic patients than in the controls. Activations in schizophrenic patients were in between. Prediction error signals as transmitted by the dopamine system upon receipt or omission of reward have been implicated in learning, planning, decision making and goal-directed behavior. Our findings can help to understand deficits in these functions in patients with psychosis.

COEXISTENCE OF MR FUNCTIONAL ABNORMALITIES AND GRAY MATTER DENSITY REDUCTIONS IN PATIENTS WITH SCHIZOPHRENIA AND CHRONIC AUDITORY HALLUCINATIONS

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The purpose of this study was to explore possible associations between functional magnetic resonance imaging abnormalities under an emotional auditory paradigm and focal brain density reductions in patients with schizophrenia and chronic auditory hallucinations. The sample was comprised of 21 right-handed male chronically hallucinating patients (selected out of a sample of 160 patients with auditory hallucinations) and 10 healthy controls. All patients underwent an emotional auditory paradigm that was designed to replicate those emotions related to the patients' hallucinatory experiences (1). Functional EPI-T2* weighted and morphometric 3D GRE-T1 weighted MR images were analyzed using Statistical Parametric Mapping (SPM2) software. Obtained maps were overlaid in order to identify those common findings with both techniques. A coincidence map corrected for multiple comparisons was generated by voxel-by-voxel multiplying the emotional subtracted functional images (activation with emotional vs non-emotional words) with the gray matter concentration differences (obtained by optimized voxel-based morphometry technique). Large coinciding brain clusters were found in the left and right middle temporal and superior temporal gyri. Smaller coinciding clusters were found in the left posterior and right anterior cingular gyri, left inferior frontal gyrus and middle occipital gyrus (Table 1). In conclusion, several brain areas which are extensive in middle and superior temporal, and cingular gyri, show coexistent volume loss and activation on an emotional auditory paradigm. These data probably indicate a compensation phenomenon in which regions with decreased volume need a larger hemodynamic dysfunctional response to a defined paradigm and support the implication of these areas in the neural networks responsible for auditory hallucinations. 1. Sanjuan J, Lull JJ, Martí-Bonmatí L, et al. Emotional auditory paradigm in neuroimaging: a base for the study of psychosis. Actas Esp Psiquiatr 2005;33:383-389.

Coincidence Area	fMR t value	MR t value	Talairach coordinates	Brodman areas
Left temporal middle	4.81	4.98	(-54,-30,0)	21-22
Left temporal superior	4.26	4.92	(-57,-16,9)	48
Right temporal middle	4.47	4.30	(60,-15,-12)	21
Right temporal superior	3.96	4.07	(57,3,-11)	38
Left frontal inferior opercular	4.54	4.18	(-50,10,14)	44
Right anterior cingulate	3.96	4.35	(5,45,12)	33
Left posterior cingulate	4.62	4.01	(-3,-42,31)	23
Right occipital middle	3.91	4.04	(41,-70,10)	37

ALTERED CONNECTIVITY DURING VERBAL ENCODING IN INDIVIDUALS WITH AN AT RISK MENTAL STATE

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Impaired verbal episodic memory is considered a core deficit in schizophrenia. This impairment appears to be due to encoding and retrieval deficits and is associated with disrupted frontotemporal function. In particular, activation the left prefrontal (PFC) and medial temporal (MT) cortices appears to be altered. However, the extent to which such alterations are apparent in the prodromal phase of the illness is unclear. Participants with an At Risk Mental State (ARMS) were recruited from the OASIS service at the Maudsley Hospital, London and assessed using the Comprehensive Assessment of At Risk Mental States (CAARMS). 15 ARMS participants and 15 healthy controls took part in the study, matched for age, verbal IQ and

digit span. During a verbal encoding task participants were asked to read aloud 160 single words presented visually every 4 seconds. Functional MRI data was collected using a compressed acquisition sequence at 1.5T. Memory performance was assessed later during a retrieval task in which participants were required to indicate whether a visually presented word had been presented during the encoding task or not. There were no significant differences in the total number of correct recognition responses between the ARMS and control groups (t= .004 df= 29, p = .90). Activation associated with the encoding task relative to rest activated a network of the left dorso and ventrolateral PFC, anterior cingulate, left middle temporal, posterior parietal and MT regions. Activation in left DLPFC was attenuated in ARMS compared to controls (P cluster = .01). An effective connectivity analysis using dynamic causal modelling in SPM2 revealed that the ARMS group showed reduced coupling between the LDLPFC, LVLPFC and the LMT gyrus compared to controls during encoding. Despite unimpaired retrieval performance ARMS subjects demonstrate reduced PFC activation and fronto-temporal coupling during verbal encoding compared to health controls. Such alterations may represent early neurophysiological alterations associated with the prodromal phase of the illness that precede overt memory impairments.

CHALLENGING THE SOCIAL BRAIN IN SCHIZOPHRENIA: AN FMRI STUDY

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Background: Patients with schizophrenia often display poor social skills, frequently misinterpret social cues and numerous studies report specific abnormalities of social information processing in these patients. Sufficient social information processing capabilities are crucial for detection of threat in the social environment and play an important role in adequate social functioning. Consequently, impaired social cognition often causes social isolation of patients with schizophrenia, making it one of the most disabling clinical features of the disease. The aim of the present study was to explore differences between patients with schizophrenia and healthy controls with regard to neural activity during social information processing. Methods: In the present study we measured brain activity of 12 patients with schizophrenia using fMRI and compared their brain activation patterns with those of 21 healthy control subjects. During scanning, subjects were required to perform a social information-processing task that involved making trustworthiness judgments about faces that were presented during both implicit and explicit task conditions. During the explicit condition, subjects were instructed to judge whether faces were trustworthy or untrustworthy, while during the implicit condition, subjects were instructed to judge whether faces were older or younger than 30 years old. After scanning, subjects were asked to rate each face in terms of trustworthiness on a scale of 1 to 7. Functional images were realigned, normalized and smoothed. Subsequently, appropriate statistical contrasts were computed in SPM 2 using the general linear model. For analyzing neural activation we performed subsequent region of interest (ROI) based analyses using functionally defined ROIs. Results: Both patients and controls displayed task-related neural activation in a network that includes the amygdala, prefrontal cortex, insula, anterior cingulate cortex as well as visuomotor processing areas. However, patients displayed significantly less activation than healthy controls in the medial orbitofrontal cortex, the amygdala and the fusiform face area. We did not find significant effects of task condition. Conclusion: These data suggest that the impairments in social cognition that are often seen in patients with schizophrenia might be associated with an inability to activate the medial orbitofrontal cortex, the amygdala and fusiform face area.

FUNCTIONAL MRI CHANGES RELATE TO BDNF VAL66MET POLYMORPHISM IN THE EDINBURGH HIGH RISK STUDY

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Background: A single nucleotide polymorphism (val66met) in the Brain Derived Neurotrophic Factor (BDNF) gene has been shown to be a risk factor for schizophrenia in some populations. BDNF genotype has been shown to have a structural effect on schizophrenic brain morphology and neuropsychological variables. Functional Neuroimaging and cognitive changes have been well documented in schizophrenic brains. This study aims to correlate BDNF haplotypes with functional MRI in a population at high risk for schizophrenia as a putative mechanism for the schizophrenogenic effects of this gene. Methodology: The Edinburgh High Risk study has followed subjects at high genetic risk of schizophrenia (due to two or more affected relatives) from adolescence. Neuroimaging, neuropsychological and clinical data were gathered on several occasions prior to, during and after the onset of symptoms. Some 10% of these subjects went on to develop schizophrenia. 78 subjects (including affected and non affected subjects) from the Edinburgh High Risk Study were genotyped for BDNF val66met polymorphism. They underwent functional MRI scanning where prefrontal executive function was measured by the Hayling sentence completion task. Results: Increased activation was found in Midline cingulate gyrus (p=0.024), L fusiform gyrus (p=0.052), R medial frontal gyrus/anterior cingulated (p<0.001), R fusiform gyrus (p=0.017), L posterior cingulate gyrus (p=0.001) in val/val subjects compared with val/met and met/met subjects. Discussion: Hippocampal structure and function have been studied with regard to BNDF genotype but frontal lobe function, although implicated widely in schizophrenia, has not. These results suggest that the BDNF gene may mediate its schizophrenogenic effect though deficiencies in the activity of these brain areas.

IMAGING GENETICS AND RESPONSE TO ANTIPSYCHOTICS

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Dysfunction of the dorsolateral prefrontal cortex (DLPFC) during working memory and of the hippocampal formation (HIPPO) during declarative memory have been described in schizophrenia. Neuronal firing in these two brain areas is fundamentally modulated by dopamine. Moreover, dopamine signaling is modified by atypical antipsychotics. We have evaluated the potential effect of genes regulating dopamine signaling on neuronal activity measured with fMRI at 3T during performance of working memory (WM) and of declarative memory. These studies were performed in healthy subjects and in patients with schizophrenia undergoing treatment with olanzapine in monotheraypy. Consistent with earlier studies, we demonstrated robust effect of the Val158Met catechol-O-methyltransferase (COMT) polymorphism in DLPFC during WM in healthy subjects. Carriers of the Met158 allele had less activation of DLPFC despite similar behavioral performance, suggesting more

efficient engagement of this brain region. Similarly, patients with schizophrenia carrying the Met158 allele showed greater improvement of DLPFC efficiency after treatment with olanzapine. Furthermore, consistent with this differential improvement in DLPFC efficiency, we also demonstrated that patients homozygous for the Met158 allele treated with olanzapine have greater frequency and faster time of response in negative symptoms. We have also demonstrated in healthy subjects that the 10-repeat allele of the 3' VNTR polymorphism of the dopamine transporter (DAT) gene is synergistic with COMT and it is associated with more efficient DLPFC engagement during WM. As for activity during declarative memory, we have found that the Val158Met COMT polymorphism is associated with differential modulation of activity in HIPPO and in ventrolateral prefrontal cortex as well as of their coupling during declarative memory in healthy subjects. Taken together, these results suggest that genetic variation of dopamine signaling is crucial for modulation of brain areas sub-serving memory in healthy subjects and in patients with schizophrenia. Moreover, use of intermediate phenotypes may contribute to shed light on the genes involved in susceptibility to schizophrenia and in its pharmacological treatment.

EFFECT OF DELTA-9-TETRAHYDROCANNABINOL ON VERBAL EPISODIC MEMORY- A FUNCTIONAL MRI STUDY

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Cannabis is the world's most widely used illicit drug. Although its effects on verbal memory are well-known, few studies have investigated the neural basis of these effects in man. The aim of this study was to clarify how one of the main psychoactive ingredients of cannabis, delta-9-tetrahydrocannabinol (THC) acts on the brain to influence memory processing. 15 healthy males, who had less than 25 total exposures to cannabis in lifetime, were studied on 2 occasions at least 3 weeks apart, following oral administration of 10mg of delta-9-Tetrahydrocannabinol (THC) or placebo 1 hour prior to scanning, in a double-blind design. MR images were acquired on a 1.5T GE camera while subjects performed a Verbal paired associates task with separate encoding and retrieval conditions. Image acquisition was compressed during the task to permit processing of auditory-verbal stimuli in silence. Task responses were recorded on-line. We examined the main effect of drug, main effect of task and drug- task interactions. Administration of THC led to a 10-point mean increase in PANSS total score ($p<0.05$). There was no difference in accuracy of retrieval between the THC and placebo conditions. During the encoding condition, compared to placebo, THC attenuated activation in the left parahippocampal gyrus extending to left superior temporal gyrus, which persisted after covarying for anxiety, intoxication and PANSS positive symptom scores. During the retrieval condition, compared to placebo, THC attenuated activation in the right superior frontal gyrus extending to medial frontal gyrus, and increased activation in the right precentral and postcentral gyrus extending to right superior temporal gyrus, which persisted after covarying for anxiety, intoxication and PANSS positive symptoms. THC significantly modulated activation in brain areas involved in the encoding and retrieval of verbal material, independent of its symptomatic and behavioural effects. These observations are consistent with impaired verbal memory in long term cannabis users, and with the putative role of cannabis in the aetiology of psychosis

THE MIND CLINICAL IMAGING CONSORTIUM AS A CASE STUDY FOR NOVEL NEUROINFORMATICS TOOLS TO SUPPORT MULTI-INSTITUTIONAL HETEROGENEOUS PSYCHIATRIC RESEARCH STUDIES

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The MIND Clinical Imaging Consortium (MCIC) was founded in 2003 as a collaboration among four university research groups engaged in multi-site psychiatric research: The University of Minnesota, The University of New Mexico, The University of Iowa, and Harvard University. The psychiatric research domains utilized in the MCIC research protocol include: socio-demographic assessments, comprehensive neurological and psychiatric assessments, a neuropsychological battery, genetic sample, an anatomical neuroimaging session that collects morphological and diffusion-weighted sequences, and a functional neuroimaging session that collects calibration information and two cognitive tasks conditions. The design of the MCIC study includes two connected sub-studies: a cross-sectional component, and a longitudinal component. The cross-sectional component of the protocol evaluates chronically ill patients with schizophrenia and matched healthy normal volunteers (HNV)s. The longitudinal component of the MCIC evaluates first episode patients with schizophrenia compared to a matched group of HNVs. Neuroinformatics is a hybrid of neuroscience and computer science disciplines whose major goal is to efficiently manage, manipulate, and provide access to the vast amounts of data produced in neuroscience studies. A comprehensive set of requirements and neuroinformatics tools including a research database, web-based data-entry, tablet-pc application, and a collaboration portal have been developed and implemented to support the needs of the MCIC project. The solution to efficiently manage, manipulate, and provide access to vast amounts of data is to apply best practices learned from other disciplines that engage in multi-center projects, create a team of people representing all sites and facets of the research, understand and identify the requirements of tools needed, and collaborate with other members in the community that have similar problems. The neuroinformatics tools implemented and tested for conducting the MCIC project can serve as a generic solution of how to meet the demanding needs of large multi-center psychiatric research projects that integrate heterogeneous data sources. Acknowledgements: Kathleen Kelly, Lori Hallstrom, John Rasure, The MIND Clinical Imaging Consortium, Funding from DOE Grant No. DE-FG0-99ER62764

ACUTE Δ-9-TETRAHYDROCANNABINOL (THC) EFFECTS ON BRAIN ACTIVATION DURING RESPONSE INHIBITION

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Introduction: Cannabis use is associated with cognitive impairments, transient psychotic symptoms and more recently it has been suggested

that using the drug in early adolescence may be a risk factor for schizophrenia. We investigated the acute effects of THC, the main psychoactive in the cannabis plant, using functional imaging. The aim of the present study were to examine the effect of THC on brain activation during a response inhibition task. Method: Functional MRI was used to study healthy volunteers whilst they performed the Go/No-go task after intake of either a THC or CBD or placebo in a randomised, double-blind design. 15 healthy males were studied on 3 occasions, following oral administration of either 10mg of Δ-9-THC or 600mg CBD, or a placebo one hour prior to scanning. During each session, images were acquired on a 1.5T GE scanner while subjects performed the Go/No-Go response inhibition task. The basic task was a choice reaction time task, where arrows (of 500-ms duration each) pointing to either the left or right side appeared on the screen with a mean Inter-Stimulus Interval (ISI) of 1.8 s. Results: There was a significant drug effect for left/right errors with more errors in the THC condition, but no other significant behavioural effects. Plasmatic THC level peaked after 2 hours and outlasted the duration of the study, namely 3 hours. Activation during Nogo-trials relative to Go-trails engaged a network of the right inferior frontal gyrus, anterior cingulate and precuneus. During THC administration relative to placebo NoGo-trials were associated with increased activation in the right hippocampus and reduced activation in the right inferior frontal gyrus Covarying for sedation (VAMS-Mental), anxiety (STAI-S), and intoxication (ASI) did not account for these findings. However, the altered activation in the right inferior frontal gyrus during THC administration was accounted for by changes in positive symptomatology (as measured by the positive symptoms scale of the PANSS). Discussion: The present study sought to examine the neural effects of THC during a response inhibition task. THC modulates the activation of brain regions that mediate response inhibition in the absence of behavioural effects. The attenuated activation in the right IFG can be attributed to subjective psychotic symptoms.

FUNCTIONAL NEUROANATOMY ASSOCIATED WITH THE DEVELOPMENT OF WORKING MEMORY: IMPLICATIONS FOR A HIGH-RISK POPULATION

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Individuals with schizophrenia and their relatives demonstrate impaired working memory and brain abnormalities. However, few studies have examined neural correlates of working memory deficits in children at risk for schizophrenia. In order to study neural correlates of working memory in young clinical populations, one must understand the developmental trajectory of working memory abilities and associated brain activation in typically developing children. This study used an n-back task and functional magnetic resonance imaging to assess changes in working memory capacity and brain function during normal development. We administered "0-, 1-, and 2-back" versions of the "nback" task, a well-validated measure of working memory and executive control. Participants saw a sequence of letters and pushed one button (target) if a stimulus was the same as that seen a specified number of trials back and another button if the stimulus was not the same (non-target). Further, we used a state-item design that differentiated between sustained maintenance-related activity and transient activity that may reflect manipulation demands. Children (ages 9-12) performed worse than adults (ages 18-21) at the 2-back level which places the greatest demand on both storage and manipulation components of working memory. Additionally, adults showed greater frontal activity in the main effect of load for sustained activity and more parietal activity for the main effect of load for transient activity. Children showed more diffuse sustained-related activity relative to adults. Additional analyses will focus on the shifts between sustained and transient activity with development, and on load-neural activity changes with development, as distinguishing between sustained activity and item-related activity may provide a more sensitive picture of developmental changes in brain activity as a function of load. This study serves as pilot data for an upcoming study looking at abnormal brain development in children at risk for developing schizophrenia.

DIFFUSION TENSOR AND REGIONAL WHITE MATTER VOLUME IN SCHIZOPHRENIA

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We examined white matter correlates of schizophrenia in three cohorts. First, high-resolution anatomical and 1.5T diffusion tensor MR images were acquired in adult patients with schizophrenia (n=106) and normal adult comparison subjects (n=42). Second, we examined a subset of 37 schizophrenic adults and an additional 29 adolescents (15m, 14f, mean age=16.07, SD=2.00, range=13-21) experiencing their first psychotic episode and age and sex-matched normal adolescents (10m, 11f, mean age 16.3). Third we examined the same areas in an entirely new cohort of images obtained on 64 patients with schizophrenia and 55 normal volunteers with 3T imaging to replicate and extend earlier results. Images were aligned and warped to a standard brain and anisotropy in normal volunteers and patients compared with significance probability mapping. In all samples, patients showed reduced anisotropy widely, including frontal white matter, the corpus callosum and the frontal longitudinal fasiculus. Patients with early onset schizophrenia had more marked volumetric deficits than older patients and these were most marked in the gray matter of the left temporal lobe. White matter was most decreased in the medial frontal lobe, cingulate gyrus, and frontal pole and relatively increased in other frontal and temporal areas. Diffusion tensor analysis showed lower than normal cingulate anisotropy in adults with schizophrenia but higher values than normal in adolescents with schizophrenia. A similar pattern was seen in the anterior thalamic radiations. Patients with schizophrenia had tract paths that were significantly shorter in length from the center of internal capsule to prefrontal white matter. These tracts, the anterior thalamic radiations, are important in frontal-striatal-thalamic pathways. These results are consistent with findings of smaller size of the anterior limb of the internal capsule in patients with schizophrenia, diffusion tensor anisotropy decreases in frontal white matter in schizophrenia and hypothesized disruption of the frontal-striatal-thalamic pathway system.

ABNORMAL SOCIO-EMOTIONAL NEUROCIRCUITS IN SCHIZOPHRENIA

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Introduction: Social and emotional information processing is carried out in cortical midline structures, such as anterior medial frontal cortex (aMFC) and posterior cingulate cortex (PCC)/precuneous.

Although schizophrenia typically presents with significant disturbances in socio-emotional behavior, relatively few investigations have targeted these 'socioemotional' neurocircuits, in spite of data demonstrating abnormalities of the aMFC region during resting states and cognitive challenges. Recently, we reported a hyperactive fMRI BOLD signal in the aMFC of patients with persistent psychosis in response to mildly stressful visual stimuli. We also noted reduced aMFC activity while viewing non-stressful, salient visual stimuli. In the current study, we extended our investigation of aMFC activity with a set of emotional faces, testing the hypothesis that patients would have an exaggerated aMFC response to negative emotional faces. Method: Twenty-one stable, schizophrenic/schizoaffective patients (7 females; Age: 40.8±9.3) and 21 matched healthy controls (6 females; Age: 40±9.6) viewed emotionally salient faces: positive, negative (primarily fearful) and neutral. They indicated preference judgments about each face (like/dislike) or identified the gender (GI) with a button press. Pseudo-randomized blocks of each type were separated by passive baseline blocks. BOLD-sensitive fMRI scans were obtained using a reverse spiral sequence. Realigned and normalized images were analyzed in a standard, random effects model. Results: During scan acquisition, there were main effects of group (SZ > HC: p=0.002) and task (Preference > GI: p<0.001) for reaction time measures. Relative to baseline, the patients exhibited less aMFC and PCC/precuneus activity than the controls for both preference and GI. Relative to GI, preference engaged aMFC and posterior MFC in both groups. In response to negative facial stimuli during the preference task (-GI), the patients showed a greater signal in aMFC (BA 9/10: -3, 42, 25; Z=3.26), pMFC (ACC, BA24/32: -9, 27, 24; Z=4.59) and PCC/precuneus (BA 7/31: 6, -72, 45; Z=4.18). Discussion: The results demonstrate aberrant activation of socioemotional neurocircuits in schizophrenic/schizoaffective patients. Because aMFC and PCC/precuneus are thought to play key roles in the integration of salient social stimuli, these results reinforce the importance of these brain structures to psychotic processes.

A MULTI-SITE FMRI STUDY OF SCHIZOPHRENIA: EFFECTS OF ILLNESS TYPE AND DURATION ON BRAIN FUNCTION AND CONNECTIVITY

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While schizophrenia is known to be associated with alterations in brain function across a wide range of tasks, little is known regarding the relationship between these alterations and specific features of the disease. These features include the type of symptoms, severity of symptoms and the duration of illness, as well as other characteristics. It is also not well understood how these alterations in brain function compare across experimental paradigms. Additionally, the manner in which communication among brain regions is altered in schizophrenia is not well understood. This might include an overall reduction in information flow or a change in the pattern of information flow among specific brain regions. In the present study, data was collected from subjects using three different experimental tasks, including an auditory oddball task, a visual Sternberg task, and a sensorimotor control task. FMRI data was obtained at each of 4 sites, using 3 Tesla (Siemens Trios at UMN, U Iowa and MGH) and 1.5 Tesla systems (Siemens Sonata at UNM). Whole-brain, gradient-echo, echo planar imaging data (TR= 2 sec) was acquired. Data were analyzed from single subjects using AFNI, SPM and fMRISTAT, and level II group effects using SAS. Dynamic Bayesian Network (DBN) analysis was used to identify functional correlations among neuroanatomical regions of interest, and differences in these connections associated with schizophrenia. To date, fMRI data has been obtained from over 140 patients, 41 of these being first episode patients (FE), and 167 healthy normal volunteers (HNV). Comparisons between patients and HNV revealed widespread reductions in response amplitude across most brain regions. This general pattern was replicated across paradigms, with some differences. Response differences were also found to be sensitive to the duration of illness and to the type and severity of symptoms. DBN analysis showed significant changes in connections among brain regions between patients and HNV, with the largest changes found in connectivity of the thalamus and paralimbic brain areas. Multi-site collaborative studies provide larger sample sizes for more sensitive detection of differences in brain function and their relationship to disease symptoms, severity and duration. Responses found in FE and non-FE patients across tasks were consistent with widespread changes in brain networks, with progression of deficits over time.

FMRI IN FIRST-EPISODE SCHIZOPHRENIA AND HEAVY CANNABIS USERS

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Background: The changes in the patterns of cerebral activation associated with the overlapping cognitive features of heavy cannabis use and schizophrenia have not been systematically studied. We used the Tower of London Task (TOL) to assess functional brain activation in these two groups and in first-episode schizophrenia patients who were heavy cannabis users. Method: Event-related functional magnetic resonance imaging measured cerebral activation during the TOL task in 12 first-episode schizophrenia patients, 17 recently abstinent long-term cannabis users, 7 recently abstinent cannabis using schizophrenia patients and 17 healthy subjects. A two-stage random effects analysis was used to model the BOLD response to assess cortical activation as a function of increasing task difficulty and to assess for the main effect of each diagnosis. Results: We found prefrontal activation deficits in schizophrenia patients that overlapped with cannabis users. A statistical trend in the comorbid subjects for reduced BOLD activation in the left superior parietal lobule and prefrontal cortices was observed. The diagnosis of schizophrenia largely accounted for the prefrontal activation deficit, whilst a history of heavy cannabis use was associated with increased BOLD activation in the visual cortex. Conclusions: There were common deficits in activation of the dorsolateral prefrontal cortex to the most difficult tasks for schizophrenia and cannabis using participants. In both singly diagnosed groups, ancillary brain regions were recruited, possibly to subserve the demands of complex TOL tasks. The combination of cannabis use and schizophrenia may exert a synergistic effect on altering frontal lobe recruitment during high demand cognitive tasks.

DOES FRONTO-LIMBIC FUNCTIONAL CONNECTIVITY PREDICT CLINICAL OUTCOME IN SCHIZOPHRENIA?

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Background: It is increasingly recognized that deficits in social cognitive processes, such as emotion recognition, add uniquely to the pre-

diction of schizophrenia outcomes. Understanding emotion dysfunctions at an early stage of illness may help in developing early intervention strategies. In a series of studies we have observed impairments in negative emotion processing in individuals with schizophrenia, using behavioural, cognitive and brain function measures. A study of functional magnetic resonance imaging (fMRI) with connectivity analysis has shown a reversal of the normal frontal-amygdala connectivity in response to fearful facial expressions in patients with first episode schizophrenia (FES). This study aims to investigate whether disturbances in connectivity predict clinical outcome in FES. Method: fMRI data were acquired for 26 FES patients (18M, 8F; Mean=20.3±2.8) and 29 matched healthy controls (19M, 10F; Mean=20.3±4.6) during a pseudorandom sequence of fearful and neutral facial expression stimuli (500ms duration). Ninety T2*-weighted images were acquired using a 1.5T Siemens VISION Plus system: 15 axial, 6mm (10% gap) slices, TE 40ms, TR 3.38s, matrix 128x128. A random effects model was employed in SPM2 with the following ROIs: amygdala, brainstem, thalamus, sensory cortex and the medial prefrontal cortex (MPFC). Following group comparisons, we used psychophysiological interaction analysis to examine coupling of amygdala with other ROIs. We used the effect size of differences in coupling in regression analyses to predict patients' clinical profile assessed with the PANSS and WHOQOL-Brief. Results: Relative to controls, FES patients showed reduced amygdala responses to fear, and a differential pattern of coupling between amygdala-midbrain and amygdala-MPFC ($p<.001$). A greater impairment in amygdala-MPFC coupling in FES predicted a greater severity in suspiciousness and depression, which reflect a poorer quality of life. Conclusion: These results suggest that abnormal amygdala connectivity could provide an insight into the mechanisms of poor functional outcome in patients with FES. The findings will be extended using longitudinal testing of these patients.

MODULATION OF KETAMINE-INDUCED BLOOD-OXYGEN LEVEL DEPENDENT RESPONSES BY HALOPERIDOL AND CLOZAPINE

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We previously established localized changes in blood-oxygen level dependent (BOLD) contrast in the rat brain following psychomimetic doses of ketamine (KET) in regions relevant to schizophrenia using direct pharmacoMRI. To further investigate KET pMRI as a preclinical model, rats were pretreated with haloperidol (HAL) or clozapine (CLZ). Young adult male rats were anaesthetized with alpha-chloralose and placed in a small bore 7T horizontal superconducting magnet. BOLD sensitive T2*-weighted images were acquired using a gradient echo sequence (GE). A 2.5 cm surface coil was used for excitation and detection. Ten minutes before the start of functional imaging, either vehicle (VEH), CLZ (10 mg/kg) or HAL (0.1 mg/kg) was injected (i.p.). Eleven contiguous 1 mm thick axial slices were collected per volume. In total 72 volumes of 70 seconds were collected, with 18 volumes (20 minutes) baseline scans and 52 post-injection scans (63 minutes). KET (30 mg/kg s.c.) was injected at the start of volume 19. Data were preprocessed and analyzed using a general linear model in SPM2. For each individual subject, averaged baseline values were subtracted from post-injection time which was divided into six time bins of 9 volumes each. Statistical group comparisons were made for each time-bin using a block design. VEH+KET treatment resulted in activations in the prefrontal cortex and sensory motor cortex and deactivations in the hippocampus and geniculate nucleus. KET animals pretreated with HAL or CLZ showed no activations in the prefrontal cortex (PFC). HAL+KET treatment produced clusters of activation in the cortex and deactivations in the striatum and geniculate nucleus. HAL+VEH produced small clusters of activation in the frontal cortex and deactivation in the hippocampus. CLZ+KET treatment resulted in bilateral deactivations in the hippocampus and cingulate cortex and large clusters of activation in the auditory and sensory cortex. CLZ+VEH resulted in deactivations in the frontal association, prelimbic and motor cortex. This study demonstrates that pretreatment with a typical or atypical antipsychotic blocks KET induced BOLD changes in the PFC but CLZ enhanced KET changes in the hippocampus and sensory motor cortex. In conclusion, rat pMRI at 7T is sensitive method to detect drug-induced changes with high anatomical and temporal resolution and offers novel ways to evaluate potential antipsychotic drugs. This work was supported by a NARSAD YIA Stone Award (CdG).

PREFRONTAL CORTEX FUNCTION IN INDIVIDUALS AT HIGH-RISK FOR SCHIZOPHRENIA

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Cognitive dysfunction is a hallmark feature of schizophrenia. Probands show a variety of deficits in many domains of cognitive functioning, including intelligence, episodic memory, working memory, attention, executive function, spatial ability, and language function. In recent years, it has been proposed that deficits in at least some of these domains, such as working memory, attention, and inhibition, can be explained as a single deficit in context processing. Context processing has been conceptualized as a type of executive function that refers to the ability to represent and maintain information and use it effectively to guide behavior. Previous research suggests that context representation is processed and maintained in the dorsolateral prefrontal cortex (DLPFC). Studies have found that schizophrenia probands show deficits on context processing tasks and that this deficit is associated with abnormal functional activation of the DLPFC. Healthy, first-degree relatives of schizophrenia probands also show a deficit in context processing. However, it is unclear whether this genetic high-risk group displays functional abnormalities similar to those observed in probands. We used the AX-CPT, a variant of the Continuous Performance Task (CPT), to test whether non-psychotic siblings of schizophrenia patients show deficits in context processing. We also examined whether this high-risk group displays abnormal task related activation of the DLPFC. We found no significant differences on AX-CPT performance between proband siblings and controls. However, we found a significant increase in task-related activity in the DLPFC among proband siblings. Data support the notion that inefficient processing of context information is related to increased vulnerability for developing schizophrenia.

EARLY DETECTION AND LONGITUDINAL FOLLOW-UP OF SCHIZOPHRENIA USING MRI

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Early detection of individuals who are most likely to develop schizophrenia is important for prevention of the serious chronic consequences of this illness. Since structural brain changes that are likely

progressive are known to be present once an individual has been diagnosed, detecting subtle evidence of these changes early may be useful. We have been studying individuals at genetic high-risk for developing schizophrenia because they have biological first-degree relatives already diagnosed and are within the peak age range (12-30) for illness. These individuals are compared to their siblings with schizophrenia and to age- and sex-matched controls. Currently, pilot data are available on 15 high-risk, 15 schizophrenia, and 15 control subjects from a cohort of over 100 schizophrenia, genetic high-risk, and control subjects. 10 first-episode schizophrenics have been examined one year after the initial scan and the analyses are currently in progress to be reported at the symposium. MRI scans included diffusion tensor (DTI), structural and fMRI sequences, the latter during a language activation task. Volumetric measurements failed to distinguish the high-risk individuals from controls. Ventricular size and frontotemporal regional measurements in high-risk subjects were similar to controls, whereas ventricular enlargement was present in those with chronic schizophrenia as would be predicted. An Apparent Diffusion Coefficient calculated from the DTI sequences was increased in the individuals at high risk and in their siblings with schizophrenia in the left parahippocampal, right superior temporal, left superior frontal, and left middle frontal gyri, with the greatest increases in those with schizophrenia. Similarly, the DTI measurements of Fractional Anisotropy (white matter integrity) were reduced in frontotemporal regions in those at high risk and patients with schizophrenia. Functional differences were observed in both groups compared with controls, such that language was processed in a less efficient and less lateralized manner in both high-risk and schizophrenia individuals than in normal controls. DTI and fMRI may be useful future tools for early detection of schizophrenia. However, the paradigms and findings from these studies need longitudinal validation, currently under way, that would identify those individuals who eventually develop schizophrenia from the high-risk cohort and then determine whether the MRI findings were indeed elevated risk factors.

ABNORMAL PROSODY PROCESSING AND PRODUCTION IN SCHIZOTYPAL PERSONALITY DISORDER: A PILOT FMRI AND BEHAVIORAL STUDY

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Schizotypal personality disorder (SPD) is characterized by impoverished friendships and odd speech. One aspect of social reciprocity is prosody (changes in vocal inflection needed to convey meaning). The question of whether processing of prosody as measured by fMRI and prosodic speech production by SPD subjects differed from controls was the focus of this pilot study. FMRI experiment: Subjects (SPD=3, NC=5) heard 30 semantically neutral sentences read in a happy, sad, sarcastic, or neutral tone of voice. Contrast images for neutral and all emotions (happy, sad, and sarcastic), were created for the two diagnostic groups. The extent of activation on combined left and right were compared at threshold $p<0.001$, using a random-effects model. Prosodic production experiment: Subjects (SPD=4, NC=5) were recorded as they read neutral and emotional statements and responded to neutral (tell me about a recent trip to the store) and emotional (tell me who you most admire and why) probes. Blind raters trained on aspects of prosody, rated voice inflection and emotionality as well as how much they would like to hear more from the subjects, using a 7-point Likert scale. SPD subjects differed from controls in both the processing and the speech production of prosody. FMRI: One-sample t tests for controls revealed the expected right greater than left extent of activation in the region of the superior temporal sulcus (STS) for each contrast. SPD subjects did not show normal asymmetry, instead, had a left > right extent of activation for each contrast. In combined left and right STS, control subjects had a 7% greater extent of activation while processing emotional vs. neutral sentences, whereas SPD subjects had a 36% increase, mainly due to the sarcastic condition (41% increase). There was no difference in reaction time or correct responses, suggesting that both groups were able to perform the task. Prosodic production: SPD compared with control subjects spoke with less emotion (effect size=.41); less voice inflection (effect size=.72); and, as a result, raters had little desire to spend more time with them (effect size=.47). Taken together these preliminary data suggest that SPD subjects compared with controls may have deficits in processing and verbal production of prosody, key aspects of verbal communication. If these findings hold as the subject N enlarges, then this may point to an important avenue for social remediation research.

FUNCTIONAL DEFICIT IN MEDIAL PREFRONTAL CORTEX IN SCHIZOPHRENIC PATIENTS: A CAUSE OF IMPAIRED COMMUNICATION AND SOCIAL INTERACTION?

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Objective: Schizophrenia is characterized by language and communication disorders and impaired theory of mind (ToM), the ability to infer another's beliefs and intentions. The objective of this neuroimaging study was to investigate whether misunderstanding of someone's speech encompassing characters is a defect in the neural network of language comprehension or a deficit of activity in the neural network that underlies ToM. Methods: Functional magnetic resonance imaging (fMRI) was used to screen thirty-seven pairs of subjects; 37 schizophrenic patients (DSM-IV) were matched on 37 controls for handedness, age, sex, and level of education. fMRI was performed as subjects listened to a factual story involving complex social interaction. Signal variations were analyzed individually and by group comparisons. Results: Mean comprehension score was significantly lower in patients (mean $\pm$ SD=5.6 $\pm$ 3.3) than in controls (8.1 $\pm$ 2.5; t=-4.3, df=36, p=0.0001). Schizophrenic patients also presented significantly lower fMRI signal variations in the left medial superior frontal gyrus (MF1, x=-8 y=58, z=36, Zscore=4.27; $p<0.001$ uncorrected; extend=103 voxels) than did controls. Two of 37 controls and 19 of 37 patients demonstrated a negative signal variation in the left MF1. Intra-pair comparison (patient minus control) yielded a negative difference for 28 of 37 pairs, indicative of lower signal variation in patients compared to matched controls. Conclusion: A functional deficit was observed in a core region of the ToM network in most of the patients as they listened to a story involving characters and cheating. This functional defect could represent a neural basis for impaired social interaction and communication in schizophrenic patients.

LEFT AMYGDALAR HYPERACTIVATION DURING GENDER TASK IN SCHIZOPHRENIC PATIENTS: AN 18FDG-PET STUDY

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The role of amygdala during facial emotion recognition (FER) tasks among schizophrenic patients remains unclear as its clinical implications. While most of authors have reported hypoactivation (related to their failure in emotion experience), recently few reports of medial temporal lobe (namely amygdala and hippocampus) hyperactivation have been published. It has been interestingly suggested that patients exhibit a lack or slower adaptative habituation phenomena (a neural mechanism for avoiding repetitive irrelevant stimuli) maybe due to their misattribution of affective meaning to neutral or ambiguous information. We propose to study FER task with 18 [F] fluorodeoxyglucose (FDG) PET techniques. Pharmacokinetics of FDG differs from the other brain techniques; because it includes 30 minutes of uptake period. We have hypothesized that the most irrelevant stimuli should habituate faster and then be showed as hypoactive, in contrast to relevant stimuli with slower habituation. Thus, if the rate of habituation in amygdala and hippocampus is slower in contrast to healthy subjects, FDG radiotracer could detect differences in activation degree. We studied amygdalar response during FER tasks with 18FDG-PET technique in eight right-handed healthy volunteers and eight right-handed non acute schizophrenic patients, who underwent two scans on different days in a random order, with both 20 minutes of continuous emotional (ET) and control task (CT). SPM2 analysis presented in this work only includes the results of CT task, consisted in a gender discrimination task of men and women expressionless. SPM2 was used for a ROI (amygdala – hippocampus) contrast of Schizophrenic patients>Healthy subjects, showing high left amigdalar response in schizophrenic patients ([-20, -2, -16]; $t = 4.84$; $p < 0.001$) while no other ROI area exhibited statistically significant differential activation. In conclusion, schizophrenic patients exhibit amygdalar hyperactivation during a continuous gender task of men and women expressionless, which could be related to their symptoms of misattribution.

IMAGING STRUCTURAL AND FUNCTIONAL CONNECTIVTY IN SCHIZOPHRENIA

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Background: Despite the advances made with diffusion tensor imaging (DTI) in understanding altered connectivity patterns in schizophrenia, this imaging modality only provides an index of the anatomical integrity of white matter structures, which cannot be directly equated with their functional connectivity. It is an intriguing hypothesis that abnormalities in the structure of white matter tracts may be important to the observed reductions in activation of interconnected networks as demonstrated by functional magnetic resonance imaging (fMRI); however, the simultaneous study of DTI changes and functional brain activation in schizophrenia is lacking. Methods: 21 medicated schizophrenic subjects received DTI on a 3T Allegra MRI scanner (Siemens, Ehrlangen, Germany) and BOLD fMRI on the same machine with a gradient echo-planar sequence in the same slice locations as the DTI. The specific effects of working memory load on brain activation was assessed with the N-Back working memory test. Results: Functional activation of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) were positively correlated with white matter integrity (as indexed by fractional anisotropy measures) of both left and right anterior cingulum bundle (CB). Moreover, these correlations were weaker on the left compared with the right for ACC ($r=.49$ vs $r=.86$, all $p<.05$). Although overall correlations with DLPFC were similar for left and right CB ($r=.66$ vs $r=.76$, all $p<.05$), the area of cortex which correlated was substantially smaller on the left. Discussion: These findings show that the magnitude of event related activation of the ACC and DLPFC are related to the integrity of the CB in patients with schizophrenia. We are currently analyzing this data to determine if the magnitude of synchrony between DLPFC and ACC during working memory performance are related to DTI measures of the integrity of CB. These results will be presented as well.

INCREASED BILATERAL FRONTAL ACTIVATION DURING VERBAL WORKING MEMORY IN SCHIZOPHRENIA: A NEAR INFRARED SPECTROSCOPY (NIRS) STUDY

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Introduction: Working memory (WM) is an active short-term memory system for maintaining and manipulating information. There is overwhelming evidence suggesting WM deficits in schizophrenia patients (SZ) are associated with abnormal activation patterns in the PFC. The present study examined PFC function with NIRS in SZ during verbal WM (VWM). NIRS is a non-invasive imaging technique that detects concentrations of oxy- and deoxy-hemoglobin in the cortex and is an excellent alternative method for studying cortical functions in psychiatric populations unable to tolerate fMRI. NIRS provides good temporal and acceptable spatial resolution. Encoding and maintenance of verbal material has been associated with greater activation in left vs. right PFC in non-psychiatric individuals. We expected reduced activation in the left PFC in SZ during VWM. Method: Oxy-Hb concentration in the bilateral PFC was examined during a delayed match-to-sample VWM task in SZ and healthy controls (CO). Oxy-Hb concentration during the delay period was obtained and we compared PFC activation in SZ and CO when performance was matched. Results: PFC activation patterns differed between the two groups despite comparable accuracy in SZ and CO. A comparison of oxy-Hb concentration between groups during correct trials showed greater bilateral activation in dorsal PFC in SZ compared to CO. Oxy-Hb concentration during correct trials versus incorrect trials showed increased activation in the left PFC and reduced activation in the right PFC for CO and bilaterally reduced activation in SZ. Discussion: Although performance was comparable between the two groups, neural activation patterns differed, suggesting that the two groups may recruit different neural systems during WM maintenance. Contrary to the expectation that SZ would show reduced activation during VWM, they showed greater activation compared to CO. The activation pattern observed when controlling for task performance suggests that SZ may recruit several neural areas while CO are able to perform the task efficiently.

REPRODUCIBILITY OF THE HAYLING SENTENCE COMPLETION TASK IN THE EDINBURGH HIGH RISK STUDY

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The Edinburgh High Risk study examines young people who are at enhanced risk of schizophrenia for genetic reasons. As part of the study fMRI was performed on two occasions using the Hayling Sentence Completion Task (SCT). The reproducibility of the sentence completion versus rest contrast is examined here separately in healthy controls with no psychotic symptoms (16), participants in high risk of schizophrenia with no psychotic symptoms (32) and participants in high risk of schizophrenia with psychotic symptoms (31). In order to examine cortical areas previously found to be robustly activated in the task [1], masks were created covering the left inferior frontal gyrus and insula, the left precentral gyrus, the left supplementary motor area and the middle temporal gyrus. The data was analysed using SPM2. To assess the reproducibility of first-level contrast images, voxel-wise Intraclass Correlation Coefficients (ICCs) were employed. In order to identify voxels activated in both visits a null conjunction was performed at the group level and the resulting maps were masked using the selected regions of interest. Mean ICCs are comparable between the three groups, with the middle temporal gyrus showing the highest reproducibility (Table 1). The Hayling SCT is a cognitive task involving high level processing and these values indicate that it has medium/high reproducibility in the areas examined across all groups. This demonstrates a useful methodology which can be informative in longitudinal and mulitcentre studies.
[1]Whalley et al. (2004), Brain 127:478-490. This work was funded by an MRC programme grant.

Table 1. Mean ICC for Sentence Completion vs. Rest

Area	Controls	High risk with no symptoms	High risk with symptoms
All significant voxels	0.38 (SD 0.28)	0.38 (SD 0.22)	0.36 (SD 0.23)
Inferior frontal gyrus	0.40 (SD 0.23)	0.44 (SD 0.16)	0.48 (SD 0.15)
Precentral gyrus	0.59 (SD 0.13)	0.52 (SD 0.18)	0.51 (SD 0.17)
Supplementary motor area	0.54 (SD 0.19)	0.46 (SD 0.13)	0.45 (SD 0.18)
Middle temporal gyrus	0.62 (SD 0.14)	0.60 (SD 0.15)	0.54 (SD 0.16)

FMRI OF AFFECTIVE RESPONSIVITY IN MARIJUANA SMOKERS: IMPLICATIONS FOR SCHIZOPHRENIA

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Schizophrenic patients are often comorbid for marijuana (MJ) use, and changes in the endogenous cannabinoid system, including increased CB1 receptor binding within the anterior cingulate cortex (ACC), have been demonstrated in these patients. The ACC has been shown to play a key role in affective regulation and the inhibition of impulsive behavior, and changes in this region have been suggested in the pathology of schizophrenia, specifically in relation to negative symptoms. Chronic MJ smoking has been associated with reduced attention, motivation, and affective and perceptual perturbations, similar to characteristic negative symptoms of schizophrenia. Given the alterations in mood and perception demonstrated by individuals who smoke MJ, we hypothesized altered cingulate response in MJ smokers relative to control subjects while viewing masked faces. Thirteen chronic heavy MJ smokers who smoked at least 3,000 joints in their lifetime and 13 control subjects who had not smoked more than five times completed the study. fMRI stimuli consisted of black and white photographs of males and females posing in several states (happy, angry,). Each trial consisted of an emotional target face presented for 30 ms, followed immediately by a neutral masking face of the same poser for 170 ms. Subjects indicated the sex of each face, and were unaware of the backward masked nature of the paradigm. While viewing masked angry faces, controls produced significantly more activity of the ACC (MNI coordinates -2, 20, 30) than MJ smokers, who produced greater activity than controls in a posterior cingulate gyral region (MNI coordinates 2, -36, 42). Viewing masked happy faces produced greater activity in normal control subjects relative to MJ smokers within the ACC (MNI coordinates 10, 14, 32) while MJ smokers had greater activity in a more posterior region (MNI coordinates -14, -38, 42). These findings indicate that MJ smokers demonstrate altered activation of the ACC, an area noted to play a key role in affective regulation, which has also been implicated in the pathophysiology of schizophrenia. These data are consistent with recent autoradiographic studies which have reported high CB1 receptor density in this region. Changes within the ACC of MJ smokers which are related to the endogenous cannabinoid system may be associated with the pathophysiology of schizophrenia, especially with regard to negative symptoms.

FACIAL AFFECT PROCESSING IN SCHIZOPHRENIA: RELATION TO SOCIAL COGNITION

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Efforts to understand social cognition in schizophrenia have benefited from studying facial affect processing. We have developed and validated a standardized digital database of faces expressing happy, sad, anger, fear, disgust and neutral affect. Patients with schizophrenia showed deficits in emotion identification, which was most pronounced for identifying fear where their relatives also showed slow performance. Using fMRI, we examined neural activation facial affect processing, and found specific abnormalities of activation related to whether the emotion is predominantly social - happy and sad - or threat-related – anger and fear. As in earlier studies, healthy participants showed overall greater activation for the emotion identification task compared to patients. However, the design permitted evaluation of event-related changes, separating correct from incorrect responses. The event-related analysis revealed that patients had similar activation to controls for happy faces, but underactivated for incorrect responses compared to controls for sad faces, especially in superior temporal, superior parietal and postcentral regions. For anger and fear, by contrast, unlike controls who had greater amygdala activation for correct than for incorrect responses, in patients incorrect responding was associated with greater amygdala activation. The abnormalities in activation also showed a different pattern of associations with symptom severity. Abnormalities in activation for sad faces were associated with asociality and some positive symptoms, while abnormal amygdala activation to fearful faces was strongly associated with severity of flat affect. These results suggest that social cognition deficits may have a separable neural substrate, which involves posterior cortical regions, while deficits in threat-related aspects of emotion processing relate to limbic dysfunction. The results also underscore the need for developing objective measures of emotion processing, and initial efforts will be presented apply digital photography and deformation based mor-

phometric analysis of facial expressions. Early detection and intervention may be an essential tool to ameliorate symptoms related to social cognition and hopefully their adverse effects on social adjustment and outcome.

NEURAL CORRELATES OF FLAT AFFECT IN SCHIZOPHRENIA

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Flat affect has been recognized as a major negative symptom of schizophrenia that portends poor outcome. Advances in neuroscience enable examination of neural processes associated with affective dysfunction in schizophrenia. We evaluated flat affect in a series of studies integrating clinical, neurocognitive and emotion processing measures. We found that patients with flat affect show greater clinical impairment, worse functioning and outcome, and deficits in verbal memory and in emotion identification. To further investigate neural substrates of emotion processing in schizophrenia, we conducted a series of event-related fMRI studies using happy, sad, angry, fearful and neutral faces. We found that patients had reduced amygdala activation for the "top-down" requirement of emotion identification tasks. However, and event-related analysis revealed that amygdala activation can predict the degree of flat affect in patients. Specifically amygdala activation in both patients and controls predicted the likelihood of correct identifications, but for threat-related emotions the effect was opposite for the two groups. For the emotions of anger and fear, greater amygdala activation in controls was associated with correct identification, while in patients greater amygdala activation portended incorrect responses. This effect was highly correlated with severity of flat affect. Notably, in family studies we found that family members of patients with schizophrenia were specifically impaired in recognizing fearful expressions. The results support the importance of emotion processing deficits in relation to flat affect in schizophrenia and suggest amygdala dysfunction as a core neural system.

NEURAL CORRELATES OF EMOTION PROCESSING IN SCHIZOPHRENIA

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There has been increased interest in the study of brain systems regulating emotion processing, and the role of amygdala and other limbic structures has been greatly elucidated in functional imaging studies. The main finding has been of increased amygdala activation for fearful or threatening stimuli, with more mixed results on other emotions. Patients with schizophrenia show impairment in emotion identification tasks and reduced amygdala activation while performing such tasks. However, there is limited knowledge on how schizophrenia affects the brain's response to the appearance of emotional faces and how this relates to performance. We conducted a series of event-related fMRI studies using happy, sad, angry, fearful and neutral faces. We found that patients had reduced amygdala activation for emotion identification tasks. However, its activation in patients and controls showed opposite associations with performance depending on the specific emotion. For threat related emotions of anger and fear, greater amygdala activation in controls was associated with correct identification, while in patients greater amygdala activation portended incorrect responses. This paradoxical effect was highly correlated with severity of flat affect. These results suggest that affective blunting in schizophrenia relates to overactivation of the amygdala in response to threatening stimuli.

EMOTION AND COGNITION: DYSFUNCTIONAL INTEGRATION IN SCHIZOPHRENIA

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Emotion and cognition are mostly investigated as different entities, while practically both functions are inseparable and are interacting with each other continuously. Schizophrenia patients demonstrate numerous deficits in each domain and neuropsychological as well as neuroimaging studies characterized the various dysfunctions. However, interactions between emotion and cognition have not been investigated in greater detail in patients. Similarly, in healthy persons there are only a few and rather contradictory studies exploring the effects of emotion on cognitive function. We developed and validated tasks investigating the interplay between emotion on cognition, applying mood induction techniques but also using emotional material to investigate the interaction between emotional and self-referent verbal material on memory. Our neuropsychological as well as neuroimaging data reveal a complex dysfunctional interaction in patients, where especially frontal and cingular regions show aberrant activation patterns. Hence, regions of major importance in emotion regulation and integration are affected. Further longitudinal fMRI studies evaluate the possibility to reduce cognitive and emotional impairments with specific psychological as well as pharmacological therapies. A normalized activation pattern in patients can be observed which points to the benefit of neuroimaging procedures for clinical as well as basic research.

ASSESSMENT OF LATERALIZED HIPPOCAMPAL FUNCTION IN SCHIZOPHRENIA

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The hippocampus has long been known to be important for memory, with the right hippocampus particularly implicated in visuospatial memory and the left in verbal/narrative or episodic memory. Despite this hypothesized lateralized functional difference, there has not been a single task that has been shown to be able to dissociate the activity of the right and the left hippocampus using neuroimaging. This ability to dissociate the two hippocampi would be an invaluable tool for assessing lateralized hippocampal function in a variety of clinical populations, such as schizophrenia. The transverse patterning (TP) task is a strong candidate for this purpose, as it has been shown in human and nonhuman animal studies to theoretically and empirically depend on the hippocampus. In TP, subjects choose between stimuli presented in pairs, with the correct choice being a function of the specific pairing: A+B-, B+C-, C+A-, where the subject is to choose the stimulus marked "+". In this project, the TP task was used to assess right and left hippocampal function in humans by varying its dependence on verbal material, with the goal of dissociating the two hippocampi. Nine control subjects performed the verbal (pronounceable nonsense

words) and nonverbal (abstract pictures) versions of TP while collecting magnetoencephalographic (MEG) data to verify and validate the tasks' lateralized dependence on the hippocampus. Data were also recorded from nine schizophrenia patients to determine whether they exhibited a lateralized hippocampal deficit. The MEG data were collected at the Mental Illness and Neuroscience Discovery Institute using a 275-channel CTF/VSM system. The analysis was conducted using the standardized Low-Resolution Brain Electromagnetic Tomography (sLORETA) method in Curry software. Initial results show that 8 of 9 controls activated the right hippocampus during the nonverbal version of TP, and 8 of 9 controls activated the left hippocampus during the verbal version of TP. Importantly, patients showed less lateralized hippocampal activation, and their mean level of behavioral performance was poorer than controls' on both versions of TP. In contrast, patients had no decrement in performance on a verbal and nonverbal version of the non-hippocampal-dependent elemental task. These preliminary data demonstrate the capacity to discriminate right and left hippocampal function and suggest a bilateral hippocampal deficit in schizophrenia.

FUNCTIONAL AND STRUCTURAL NEURAL CORRELATES OF TRAIT ANHEDONIA IN HEALTHY SUBJECTS

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Objective: Anhedonia, the inability to gain pleasure from pleasurable experiences, is a key symptom of major depression and schizophrenia. This symptom is likely the result of a basic neuropsychophysiological dysfunction and a vulnerability marker that precedes and contributes to the liability of developing psychiatric disorders. The characterization of its structural and functional neuroimaging correlates in non-clinical subjects may provide new insights for the early detection of such psychiatric diseases. Method: Trait anhedonia was measured in twenty-nine individuals using the Chapman Revised Physical Anhedonia Scale. The authors used a combination of fMRI, semi-automated and automated structural MRI segmentation techniques to explore the functional and structural correlates of trait anhedonia. Results: Anhedonia level was inversely related to anterior caudate volume but positively related to ventromedial prefrontal cortex activity during the processing of positive information. Conclusions: This neural picture likely defines a specific kind of vulnerability for developing psychiatric affective disorders and suggests that anhedonia is linked to a prefrontal compensatory mechanism that counteracts attenuated responses to hedonic saliency.

COGNITIVE REMEDIATION AND CHANGES IN PREFRONTAL CORTICAL FUNCTION IN SCHIZOPHRENIA: BEHAVIORAL VS FUNCTIONAL SENSITIVITY TO CHANGE

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Patients with schizophrenia tend to suffer from a range of impairments in cognitive functions, including executive functions such as attention and memory. Recent evidence suggests that patients with schizophrenia exhibit improvement on a range of cognitive tasks following cognitive remediation training. This study sought to examine the effects of cognitive remediation training on behavioral performance extent the analysis to include possible changes in correlated functional brain activity in schizophrenia. Patients with schizophrenia and matched controls participated in two fMRI testing sessions six weeks apart. The patients were randomized into two groups: one received 20-25 hours of cognitive remediation (CR) and one received an equal amount of group skills training (ST) during the interim period. The CR training focused primarily on tasks using attention and memory while the ST training focused primarily on communication and relapse prevention skills. Patients were tested on two n-back working memory tasks (a word n-back and an animal n-back) while fMRI images were obtained. The word n-back was also practiced by the CR group during training sessions and the animal n-back was not practiced by either group. In addition, subjects were tested on a lexical decision task. Behavioral results indicated that patients in the CR group showed significant improvement in d-prime of 1.25 on the word working memory task and .94 on the animal working memory task, both of which are a significant improvement ($p<.01$). Patients in the ST group and controls did not show any significant changes in d-prime. Voxels that showed increased activity with load in control subjects were isolated in bilateral dorsolateral prefrontal cortex (DLPC, BA 9) and anterior cingulate cortex (BA 32/24) and were used as functional regions of interest. A repeated measures ANOVA was then performed in these regions to examine change in activation from session one to session two. While there were trends suggesting decreased ACC activation and increased DLPFC activation in the CR groups, these changes were not significant. These findings suggest that behavioral changes in working memory in patients with schizophrenia are more sensitive the functional changes. The evidence for functional plasticity will also be discussed.

DO WOMEN AND MEN PROCESS EMOTIONAL STIMULI DIFFERENTLY?

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Men and women appear to differ in the manner in which they perceive, process, express and experience emotion. On the whole, females tend to be more emotionally expressive than males and the two sexes show differences in their responsiveness to affectively charged stimuli. Females tend to rate their emotions more intensely, show stronger evoked potential responses to emotional faces and demonstrate greater ease at decoding nonverbal messages than males. While many of the differences between men and women in processing emotions may be attributable to social factors and learned patterns of behavior, it is likely that emotional differences also reflect genotypic differences in the sexual dimorphism of the nervous system. We conducted a series of event-related fMRI studies using positive and negative visual stimuli taken from the IAPS as well as positively and negatively valenced words. During stimulation with pictures, regional group differences were only significant when subtracting the activation values of women from those of men. Females had relatively greater activation in the right posterior cingulate, the left putamen and the left cerebellum during positive mood induction, and in bilateral superior temporal gyri and cerebellar vermis during negative mood induction. In contrast, a direct comparison of brain activation during stimulation with words revealed differential activation in the right putamen, the right superior temporal gyrus, and the

left supramarginal gyrus during positive mood induction for women versus men. Furthermore, during negative mood induction, relatively greater activation was seen in the left perirhinal cortex/hippocampus for women versus men, and in the right supramarginal gyrus for men versus women. These findings suggest gender-related neural responses to emotional stimuli and could contribute to the understanding of mechanisms underlying gender-related vulnerability of the prevalence and severity of neuropsychiatric disorders.

PRE-SYNAPTIC STRIATAL DOPAMINE SYNTHESIS CAPACITY IN SUBJECTS AT RISK OF PSYCHOSIS

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Introduction: We compared pre-synaptic striatal dopaminergic function in patients with 'at risk mental states' (ARMS), who are at ultra high risk of psychosis, patients with psychotic illnesses and healthy controls. Method: The following age-matched groups have received an [18F]-DOPA PET scan: 1) individuals with ARMS (n= 19); 2) healthy controls (n=12); and 3) patients with psychotic illnesses (n=7). All subjects were antipsychotic naïve or medication free prior to the scan. [18F]-DOPA influx constants (Ki) were calculated from region-of-interest (ROI) derived time-activity curves using Patlak analysis with a cerebellar reference region following frame-by-frame movement correction. The ROIs were the whole striatum, and limbic (LS), associative (AST) and sensorimotor (SMST) subdivisions, reflecting striatal functional connectivity. Results: Mean (SD) Ki values (min-1) in striatal ROIs are presented in table 1. Independent t-tests were used to compare Ki values between groups at each ROI. There was a significant difference between controls and psychotic patients in the AST (t=3.4, df=17, p=0.004) and whole striatum (t=2.5, df=17, p=0.023), and between controls and at risk subjects (ARMS) in the AST (t=2.4, df=28, p=0.016) and whole striatum (t=2.4, df=28, p=0.014). Discussion: These preliminary findings indicate that striatal dopamine synthesis capacity is elevated people at risk of psychosis compared to age-matched controls. Further subjects are being recruited and existing subjects followed-up to determine if at risk subjects who subsequently develop psychosis have raised dopamine synthesis capacity compared to those who do not convert.

Table 1: Dopamine synthesis capacity in the striatum

	AST	SMST	LS	Whole striatum
Controls	0.0137 (0.0012)	0.0154 (0.0018)	0.01396 (0.0027)	0.0142 (0.0012)
At risk (ARMS)	0.0148 (0.0016)	0.0167 (0.0017)	0.0154 (0.0013)	0.0154 (0.0012)
Psychoticpatients	0.0156 (0.0018)	0.0165 (0.0020)	0.0144 (0.0018)	0.0157 (0.0013)

A FUNCTIONAL MRI STUDY OF THE NEUROCOGNITIVE EFFECTS OF QUETIAPINE COMPARED TO HALOPERIDOL IN SCHIZOPHRENIA

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Conventional treatment paradigms for schizophrenia have typically focused on reducing positive symptomatology; however, it is increasingly apparent that negative and cognitive symptoms are also important treatment targets. While traditional antipsychotics have little or even a detrimental effect on neurocognitive impairment in patients with schizophrenia, available data suggest that cognitive function may be improved during treatment with atypical antipsychotics. This double blind study compares the cognitive effects of haloperidol, as measured by a battery of neuropsychological tests, and correlated regional cerebral blood flow changes, as reflected by functional MRI (fMRI), with the cognitive effects of quetiapine, a second generation neuroleptic. Methods: The patients (N=14) were randomly assigned to one of three study groups: haloperidol (5-10mg; N=4), low dose quetiapine (600-800mg; N=5) and high dose quetiapine (1000-1200mg; N=5). The study had three segments: an initial three-day inpatient washout period followed by a two-week inpatient segment during which study medications were titrated up to a therapeutic dose followed by a six-month outpatient follow up. Efficacy measures, neurocognitive assessments and fMRIs using a cognitive task (N-back) specifically targeting the prefrontal cortex were obtained at the end of the washout period, at the end of the inpatient segment and at the end of the study. Neurocognitive assessment battery was designed to provide an assessment of new learning and memory, working memory, and several aspects of attention/executive function. The Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions (CGI) scale were used to rate the symptoms of schizophrenia. Results: Attention scores worsened slightly while memory scores improved at week 2 in all treatment groups. PANSS total scores were significantly reduced at week 6 in all treatment groups but greater reductions in PANSS scores were observed with low dose quetiapine (31.5) and high dose quetiapine (22.5) compared to haloperidol (-15.75). Additional data (including fMRI data with N-back) will be reported at the time of the presentation. Conclusion: Preliminary data suggest that both quetiapine and haloperidol reduce severity of symptoms and may improve memory in schizophrenia. Additional data is needed to compare the cognitive effects of quetiapine and haloperidol.

THE FUNCTIONAL MRI STUDY UNDERLYING DECREASED FOOD CRAVING IN SCHIZOPHRENIC PATIENTS TAKING SECOND GENERATION ANTIPSYCHOTICS

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Objectives: To explore the neural correlates of food craving in schizophrenic patients taking second-generation antipsychotics Methods: A T2*-weighted echoplanar imaging sequence was used to collect 120 BOLD images while a food paradigm was displayed. After a meal, ten healthy volunteers and ten schizophrenic patients taking second-generation antipsychotics viewed a paradigm consisting of three blocks of food images and three blocks of images of various natural objects. The imaging data was analyzed to find differences between healthy volunteers and schizophrenic patients in the food cue and craving related network. The relationship between food-related neural activity and clinical variables was explored. Activation maps were acquired with the random effect model using SPM2. Results: In schizophrenic patients taking second-generation antipsychotics, less extensive food cue and craving related regions were activated after a meal compared to healthy volunteers. Neural activity in both the hypothalamus and thalamus were correlated with the duration of prescribed antipsychotic use. Conclusions: This study demonstrated that after a meal, schizophrenic patients are less responsive to food cues than healthy volunteers, even if they are

taking second-generation antipsychotics. Lower activation of food cue and craving related neural circuits might be due to the decrease in hypothalamic activity related to the duration of prescribed antipsychotic use.

DISSOCIATING THE NEURAL BASIS OF SUSPICIOUSNESS FROM RATIONAL MISTRUST AND RISK AVERSION: AN FMRI STUDY OF THE MINNESOTA TRUST GAME

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Although persecutory ideation is a common manifestation of psychosis in schizophrenia, our understanding of its neural basis is just beginning. In order to understand the neural basis of persecutory beliefs we sought to deconfound feelings of suspiciousness, a subclinical manifestation of persecutory ideation, from general anxiety and the rational mistrust of others. General anxiety or risk aversion was accounted for by including a condition in which payment outcome was determined by a coin flip, and rational mistrust was accounted for by including a condition with an incentive for a human partner to betray the participant. In 2 samples we have demonstrated that this task, known as the Minnesota Trust Game, is capable of 1) evoking suspiciousness of a partner in an experimental setting, and 2) distinguishing decisions based on suspiciousness from those based on general anxiety and rational mistrust of their partner. These findings support the idea that there is an affective component to persecutory thinking. Next we sought to understand the neural basis of the interaction of cognition and affect during the Trust Game. Preliminary functional imaging analyses of 12 control participants indicate that the right insular cortex is activated when participants decided to avoid a risky situation in which chance would determine the outcome. However, robust and bilateral insular activity was also found when the decision-agent was human as opposed to chance. These results are consistent with the idea that the insula creates an internal representation of expected punishment, regardless of whether the outcome is determined by a non-human or human agent. However, they also show that the insula is more engaged when the potential punishment is accompanied by strong negative emotions, such as when the decision-agent is another human.

ABERRANT CEREBRAL MAGNETIC FIELDS AND HEMODYNAMIC SIGNALS IN SCHIZOPHRENIA DURING CONTROLLED PROCESSING IN SPATIAL WORKING MEMORY

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Spatial working memory dysfunction has been considered a candidate endophenotype of schizophrenia. Some imaging studies have reported that working memory deficits in schizophrenia are associated with abnormal activation of prefrontal cortex (PFC). In addition, primate cell recordings provide evidence that PFC mediates spatial working memory by modulating visual input to posterior parietal cortex (PPC) through reciprocal projections. To reveal the nature of abnormal neural processes associated with spatial working memory deficits in schizophrenia we developed a visual object construction (VOC) task to characterize dynamics of the distributed PFC-PPC system subserving spatial working memory. The VOC task requires a subject to perform analysis of spatial dimensions of visual input in comparison to material in spatial working memory. In the present study we collected magnetoencephalography (MEG) data as well as functional magnetic resonance image (fMRI) data from normal controls and schizophrenia subjects during the VOC task. Analyses of behavioral data revealed schizophrenia patients to exhibit impaired accuracy and an increased reaction time on the VOC task that were independent of the length of delay period. We predict that integration of MEG and fMRI data from the VOC task will show schizophrenia patients to exhibit abnormal neural activity in PPC as well as in PFC during spatial working memory. In our previous analysis of MEG data using time-frequency transform analysis poor VOC task performance in schizophrenia patients was associated with reduced delta frequency activity over parietal cortex during spatial analysis of stimuli. Use of fMRI data will enhance localization of neural abnormalities elicited by the spatial working memory task. The specific timing as well as locations of abnormal cortical activity during spatial working memory will provide valuable information regarding the neural basis of this candidate endophenotype in schizophrenia.

DOES COMPUTERIZED COGNITIVE SKILLS TRAINING CHANGE BRAIN ACTIVATION PATTERNS IN SCHIZOPHRENIA : AN FMRI STUDY

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Abnormalities in the domains of attention, memory, working memory (WM) and information processing are important features of schizophrenia. WM functions appear to be mediated by neural networks involving the dorsolateral prefrontal cortex (DLPFC, Brodman's areas 46 and 10), anterior cingulate, parietal cortex, and precuneus. There is growing literature that cognitive remediation therapy (CRT) can produce modest improvements in cognitive functioning in patients with schizophrenia, suggesting that systematic efforts at improving cognitive functioning are feasible. Cognitive improvement after CRT may correlate with changes in brain activation patterns in specific areas. However, until today, there are few studies that have examined these critical brain areas in patients with schizophrenia, after neurocognitive interventions. The aim of this study was to investigate changes in activation patterns of the DLPFC in inpatients with schizophrenia who received a 12-week CRT program. Changes in DLPFC will be detected using functional magnetic resonance imaging (fMRI) while completing a stimulation task involving verbal working memory, such as the N-back task. Our hypothesis states that (1) patients receiving CRT will show greater increase (baseline minus endpoint) in activation patterns in DLPFC as compared to controls. (2) The degree of change in DLPFC activation patterns will correlate with improvement on neurocognitive tests associated with WM and other executive functions. Methods: Patients were randomized to a 12 week trial of CRT using COGPACK (Marker Software) or to a 12-week control condition. Patients will continue their antipsychotic treatment with an atypical antipsychotic for at least 4 weeks prior to the study (Phase A). Following Phase A they will receive baseline evaluations, including an fMRI scan with a cognitive activation task (N-back task), MATRICS neuropsychological test battery, and psychiatric, social functioning and symptoms assessment. Patients will then enter Phase B with randomization to control or CRT for 12 weeks. At the end of week 12, endpoint evaluations will include fMRI scan with N-back task, MATRICS, psychiatric and social functional assessments. Results:

Preliminary data of this ongoing project will be presented on 9 patients (5 CRT and 4 controls) indicating the change in DLPFC and correlation between change in DLPFC and neurocognitive change.

CHANGES IN THE OCULOMOTOR SYSTEM AFTER ANTIPSYCHOTIC TREATMENT IN FIRST-EPISODE SCHIZOPHRENIA: AN FMRI STUDY

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While much is known about receptor-level effects of antipsychotic medications, less is known about how they impact functional brain systems that support cognition. fMRI was used to study antipsychotic treatment on the oculomotor system in initially untreated schizophrenia patients. Data was collected during a saccadic eye movement paradigm on a 3T GE magnet from 10 untreated schizophrenia patients before and after 4-6 weeks of antipsychotic medication. Matched healthy individuals were scanned at a similar interval for comparison. At baseline, patients had reduced activation relative to healthy individuals in dorsal cortical areas known to support saccadic eye movements. Patients also displayed greater activation in posterior temporal-parietal extrastriate areas, regions that were not active for healthy individuals. At follow-up, relative to healthy individuals, schizophrenia patients displayed a relatively greater reduction in activation over time in dorsal cortical areas including the frontal, presupplementary, and parietal eye fields. Schizophrenia patients also demonstrated a reduction of activation in the caudate nucleus, an area where antipsychotic drugs block D2 receptors and which plays an important role in saccade control. Reductions in activation in schizophrenia patients after treatment were also seen in ventral anterior cingulate, the cingulate motor area, and precuneus, relative to healthy individuals. This study provides new evidence documenting the impact of antipsychotic medication on functional brain systems. Findings illustrate the potential value of functional neuroimaging biomarkers for tracking drug effects on brain systems, and provide insight into the origins of antipsychotic effects that have been reported previously in laboratory studies of oculomotor changes in first episode schizophrenia patients.

DRD2 TAQ1A GENOTYPES AFFECT BRAIN METABOLIC RESPONSE TO ARIPIPRAZOLE : A [^{18}F]FDG-PET STUDY IN HEALTHY MALE VOLUNTEERS

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The aim of the present study was to evaluate the effects of polymorphism in dopamine D2 receptor (DRD2) on brain metabolic response to aripiprazole in healthy male volunteers. Twenty healthy male volunteers were recruited in the present study, and were divided into two groups of ten subjects according to their genotypes (A1A1, n=10; A2A2, n=10). The subjects received 10 mg single oral doses of aripiprazole and placebo according to a single-blind placebo-controlled crossover study design. Brain glucose metabolism was measured using positron emission topography with ^{18}F-Fluorodeoxyglucose at the 12th hour after the administration of each drug. In voxel-based analysis using SPM2, subjects with A2A2 genotype showed decreased metabolism in frontal lobe, temporal lobe and posterior cingulate gyrus, as opposed to subjects with A1A1 genotype who showed increased metabolism in caudate head without any brain region of decreased metabolism. In region-of-interest analysis, significant interactions between drug and genotype were observed in right medial orbitofrontal gyrus and left caudate nucleus. This result suggests that clinical response to aripiprazole could be different according to DRD2 Taq1A genotypes.

THE PROCESSING OF AMBIVALENT STIMULI IN SCHIZOPHRENIA : A [15O] H2O PET STUDY

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The disturbance in emotional processing in schizophrenia is manifested in symptoms of ambivalence, anhedonia and possibly psychotic symptoms, too. It also has been demonstrated in blunted affective response and decreased negativity bias in an emotional response task in our previous study. In this study we examined the disturbance in emotional processing in schizophrenia at the evaluative level and related neural correlates. Evaluation of ambivalent stimuli by a modified word-stem completion task, consisted of four different blocks and organized according to stimuli valence (x2) and response instruction (x2), was performed by 12 normal controls and 12 patients with schizophrenia while undergoing [15O] H2O PET scanning. In normal controls, the dorsolateral prefrontal cortex (DLPFC), right ventrolateral prefrontal cortex (VLPFC), inferior temporal gyrus activity was increased to ambivalent stimuli regardless of the response instruction, whereas the patient group lacked increased prefrontal activity. In forced dichotomous judgment of ambivalent stimuli, the orbitofrontal cortex and right VLPFC activity was increased in normal controls, whereas the patient group showed increased DLPFC and superior parietal gyrus activity. The failure in the recruitment of the right VLPFC, associated with stimulus appraisal involving judgment of the emotional intensity, and the orbitofrontal cortex, associated with response selection and monitoring, may reflect a dysfunction in the hierarchical emotional processing in schizophrenia.

NEUREGULIN 1 ICE-SNP IN FIRST EPISODE SCHIZOPHRENIA CORRELATES WITH CEREBRAL ACTIVATION IN FRONTO-TEMPORAL AREAS

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Linkage studies have identified a significant association of the Neuregulin (NRG1) gene with schizophrenia, but its functional implication in the disorder is largely unknown. We explored differential brain activation assessed with fMRI during a letter n-back task between patients with schizophrenia carrying the most consistently confirmed at-risk allele (SNP-ICE; SNP8_221533) from the Icelandic haplotype on the Neuregulin 1 gene to patients without this genetic risk. 28 first episode patients with schizophrenia (14 patients with the at risk SNP and 14 without) and 28 healthy control subjects were included in the study.

Group comparison within the patients during working memory load (2-back vs. 0-back) revealed that those without the at risk allele showed greater activations ($p<.05$) in a network comprising the left parahippocampal gyrus (BA 28), superior frontal gyrus (BA 9), lateral temporal lobe (BA 20), precuneus (BA 7) and the right anterior cingulate (BA 24). Brain regions previously associated with the pathology of Schizophrenia are differentially affected in those patients carrying the genetic at risk status in the NRG1 gene. Heterogeneity of structural and functional measures within schizophrenia patients characterized solely by clinical phenotypes may be in part due to this genetic variation.

IMAGING EEG SYNCHRONIZATION IN SCHIZOPHRENIA PATIENTS WITH S-ESTIMATOR

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Recently a new measure of the cooperative behavior of simultaneous time series was introduced (Carmeli et al. NeuroImage 2005). This measure called S-estimator is defined from the embedding dimension in a state space. S-estimator quantifies the amount of synchronization within a data set by comparing the actual dimensionality of the set with the expected full dimensionality of the asynchronous set. It has the advantage of being a multivariate measure over traditionally used in systems neuroscience bivariate measures of synchronization. Multivariate measures of synchronization are of particular interest for applications in the field of modern multichannel EEG research, since they easily allow mapping of local and/or regional synchronization and are compatible with other imaging techniques. We applied S-estimator to the analysis of EEG synchronization in schizophrenia patients vs. matched controls. The whole-head mapping with S-estimator revealed a specific pattern of local synchronization in schizophrenia patients. The differences in the landscape of synchronization included decreased local synchronization in the territories over occipital and midline areas and increased synchronization over temporal areas. In frontal areas, the S-estimator revealed a tendency for an asymmetry: decreased S-values over the left hemisphere were adjacent to increased values over the right hemisphere. Separate calculations showed reproducibility of this pattern across the main EEG frequency bands. The maintenance of the same synchronization landscape across EEG frequencies probably implies the structural changes in the cortical circuitry of schizophrenia patients. These changes are regionally specific and suggest that schizophrenia is a misconnectivity rather than hypo- or hyper-connectivity disorder.

USING THE STROOP TASK TO INVESTIGATE THE NEURAL CORRELATES OF SYMPTOM CHANGE IN SCHIZOPHRENIA

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Objective: Reduced cognitive inhibition in schizophrenia has been related to functional abnormalities in the anterior cingulate and prefrontal cortex. Cognitive models suggest that reduced inhibition may contribute to the development of positive symptoms. Therefore, this study examined whether any abnormalities in brain activation during a cognitive inhibition task in patients with schizophrenia resolve with reduction of positive symptoms.Method: A Stroop task consisting of congruent, incongruent, neutral and baseline conditions was used in twelve patients with schizophrenia at baseline and follow-up (interval 6 to 8 weeks), and 9 age- and education-matched healthy volunteers at baseline. Functional magnetic resonance imaging (fMRI) data were acquired in an event-related design using a clustered acquisition technique to enable monitoring of behavioural responses. Results: Compared to the control subjects, the patient group showed significantly attenuated activation within the left pre/postcentral gyrus extending into the left inferior frontal junction, and the anterior cingulate gyrus during the incongruent condition. At follow up, activation in the pre/postcentral gyrus bilaterally was significantly greater during both conditions, and additionally in the left inferior frontal junction in the incongruent condition. Conclusion: Reduced inhibitory control in patients with schizophrenia is associated with functional abnormalities in the left inferior frontal junction and the anterior cingulate gyrus. Reduction of positive symptoms may be associated with a normalisation of the activation in the left inferior frontal junction, possibly mediated by a reduced susceptibility to interference.

REWARD DYSFUNCTION AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: INSIGHTS FROM THE COMORBIDITY WITH SUBSTANCE ABUSE

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This presentation builds on the seeming paradox that individuals with schizophrenia, overall, show increased rates of most substance abuse disorders. However, high levels of negative symptoms appear to be protective against developing substance abuse disorders. Both patients with schizophrenia and substance-abusing populations show disturbances in their patterns of risky decision making that have been referred to as "reward myopia." Data will be reviewed that suggested that both schizophrenia and other populations at risk for substance abuse show deficits in the ability to activate the ventral striatum in anticipation of delayed rewards. In patients with schizophrenia, these ventral striatal activation deficits have been associated with negative symptom severity. The paradox that ventral striatal deficits associated with substance abuse risk are correlated with negative symptoms and yet high levels of negative symptoms may be protective against developing substance abuse problems among schizophrenic patients will be considered within the context of possible differential disturbances in the anticipatory and consummatory phases of reward.

ABNORMALITIES IN WHITE MATTER FRONTO-TEMPORAL CONNECTIONS IN CHRONIC SCHIZOPHRENIA

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White matter connections between the frontal and the temporal lobes have been long suspected to play a major role in the psychopathology of schizophrenia. DTI is one of the first in vivo tools used to evaluate and quantify these connections in schizophrenia.

Fiber tractography is the postprocessing tool applied to DTI images in order to delineate the entire fiber tracts. The goal of our studies is to delineate and quantify coherence and integrity of white matter fiber bundles connecting frontal and temporal brain regions, and to compare it between patients with chronic schizophrenia, and control subjects. We present results of fiber tractography based fractional anisotropy (FA- popular measure of fiber coherence and integrity) group comparison between chronic schizophrenia subjects and healthy volunteers from four major frontal-temporal fiber tracts: (1) uncinate fasciculus (UF), (2) inferior occipito-frontal fasciculus (IOFF), (3) cingulum bundle (CB), and (4) fornix. In addition, we present relationship between integrity of specific fiber tracts and several clinical, as well as neuropsychological measures. Our data provide strong evidence for a disruption of anatomical connectivity between the frontal and temporal lobes, and suggest that such disruptions may be crucial to understanding the neuropathology of schizophrenia.

NEUROPSYCHOLOGY AND NEUROANATOMY OF VERBAL SELF-MONITORING IN SCHIZOPHRENIA

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Impaired monitoring of one's own actions is proposed to be the basis of some of the core symptoms in schizophrenia. Functional neuroimaging studies in schizophrenia patients with auditory hallucinations point to defective engagement of the neural regions known to be involved in successful self-monitoring in healthy people. At present, there are insufficient data to reach meaningful conclusions about the neurocognitive correlates of this deficit. We examined neuropsychological and functional brain correlates of self-monitoring in a large group of individuals with schizophrenia (n=63). A group of healthy controls (n=27) was also studied in order to (a) establish normal activation patterns, and (b) define the 'deficit' in the patient group. All participants underwent event-related functional magnetic resonance imaging while they performed a verbal self-monitoring task in which they read out words and heard the auditory feedback which was modified experimentally. They made attributions about the origin of feedback by pressing buttons using a button box. All participants were also assessed on a neuropsychological battery comprising of tasks known to engage frontal-temporal regions. Patients, on average, showed erroneous performance when judging the source of their own distorted voice or someone else's (undistorted) voice. Self-monitoring performance showed positive associations with performance on putative neuropsychological probes of frontal and temporal lobe functioning, namely immediate verbal memory, verbal fluency, mental flexibility, cognitive inhibition and sustained attention. At the neural level, the group of healthy controls activated the left inferior frontal and temporal gyri and the cerebellum when making correct attribution to either their own distorted voice or someone else's (undistorted) voice. Patients who performed poorly failed to activate these areas to the same extent as controls. Interestingly, activation deficit in the cerebellum was present even in the well performing patient group. Our observations indicate a role for a number of higher order cognitive processes in intact verbal self-monitoring performance. The frontal and temporal lobe hypofunctioning, reflected in both neuropsychological and fMRI modalities, plays a part in self-monitoring deficits in schizophrenia. The cerebellar dysfunction may be more strongly associated with the presence of a schizophrenic illness. Acknowledgements: Supported by the Wellcome Trust.

DOUBLE DISSOCIATIONS IN HEMODYNAMIC MODULATION DURING THE BUILD-UP OF CONCRETE AND ABSTRACT MEANING IN SCHIZOPHRENIA: EVIDENCE FROM FMRI

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Background: Impairments in building up context, and difficulties with abstract concepts are core clinical features of schizophrenia. We conducted an event-related fMRI study to examine the neural bases of these abnormalities and their interactions. Specifically, we tested the hypothesis that they are each mediated by abnormal modulation within the same neural system. *Method:* During scanning, fifteen right-handed schizophrenia patients and 15 demographically-matched healthy controls made acceptability judgments about sentences, presented word-by-word. The final word of each sentence was either abstract or concrete and was either pragmatically/semantically congruous or incongruous with its context, i.e. Concreteness was fully crossed with Congruity. *Results:* Behavior: Accuracy was worse and reaction times were longer in patients than controls. A significant Group by Concreteness interaction reflected a selective behavioral impairment in judging the acceptability of abstract (versus concrete) words in sentences in patients relative to controls. fMRI: Effects of concreteness: Across all participants, concrete words in sentences were associated with more activity within bilateral inferior temporal and fusiform cortices, reflecting the engagement of the ventral visual stream, while abstract words in sentences were associated with more activity within left-lateralized middle temporal and inferior prefrontal cortices, reflecting the recruitment of the semantic language processing network. Controls additionally recruited bilateral superior prefrontal and inferior parietal cortices to concrete (relative to abstract) words whereas patients showed less activity in these same regions to concrete (relative to abstract) words. Effects of congruity: Across all participants, bilateral inferior prefrontal cortices were recruited to incongruous relative to congruous words in sentences. Once again, however, a double dissociation was observed within the superior prefrontal/parietal network: controls showed more activity to incongruous (relative to congruous) words whereas patients showed less activity in these same regions to incongruous (relative to congruous) words. *Conclusion:* Abnormal modulation of activity within a superior prefrontal-inferior parietal network in association with normal modulation of activity within a temporal-inferior prefrontal network may lead to both impairments in building up context and difficulties with abstract concepts in schizophrenia.

OVERVIEW OF THE MIND IMAGING CONSORTIUM

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The MIND Imaging Consortium (MCIC) is a multi-site, multiyear clinical imaging study of schizophrenia. It brings together the clinical and imaging expertise of the Universities of Iowa, Minnesota,

New Mexico, and Mass General Hospital/Harvard University. Begun in 2004, it has successfully recruited two large groups of patients (PTS): a group with first episode psychosis (FE); the other with established chronic schizophrenia (Non FE). Simultaneously, age-matched healthy normal volunteers (HNV) were collected. This presentation reports on the demographic and clinical characteristics of the sample. All subjects underwent extensive diagnostic evaluations: SCID or CASH, neurological exam, and neuropsychological testing. The WRAT is being presented as one measure of premorbid achievement. All patients received symptom and side effect ratings: SANS, SAPS, Calgary Depression, AIMS, Barnes, Simpson Angus. In total 318 Subjects were recruited and received at least one fMRI scan. A summary of their demographic and clinical characteristics is below: Demographic: 151 PTS: 41 FE (30 males; avg age 26.9 yr,11 females; avg age 26 yr; white 76% black 15% Asian 9%; Education Mean 13.09 SD 2.53; Illness length Mean 1.19 yrs SD 2.66) 110 Non FE (82 males; avg age 36.5 yr, 28 females; avg age 39.6 yr; white 80% black 11% Asian 3% Native American 1% Unknown 5%; Education Mean 13.1 SD 2.58; Illness length Mean 16.52 yrs SD 10.69) 167 HNV: 61 FE matched (38 males; avg age 26 yr., 23 females; avg age 26.9; Education Mean 14.42 SD 1.88; white 100%) 106 Non FE matched (65 males; avg age 35 yr, 41 females; avg age 36.1 yr; white 83% black 8% Pacific Islander 1%, Asian 4%, Native American 1% Unknown 3%; Education Mean 15.67 SD 2.25) Clinical: SAPS: Positive Sxs Factor (Delusions,Hallucinations) Highest Score 10 FE Pts Mean= 5.78 SD 2.24; Non FE Pts Mean 4.5 SD 2.96 SANS: Negative Sxs Factor (Affect, Alogia, Avolition, Anhedonia). Highest Score 20 FE Pts Mean= 7.73 SD 4.46; Non FE Pts Mean 7.23 SD 3.62 Calgary: Highest Score 27 FE Pts Mean= 5 SD 5.39; Non FE Pts Mean 2.93 SD 3.72 AIMS: Highest Score 45 FE Pts Mean= .03 SD 0.17; Non FE Pts Mean .06 SD 0.34 Barnes: Highest Score 14 FE Pts Mean= 0.24 SD 0.5; Non FE Pts Mean 0.2 SD 0.45 Simpson Angus Scale: Highest Score 80 FE Pts Mean= 1.84 SD 2.9; Non FE Pts Mean 2.7 SD 3.51 WRAT: Highest Score 60 FE Pts Mean= 46.91 SD 6.99; Non FE Pts Mean 46.98 SD 5.98 FE HNV Mean= 50.86 SD 3.87; Non FE HNV Mean 50.73 SD 4.43

FUNCTIONAL IMAGING DIFFERENCES IN DECISION MAKING IN HIGH SCHIZOTYPES COMPARED TO CONTROLS

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Previous research has identified that decision making processes may be implicated in the formation of delusions. In particular a jumping-to-conclusions beads task has been used to demonstrate that patients with delusions make decisions hastily based on less information. However jumping-to-conclusions decision making has been reported to only exist under conditions where there is an obvious correct response, a situation which is not present in everyday life. There are problems associated with investigating these mechanisms in patients with schizophrenia such as heterogeneity of clinical state and the effects of medication on performance. Examining correlates of psychotic symptoms in those who score highly on schizotypy is an alternative approach without the restrictions present in patients groups. In a pilot study, we tested the hypothesis that decision making processes would have distinct functional imaging signatures in high schizotypes compared to mean schizotypes from a non-clinical sample. Participants completed an adapted beads task where they had to decide whether beads were being removed from 85:15 versus 50:50 (easy decision) or 60:40 versus 50:50 (difficult decision) ratios of red to blue beads. The baseline was a counting task between each decision block. The task was completed inside a 1.5T Phillips functional imaging scanner. Participants were selected on the basis of their scores on the Schizotypal Personality Questionnaire, with the 6 high schizotypes having a mean score of 53 and 7 controls having a mean score of 28. The mean age of participants was 21 years and there were 6 females. High and low schizotypes did not differ in the number of beads they required to make a decision, however overall participants wanted to see more beads in the difficult decision compared to the easy decision ($p=0.05$). During the easy decision making condition high schizotypes over activated decision making areas, such as the orbital frontal and superior frontal gyrus relative to controls. This meant that under the difficult decision making conditions high schizotypes recruited in additional areas such as the more posterior regions of the occipital gyrus and the cuneus to complete the task successfully. High schizotypes display functional imaging differences in response to a decision making task which suggest that they are inefficient in their use of cortical activity under conditions of ambiguity.

A FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) STUDY OF BIMODAL SENSORY ATTENTION: IMPLICATIONS FOR AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA

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Schizophrenia has been framed as a cortical disconnection syndrome. Here we describe an experiment examining the effect of attention on effective connectivity of sensory cortex. Thirteen healthy, right-handed, volunteers were studied. Inside the scanner subjects performed an auditory and visual attention task. During each active condition subjects were presented simultaneously with visual and aural pseudo-random numbers (1-8) at the same rate and duration. These pseudo-random numbers were counterbalanced across the active conditions. Subjects were cued to attend to numbers presented in one modality whilst ignoring those presented in the other modality (and vice versa). The behavioural task involved using an intra-scanner button-box to judge each number as 'odd' or 'even'. The baseline condition was visual fixation and quiescent scanner room noise. fMRI was performed on the 1.5T University of Sheffield Marconi Eclipse Scanner. We utilised a sparse acquisition paradigm to ensure the obtained activation was stimulus-dependent only (TR=6000ms; TE=50ms; 27 4mm slices at each of the 72 time-points; in-plane matrix=128 128; field-of-view=240mm). We analysed images using SPM99. First, we identified the main temporal and occipital activation foci, more activated during the active conditions versus baseline condition. Then we identified which brain areas correlated with the main left temporal foci during the 'attend auditory' condition and the main occipital foci during the 'attend visual' condition (conjoint $p<0.001$, uncorrected). This revealed a correlation with a wide range of brain areas including that of the precuneus contiguous with the posterior cingulate cortex (Talairach co-ordinates x=-4 y=-26 z=46 peak T=7.47; 1161 voxels exceeded conjoint $p<0.001$, uncorrected), left inferior parietal cortex (-58 -26 28; T=5.32; 30 voxels), anterior cingulate cortex (2 40 0; T=5.13; 55 voxels) and the right frontal gyrus (50 -68 –12; T=5.04; 34 voxels). These results suggest that the areas identified exhibit enhanced connectivity with the auditory cortex (but only dur-

ing auditory attention) and the visual cortex (but only during visual attention). Our results may help explain how modality-specific attentional modulation may influence the experience of auditory hallucinations in schizophrenic patients.

PERSECUTORY IDEATION: EXPERIMENTAL FINDINGS & FUNCTIONAL NEUROANATOMY IN CONCORDANT AND DISCORDANT TWINS

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Although the field has begun to explore the cognitive basis of delusions, there is little known about the affective and neural basis of positive symptoms in schizophrenia. Because it is a prevalent symptom associated with a common affective state, *persecutory ideation may be a model symptom* for studying cognitive and affective processes in the expression of positive symptoms. To evaluate the neural and etiological basis of such persecutory ideation in psychometrically-identified schizotypes, we developed a task that revealed a persecutory decision-making bias under laboratory conditions. We have demonstrated that this task, known as the Minnesota Trust Game, is capable of 1) evoking suspiciousness of a partner in an experimental setting, and 2) distinguishing decisions based on suspiciousness from those based on rational mistrust of their partner or aversion to non-human risks. Because positive symptoms have been shown to have low heritability, a discordant twin design was used to identify brain regions affected by the environmental influence on persecutory ideation. 19 monozygotic twin pairs performed the task while undergoing 3T functional MRI. Twins were selected because at least one of the members scored above the normal range on a suspiciousness personality scale. Behavioral results replicated our previous study in undergraduates, indicating that participants were sensitive to when an anonymous partner did or did not have an incentive to betray them (logistic regression 3-way interaction z=2.75, p=.006). Furthermore, the most suspicious twins were the least likely to trust their partners on those trial in which their partners had no incentive to betray them (z=-5.09, p<.001), whereas this did not predict aversion to non-human risks (z=-.54, p=.58). Functional imaging analyses of this task in a healthy sample showed bilateral activity in the insular cortex associated with the requirement to trust the partner. The use of discordant MZ twins allows for determination of the extent to which activity here is either common across twins — suggesting this region is not affected by the environmental factors that lead to discordance – or different across twins – suggesting this region reflects the environmental factors associated with different degrees of persecutory ideation. This study is the first of its kind to use the discordant MZ twin design to evaluate the neural basis of psychosis-related cognitive processes.

MULTIMODAL NEUROIMAGING INVESTIGATIONS OF EXECUTIVE DYSFUNCTION IN SCHIZOPHRENIA

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Aim: Since performance of even simple tasks is the product of coordinated activity across a network of brain regions, a full characterization of executive dysfunction in schizophrenia requires a multimodal approach. Functional MRI (fMRI) provides excellent spatial, but poor temporal resolution. Accumulating evidence suggests that measuring the timing of neuronal processes across regions may be key to understanding neurocognitive deficits, and that optimal functionally connectivity may depend critically on the integrity of white matter connections. This talk will illustrate the use of complementary neuroimaging techniques to characterize executive dysfunction in schizophrenia. Event-related fMRI and magnetoencephalography (MEG) provide complementary information about the location and timing of task-related activity. Diffusion Tensor Imaging (DTI) assesses the microstructural integrity of white matter. We used these techniques to illuminate the neural basis of preparing to perform an effortful cognitive task and evaluating one's responses. An antisaccade paradigm was chosen because it has a well-delineated neuroanatomy and neurophysiology and because deficits on this task may index genetic liability for schizophrenia. Method: 18 patients and 15 controls performed an antisaccade paradigm during fMRI and MEG with concurrent monitoring of eye position. High resolution DTI was also acquired. Results: Patients made more errors than controls and performed correct antisaccades more slowly. Early in correct trials, patients showed abnormally increased activity in rostral anterior cingulate cortex (ACC) suggesting anomalous task preparation. Following errors, patients showed decreased activity in both rostral and dorsal ACC suggesting deficient performance evaluation. Patients also showed reduced fractional anisotropy in both rostral and dorsal ACC that was associated with increased saccadic latency. Conclusion: These findings demonstrate structural and functional abnormalities of the ACC in schizophrenia that contribute to deficient task preparation, slower correct performance, and a failure to optimally evaluate and learn from errors. These deficits likely contribute to rigid and maladaptive patterns of behavior. More generally, these findings illustrate the promise of multimodal neuroimaging to provide specific information about the location, timing, and structural basis of executive dysfunction in schizophrenia.

EMOTIONAL PROCESSING AND EPISODIC MEMORY IN SCHIZOPHRENIA: INFLUENCES OF EMOTIONAL PROCESSING ON THE AMYGDALA

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A growing literature suggests that individuals with schizophrenia provide relatively intact self-reports of valence and arousal in response to affect eliciting stimuli and also show an intact influence of emotional valence and arousal on subsequent memory. However, less is known about the integrity of neural systems that support the processing of emotional information and the influence of emotional valence and arousal on memory. This study was designed to examine whether individuals with schizophrenia demonstrate appropriate activation of regions involved in the processing of emotional information (especially the amygdala) when presented with either emotional words or pictures, and whether the degree of activation in such regions predict subsequent memory for those stimuli. We used fMRI to measure brain activity while controls and individuals with schizophrenia made valence and arousal ratings on a series of words and pictures using the SAM rating system. The words and pictures varied in emotional valence (positive, negative, neutral) and arousal (high versus low). After scanning, participants were given surprise

recall tests for the words and pictures, followed by recognition tests that asked participants to make remember/know/guess judgments. Participants were 13 individuals with schizophrenia and 11 demographically similar healthy controls. Results suggest schizophrenia individuals provide intact self-report ratings of emotional valence and arousal in response to both emotional pictures and words. Schizophrenia individuals displayed overall worse recall for words and pictures, but displayed an intact influence of emotion on subsequent recall and remember/know recognition judgments. Amygdala activation did not significantly differ between controls and individuals with schizophrenia during emotional encoding. However, later analysis of the relationship between memory and amygdala activation suggests that individuals with schizophrenia utilize the amygdala in a different way than do controls. Controls demonstrated enhanced amygdala activity while viewing emotional words and pictures that they later recalled. Individuals with schizophrenia demonstrated enhanced amygdala activity for words and pictures that they later missed recalling. An enhanced amygdala activation for stimuli later forgotten in individuals with schizophrenia may suggest that more evocative stimuli could cause an interference in their ability to process and retain this information.

IS REDUCED HEMISPHERIC SPECIALIZATION FOR LANGUAGE IN SCHIZOPHRENIA STABLE OVER TIME ?

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Background: Neuroimaging studies suggest that schizophrenic patients present a reduced leftward asymmetry of language, consistent with Crow's hypothesis of a failure of hemispheric specialization for language. In the present study, we conducted a follow-up functional magnetic resonance imaging (fMRI) experiment in order to test the stability of the decreased leftward lateralization for language as previously shown (Dollfus et al. 2005). **Methods:** Ten patients (DSMIV) and 10 controls, all right-handed, matched one to one for sex, age and level of education, were scanned twice during a story listening task, 21 months apart. An ANOVA was performed to compare the functional asymmetry indices (FAI) measured in a region of interest (LANG), gathering semantic cortical areas, across groups and sessions. The stability of the FAIs was assessed through a simple regression between the within-pair FAI differences (patient *minus* control) observed at each session. Spearman's correlations between FAIs and positive and negative PANSS scores, and task cognitive performances were computed in patients at both sessions. **Results:** A significant group effect was found, showing a reduced LANG FAI in patients as compared to controls (p=0.007). Within-pair FAI differences correlated significantly between sessions (R2=0.848, p=0.002). FAIs were unrelated to either psychotic symptoms or cognitive performances. **Conclusions:** The reduced leftward asymmetry in semantic areas in schizophrenic patients was stable over time and not related to task cognitive performances. This finding reinforces the fact that a reduced leftward hemispheric specialization is a characteristic of schizophrenia. **References:** Dollfus et al, Biol Psychiatry 2005;57:1020-1028.

AN FMRI STUDY OF MEMORY AND EXECUTIVE FUNCTIONS IN THE EARLY PHASE OF PSYCHOSIS

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People with an At Risk Mental State (ARMS) have a very high risk of developing psychosis and neuropsychological studies have reported impairments in memory and executive functions in this group. We used functional MRI to examine regional brain activation while subjects with an ARMS performed cognitive tasks that engaged these processes. Subjects with an ARMS (n=17) were compared with age- and IQ- matched groups of patients with a first episode schizophreniform psychosis (n=10) and healthy volunteers (n=17). The BOLD response was measured using a 1.5T camera while subjects performed an overt verbal fluency task, an N-Back working memory task, and a delayed matching to sample task. The ARMS and schizophreniform psychosis were defined using PACE and ICD-10 criteria, respectively. All of the ARMS subjects and 3 of the first episode patients were medication naive. The mean duration of treatment in the remaining first episode patients was 10 days. Task performance was recorded on-line and only trials associated with correct responses were used in the image analysis, performed using XBAMM. Across all 3 tasks, regional activation in the ARMS group was intermediate relative to that in the control and first episode groups. During the N-Back and an 'easy' version of the verbal fluency task, there was less lateral prefrontal activation in the ARMS group than controls but more than in the first episode patients. Conversely, during the delayed matching to sample task and a 'hard' version of verbal fluency, the ARMS group showed less activation than first episode patients but more than controls in the hippocampus and in the anterior cingulate gyrus respectively. These data suggest that the ARMS is associated with abnormalities of regional brain function that are qualitatively similar to those in patients who have just developed psychosis, but are less severe. These functional abnormalities may be correlates of their increased vulnerability to schizophrenia.

PATTERNS OF PREFRONTAL ACTIVATION DISCRIMINATE SCHIZOPHRENIA FROM BIPOLAR DISORDER

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Background and Aims: Bipolar disorder and schizophrenia are both associated with overlapping cognitive imapirments. There is however some evidence that ventral prefrontal impairment is more pronounced in bipolar disorder whist impairment of dorsolateral prefrontal cortex is more pronounced in schizophrenia. We aimed to test this hypothesis using the Hayling Sentence Completion Test. Methods: Patients with bipolar disorder, schizophrenia and controls underwent a form of the Hayling Sentence Completion Test adapted for use with fMRI. Bold related activity was measured during the task and 1) compared with rest periods (active versus rest contrast) and 2) related to an increasing level of task difficulty (parametric contrast). Results: Patinets with schizophrenia showed reduced activation of DLPFC and temporal cortex during the task. In contrast bipolar patients showed increased activation of both DLPFC and ventral

cigulate cortex during the perfromance of the task. Further data has been acquired, including diffusion weighted imaging, will be available for presentation at the time of the meeting. Conclusions: Patients with bipolar disorder and schizophrenia have separable imapirments in cortical function. These findings may provide a substrate for the non-overlappig features in each disorder.

THE EFFECTS OF DOPAMINE MODULATION ON ACTIVITY IN THE VENTRAL STRIATUM IN RESPONSE TO AVERSIVE STIMULI

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The ventral striatum is one of the primary sites of the action of antipsychotics which appear to act by blocking dopamine receptors in that area. Animal studies have found that the phasic firing of the dopamine neurons signals the presence of salient stimuli. Both the phasic activity of dopamine neurons (in monkeys) and the BOLD activity measured by fMRI in humans during reward and punishment tasks have been shown to correlate with the prediction error (PE) hypothesized by the temporal difference (TD) model (a model of machine learning). We hypothesized that dopamine modulates the PE related signal in aversive conditioning, and that haloperidol would reduce PE related activity, while an acute dose of amphetamine would increase PE related activity in the ventral striatum. Healthy participants were given an acute dose of amphetamine, haloperidol or placebo. We used fMRI to measure the BOLD signal while they carried out an aversive conditioning task, using cutaneous electrical stimulation as the unconditioned stimulus (US) and yellow and blue circles as cues (CS+ and CS− respectively). Prediction error related BOLD activity was seen only in the ventral striatum in the placebo subjects. The subjects given amphetamine showed a wider network of PE related BOLD activity including the ventral striatum, caudate, putamen, insula, anterior cingulate and substantia nigra/ VTA. Haloperidol subjects did not show PE related activity in any of these regions. Our results suggest that the limbic ventral striatum is active in response to 'salient' stimuli, and altering dopamine transmission affects the activity in this area in a conditioning paradigm. This functional alteration may be related to how antipsychotics act to reduce symptoms of schizophrenia. This study was funded by an unrestricted grant from Astra-Zeneca. The authors declare that they have no competing financial interests.

THE FUNCTIONAL EFFECTS OF NEGATIVE SYMPTOMS ON EMOTIONAL PROCESSING IN PATIENTS WITH SCHIZOPHRENIA

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Introduction Patients with schizophrenia are known to have difficulties in the recognition of facial emotional stimuli, particularly in the recognition of negative facial expressions. These difficulties appear to be more prominent in patients with severe negative symptoms. Brain lesion studies have highlighted the role of anterior cingulate circuit in the initiation of behaviour, motivation and goal orientation. This circuit is comprised of the anterior cingulate cortex, its projections to the ventral striatum which includes the ventromedial caudate, projections to the ventral anterior nucleus of the thalamus and back to the anterior cingulate cortex and other cortical areas. Imaging studies have also found this network to be associated with emotional processing in healthy subjects. We hypothesized that the increasing severity of negative symptoms in patients with schizophrenia would associate with decreasing neural responses within these regions during the processing of sad facial expression. Methods We used event-related functional magnetic resonance imaging (fMRI) to measure neural responses to neutral and sad facial expressions. Our sample consisted of 11 clinically stable patients with schizophrenia and 9 healthy controls matched for age and years of education. Results Correlational analyses in the patients' group revealed a significant negative correlation between the PANSS Negative Subscale Score and the activation within bilateral anterior cingulate gyri, right-sided caudate and thalamus during the processing of sad facial expression. Conclusions Our results indicate that patients with severe negative symptoms demonstrate dysfunctional resposes within the anterior cingulate circuit during the processing of sad facial expression and suggest an important link between sadness-responsive regions and the clinical phenomenology of negative symptoms.

MODAFINIL EFFECTS ON COGNITIVE CONTROL IN SCHIZOPHRENIA: A DOUBLE-BLIND, PLACEBO-CONTROLLED SINGLE-DOSE PHARMACO-FMRI STUDY

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Background: Schizophrenia is characterized by dysfunction of prefrontal-dependent cognition. This prominently includes impairments in cognitive control and its basis in a cortical network that includes the dorsolateral PFC (DLPFC) and anterior cingulate cortex (ACC). These areas support two component processes of cognitive control: context processing and conflict monitoring, respectively. These PFC areas are also modulated by catecholamines, and there is evidence that pro-catecholaminergic agents improve PFC-dependent cognitive performance in animal models and in humans. We sought to test whether the novel agent modafinil exerts a remediating effect on PFC-dependent cognitive dysfunction in schizophrenia. Methods: To date, 4 adults with clinically-stable chronic schizophrenia have participated in a double-blind, placebo-controlled crossover study of a single oral dose of modafinil 200 mg. Subjects were scanned between 3-4 hours after dosing, and performed the Preparing to Overcome Prepotency (POP) task during event-related fMRI with ROI analysis of BOLD contrast. In the POP task, color cues are presented which signal congruent (Green Cues) versus incongruent (Red Cues) stimulus-response mappings to subsequent targets (left or right-pointing arrows). Cue-Target delay period activity is elicited in DLPFC as a measure of context processing, whereas Post-Target period activity is elicited in the ACC as a measure of conflict monitoring. Both regional BOLD responses are stronger after Red Cues. Results: To date, the patients show higher DLPFC activity on modafinil compared to placebo, particularly for the high cognitive control demanding condition; in contrast, ACC activity is lower on modafinil compared to placebo. Conclusions: A single dose of modafinil is associated with improved DLPFC activity during context processing, which may in turn attenuate conflict monitoring demands and associated ACC activity. Additional studies are underway to evaluate the degree of neural and cognitive remediation

observed with modafinil, and the relative effects of single-dose versus sustained modafinil treatment.

PERSISTENCE OF ABNORMAL DEFAULT MODE NETWORK ACTIVITY IN SCHIZOPHRENIA: A LONGITUDINAL FMRI STUDY OF WORKING MEMORY

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Patients with schizophrenia exhibit abnormalities of brain function while performing executive function and working memory tasks. It is not known to what extent disrupted default mode network activity or failure to deactivate this network contributes to these abnormalities. In a block design fMRI study, patients with schizophrenia (n=12), participating in a cognitive remediation program, and healthy controls (n=11) performed verbal working memory and sustained attention tasks. Both groups were scanned a second time performing the same tasks 8-18 weeks later. ROI analyses revealed abnormal, mostly deficient default mode activity in the patients at time 1 in subgenual cingulate (BA25), left anterior cingulate (BA32), left primary auditory cortex (BA41), superior temporal gyrus (BA42), bilateral temporal pole (BA38), left posterior cingulate (BA31) and bilateral higher order visual cortices (BA19) during the working memory task. They also revealed overactivation in left DLPFC (BA9), left Broca's (BA44) and more caudal left ACC (BA32) relative to the controls. Mean scores were compared over time between the patient and control subgroups using linear mixed models with group as between-subjects explanatory factor and time as within-subjects factor. Group by time interactions were found for activations in left BA9 and BA32 (reduced at time 2 for the patients) and for deactivations in more rostral BA32 at time 2 for the patients on the working memory task. Failure to deactivate rostral BA32, 25, 31 and 19 did not improve at time 2 for the patients. Deactivation abnormalities were accompanied by overactivation of areas implicated in verbal working memory including DLPFC and ACC but underactivation of the subcortical areas putamen, thalamus and cerebellum suggesting that the healthy controls were able to automatize the task more quickly. Excitatory projections from neurons in PFC have been found to target upstream local inhibitory neurons in auditory temporal cortex (Barbas et al., Cerebral Cortex 15:1556-70). The increased activation of BA9 and 32 while failing to deactivate auditory areas in the patients may lend further support to 'functional disconnectivity' in schizophrenia. Alternatively, the abnormal default mode activity in schizophrenia may result from dysfunctional subcortical modulatory influence from the thalamus (Gusnard & Raichle 2001, Nat Rev Neurosci 2:685-694) suggesting that schizophrenia may be, after all, a "disorder of consciousness."

ATLAS-BASED FMRI STUDIES IN SCHIZOPHRENIA USING A STANDARDIZED TASK BATTERY

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Schizophrenia patients exhibit a broad range of cognitive impairments. The associated neurobiological and systems-level disturbances are less understood. To determine whether functional landmarks associated with aspects of working memory, language, sensory and motor processing are disturbed in schizophrenia, we used a broad survey of fMRI tasks, designed by the International Consortium for Human Brain Mapping (ICBM) to produce robust activation responses in normal subjects. Images from 20 (13m/7f) schizophrenia patients and 14 (7m/7f) healthy subjects similar in age were acquired on a Siemens 3T scanner using an EPI sequence. Activation paradigms included: 1) external ordering (working memory); 2) oculomotor (saccades); 3) hand imitation (motor coordination and planning); 4) verb generation (language); and 5) auditory naming (language). fMRI data, acquired using a block design, was analyzed with FSL. After motion correction, spatial normalization and smoothing, a random effects model compared task-related patterns of brain activity between diagnostic groups while controlling for sex (corrected cluster significance $z>2.3$; $p<.05$). Robust activations within 1) prefrontal and visual primary and association cortices for working memory; 2) oculomotor and visual cortices for oculomotor processing; 3) occipital, parietal and frontal networks for hand imitation; 4) language and primary and association auditory cortices for auditory naming; and 5) language and visual areas for verb generation, were observed. Comparing patients to controls, significant decreases in working memory-related activations were observed within diffuse cortical networks, including prefrontal regions. Brain activity was reduced in Broca's area for the auditory naming task and responses were less lateralized within language regions for verb generation. Functional landmarks associated with motor processing, including oculomotor responses, did not differ between groups. Although prior evidence suggests that all functional modalities probed by the ICBM fMRI battery are potentially impaired in schizophrenia, methodological differences hinder comparisons across studies. Our study design allows meaningful interpretation of diagnosis-related differences across tasks and functional systems. Results support selective disturbances in working memory-related cortical networks in schizophrenia, and suggest that disturbances and compensatory mechanisms occur for aspects of language processing.

ALTERED NEURONAL ACTIVATION DURING COMPLETION OF A VISUO-SPATIAL LEARNING TASK IN PRETERM ADOLESCENTS

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BACKGROUND: The aim of the present study was to investigate the ways in which the neuronal activation of individuals born very preterm is altered in the presence of perinatal brain injury. In particular, we were interested in identifying the neural correlates of selective aspects of memory functioning, with specific reference to visuospatial learning, which has been found to be impaired in a variety of psychopathologies including schizophrenia and bipolar affective disorder. This study used functional magnetic resonance imaging (fMRI) to compare the generic brain activation of 24 right-handed adolescents born very preterm of both sexes (<33 weeks of gestation), and 22 matched controls during performance of a visual paired-associate learning task. METHODS: Echo planar MR images demonstrating BOLD contrast were acquired using a 1.5 Tesla GE Signa Neurovascular MR system. Fourteen 7mm thick near axial slices were acquired parallel to the intercommisural plane with the addition of a high resolution inversion recovery EPI data-set with 3mm thick slices and an in-plane resolution of 1.5mm. Data were analysed with XBAMv3.3. The visual paired associates task consisted of 3 phases, each containing 8 stimulus pairs (e.g. abstract pic-

tures): encoding, recognition, and baseline. RESULTS: Task performance was similar in the two groups, i.e. there was no difference between groups in the number of correctly recognised pairs of pictures. However, during encoding, preterm individuals showed decreased BOLD signal response compared to controls in inferior frontal gyrus (BA 45) and increased signal in right parastriatal cortex (BA 19) and left caudate nucleus and superior frontal gyrus (BA 31). During recognition, preterm individuals showed increased BOLD signal response in right cerebellum and anterior cingulate gyrus (BA 32). These results suggest that despite good task performance, individuals who were born very preterm may activate different neural networks and use alternative strategies when performing a visuo-spatial learning task, possibly underlying a neurodevelopmental anomaly of fronto-striatal-cerebellar circuitry.

THE NEURAL SUBSTRATE OF SUSTAINED ATTENTION TO EMOTIONAL STIMULI AND MODAFINIL EFFECT ON ATTENTION IN SCHIZOPHRENIA : A [15O] H2O PET STUDY

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Modafinil is known to improve daytime drowsiness and fatigue in narcolepsy and help maintain daytime vigilance. Patients with schizophrenia suffering from disturbances in both cognitive and emotional processing maybe helped by improved vigilance. To address this hypothesis, we administered a sustained attention to emotional stimuli task(SAEST), a modified sustained attention to response task which we developed in order to measure sustained attention during response to emotional stimuli, to 12 patients with schizophrenia and 12 normal controls while undergoing [15O] H2O PET scanning before and after the ingestion of modafinil. The patients showed significantly slower correct response time and lower efficiency estimate than normal controls before medication. After medication, both groups did not show significant difference due to improved correct response time in the patient group. However, commission error rate increased in the patient group and both groups did not show significant level of improvement in performance. The dorsomedial prefrontal cortex and inferior occipital gyrus activity was increased during SAEST before medication in normal controls, whereas the patient group showed increased activity in the precentral gyrus. After medication, the patient group showed increased activity in the dorsolateral prefrontal cortex, inferior and middle occipital gyrus, and the intraparietal sulcus. Our results indicate that sustained attention to emotional stimuli may be deficient in patients with schizophrenia due to dissociation of the prefrontal region associated with attention and emotional judgement. Modafinil may have limited effect on improving attention with concurrent exacerbation of preservation in patients with schizophrenia.

USE OF HEMODYNAMIC BRAIN MODES VS CONVENTIONAL FMRI ANALYSIS AND STRUCTURAL BRAIN MEASURES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: We conducted fMRI experiments with 18 chronic schizophrenics, 12 psychotic bipolar patients and 20 healthy controls to determine if imaging markers could differentiate these groups. Because task-based fMRI studies can be confounded by variable effort and task performance, we chose a simple auditory oddball paradigm where accuracy did not differ between groups. Methods. We employed two separate analytic approaches: classic SPM and a recently developed independent component analysis (ICA) designed to identify distinct brain networks exhibiting temporally coherent activity. In addition, structural MR data were obtained and analyzed using voxel-based morphometry (VBM). Results. The SPM analysis showed relatively few differences between patient groups, although both differed from healthy controls. The ICA analysis was able to identify temporal lobe and "default" mode networks from all participants and distinguished between groups with 90% sensitivity and 95% specificity. VBM showed gray matter reductions in several overlapping frontal and temporal regions in patient groups. Discussion. The use of coherent brain networks such as the temporal lobe and default modes, may provide a more reliable measure of disease state than either conventionally employed fMRI activity and structural imaging. ICA-derived brain networks shows promise as a hemodynamic biomarker of schizophrenia and psychotic bipolar disorder.

NEURAL CORRELATES OF VERBAL SELF MONITORING IN MONOZYGOTIC TWINS DISCORDANT FOR SCHIZOPHRENIA

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Patients with schizophrenia tend to misidentify their own speech as belonging to someone else when it is distorted. The misidentification of self-generated verbal material as alien may be underlie auditory hallucinations in schizophrenia. We used fMRI to study the neural correlates of a task that engages self-monitoring in monozygotic (MZ) twins discordant for schizophrenia. We studied 10 pairs of monozygotic (MZ) twins discordant for schizophrenia and 10 pairs of healthy twins. Subjects read aloud adjectives presented visually while the sound of the spoken word was manipulated. They heard either (i) their own voice, (ii) their own voice distorted by a pitch shift, (iii) another person's voice, or (iv) another person's voice distorted. Subjects indicated the source of the voice they heard via a button box as either 'self', 'other' or 'unsure'. Images were acquired at 1.5T using a compressed acquisition sequence and analysed in a factorial design using XBAM software (Institute of Psychiatry, University of London). There was a main effect of source in the right middle/superior temporal gyrus, with greater activation in response to the 'other' voice. There was a main effect of distortion in the right superior temporal and inferior frontal gyri, with greater activation in response to distortion. We detected a main effect of group in the superior temporal gyri bilaterally and the right middle temporal gyrus, with more activation in healthy subjects than in both patients and their co-twins. There was a group x source interaction in the right middle and left superior temporal gyri, and the left inferior frontal gyrus: both the psychotic twins and their non-psychotic co-twins failed to show activation in these regions in response to the 'other' voice. These results suggest that the monitoring and appraisal of speech in patients with schizophrenia is associated with differential activation in the inferior frontal and temporal cortex. The presence of similar abnormalities in their

non-psychotic co-twins indicates that at least some of these differences are related to genetic factors, as opposed to the illness of schizophrenia.

NEURAL ACTIVATION IN RESPONSE TO COMPLEX SOCIAL JUDGMENTS IN PARANOID AND NON-PARANOID SCHIZOPHRENIA AND HIGH-FUNCTIONING AUTISM

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While functional neuroimaging studies examining schizophrenia and autism separately have consistently shown abnormal activation of structures within the social cognitive neural circuit and suggest that behavioral impairments in social cognition may be subserved by these abnormalities, no study has been able to address the similarities and nuances of these mechanisms. Here we used event-related functional magnetic resonance imaging (fMRI) to measure neural activation during both complex social judgments and nonsocial judgments of faces in four groups of individuals: paranoid individuals with schizophrenia (P-SCZ), non-paranoid individuals with schizophrenia (NP-SCZ), individuals with high-functioning autism (HFA), and non-clinical healthy controls. The schizophrenia sample was divided into two subgroups given evidence for differential neural activation and social cognitive performance in paranoid and non-paranoid individuals. Results of this study indicate that individuals with high-functioning autism and individuals with paranoid schizophrenia differ from controls and individuals with non-paranoid schizophrenia in two primary ways: 1) HFA and P-SCZ individuals show significant reductions in neural activation as compared to control and NP-SCZ individuals during tasks of complex social cognition that cannot be accounted for by generalized reductions in neural activation, and 2) whereas control and NP-SCZ participants showed increased activation of the social cognitive circuit during complex social judgments, HFA and P-SCZ individuals fail to show modulation of the social cognitive neural circuit in response to the social nature of judgments. This study offers important contributions to both the cognitive and clinical sciences by demonstrating that the proposed social cognitive circuit responds selectively to the social nature of judgments and by revealing disparities between schizophrenia subgroups and shared abnormalities in neural functioning between individuals with schizophrenia who evidence prominent paranoid symptoms and individuals with high-functioning autism. The former finding supports neurobiological models of social cognition, and the latter finding suggests that individuals with schizophrenia and individuals with autism share similar neural profiles that may underlie social cognitive deficits and social dysfunction. Support for this project was provided by the National Alliance for Research on Schizophrenia and Depression (D. Penn).

OVERACTIVATION OF BOLD FMRI RESPONSE IN SCHIZOPHRENIA DURING CONTROLLED VERSUS AUTOMATIC WORD GENERATION

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Single word generation demands allocation of considerable cognitive resources. Patient deficits are difficult to interpret because the tasks are multi-factorial and groups differ in total words generated. We manipulated retrieval and switching demands by requiring alternation between over-learned sequences in which retrieval is relatively automatic (OS) and effortful categories requiring increased retrieval demands (SC). Controlled processing was also manipulated by including switching and non-switching conditions. A modified OS/SC semantic fluency task[1] was administered during BOLD fMRI of 13 patients with schizophrenia and 14 matched controls. Images were acquired on a 3 Tesla Siemens scanner using compressed image acquisition to allow for paced overt word production. Subjects alternated between OS, SC, OS-switch, SC-switch, and baseline blocks. Total words generated, total "skip" responses, and total non-responses indexed performance. Images were pre-processed in SPM-2, and a two-stage random effects analysis tested within and between group contrasts. There were no group performance differences. fMRI analysis did not reveal any group differences during the OS non-switching condition. Both groups produced expected activation in bilateral prefrontal and inferior parietal regions. However, during the SC condition patients had greater activation than controls in left prefrontal, right anterior cingulate, right superior temporal, bilateral thalamus, and left parietal regions. There was also evidence of patient over-activation in prefrontal, superior temporal, superior parietal, and visual association areas when a switching component was added. These results indicate that patients are able to successfully perform effortful semantic fluency tasks during non-speeded conditions. When retrieval is relatively automatic there does not appear to be an effect of schizophrenia on fMRI response. However, when retrieval and controlled processing demands increase patients are characterized by abnormally increased activation. This abnormal BOLD response may explain why patients are slower and less accurate on standard self-paced fluency tasks. [1]Gurd JM, et al. Posterior parietal cortex is implicated in continuous switching between verbal fluency tasks: an fMRI study with clinical implications. Brain. 125:1024-1038, 2002.

FUNCTIONAL CONNECTIVITY IN PATIENTS WITH SCHIZOPHRENIA AND CONTROLS DURING WORKING MEMORY TASK PERFORMANCE

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Individuals with schizophrenia reliably show abnormalities in appropriate task-related activation of a network of regions typically implicated in working memory. However, less is known about the degree to which these abnormalities reflect disturbed functional connectivity among the critical elements of the working memory network. The purpose of the study was to examine possible schizophrenia related differences in functional connectivity during performance of verbal and non-verbal working memory tasks using three approaches: 1) across participants, reflecting individual differences in the degree to which participants are able to co-activate regions involved in the working memory network; 2) within-subjects across time during task performance, reflecting the trial by trial fluctuations in the coordinated activity of regions involved in working memory; and 3) within-task based on group-averaged timeseries, examining subject-invariant characteristic of the timeseries. FMRI data during performance of word and face 2-back working memory tasks was acquired from 38 individuals with DSM-IV schizophrenia and 38 demographically similar healthy controls. A set of 11 regions (bilat-

eral dorsal lateral PFC, inferior PFC, PPC, cerebellum, thalamus, and ACC) were selected that showed significant activity in both word and face working memory in both patients and controls. Between-subject connectivity analyses indicated reduced connectivity of cerebellar to cortical connections, as well as enhanced connectivity of left DLPFC region to thalamus and right PPC. In contrast, second-level analysis of within-subject correlations revealed reduced prefrontal to parietal connectivity. We also found an interaction for connections within the cerebellum and the cerebellar to right DLPFC connection, with connections being enhanced in words task and reduced in faces task. Group-averaging of timeseries produced similar results, but with added evidence for reduced inter-hemispheric connectivity, most pronounced in task with words. We hypothesize that the reduced within-subject connectivity demonstrated by individuals with schizophrenia reflects impairments in the trial-by-trial ability to appropriate coordinate activity between DLPFC regions and other cortical nodes of the working memory network. In contrast, the changed pattern of between-subject connectivity may reflect the differences in the overall ability to recruit working memory related regions.

HOW STABLE ARE CEREBRAL DEFICITS OF HAPPY AND SAD MOOD? RESULTS OF A LONGITUDINAL FMRI STUDY EXAMINING FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Objective: Flattened affect is a core symptom of schizophrenia. Mood induction paradigms may be drawn on for functional magnetic resonance imaging (fMRI) studies to investigate the underlying cerebral correlates. So far, aberrant brain activation patterns have been observed in chronic schizophrenia patients during happy and sad mood, while it has not been clarified entirely whether these differences display trait- or state-characteristics of schizophrenia. This fMRI study aimed at determining changes of mood-related neural correlates under consecutive therapy in first-episode schizophrenia. *Method:* 10 first-episode schizophrenia patients (6 males) and 10 matched healthy controls were investigated during sad and happy mood induction using facial expressions. Standardized self rating scales were used to assess the individual emotional state during the tasks. Re-assessments (T1) took place after six months during which patients underwent a standardized pharmacological and psychological therapy. *Results:* As documented by self rating scales, the tasks led to a successful mood induction in both groups at both time points. At T0, patients were mostly characterized by hypoactivations which affected brain regions involved in emotional awareness, regulation and memory processes as well as in early stages of face processing. These were accompanied by compensating hyperactivations. Furthermore, we observed therapy-related signal increases in patients. *Discussion:* This study validates previous findings examining schizophrenia patients and non-affected people at high risk pointing to the trait characteristic of these dysfunctions. Reassessments after six months on the other hand verified therapy-related changes in brain function. To summarize, our results preliminary suggest positive treatment effects over time on emotional processing in schizophrenia mediated by a widely distributed bilateral cortical network. *Acknowledgements:* Supported by the Competence Network on Schizophrenia, sponsored by the German Federal Ministry of Education and Research (BMBF 01 GI 9932).

SEROTONIN TRANSPORTER GENETIC VARIATION MODULATE AMYGDALA REACTIVITY TO EMOTIONAL STIMULI IN PATIENTS WITH SCHIZOPHRENIA

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The main objective of this study is to compare the amygdala reactivity to an auditory emotional paradigm in relation to 5-HTTLPR gene variation in patients with schizophrenia. Recent studies found amygdala hyper-reactivity to emotional provocative visual stimuli in comparison with emotionally neutral stimuli in s allele carriers in normal subjects (Hariri et al 2002). In a previous study we found an association between s carriers and the emotional response to auditory hallucinations in schizophrenia (Sanjuan 2006a). An auditory emotional paradigm based on the most frequent words heard by psychotic patients (Sanjuan 2005, 2006b) was applied to evaluate the cerebral activation using functional Magnetic Resonance Imaging (fMRI) in 50 patients with DSM-IV diagnosis of schizophrenia. All patients were clinically assessed with Positive and Negative Syndrome scale (PANSS) and Psychotic Symptoms Rating Scale (PSYRATS) .Patients were under antipsychotic treatment in the evaluation time and were classified according to 5-5HTTLPR genotype: 14 ss, 23 sl and 10 ll. Statistical test were performed using an ANOVA of the amygdala fMRI data and the 5-HTTLPR polymorphim with a $p < 0.001$ uncorrected, cluster extend (k)= 0 A greater activation in the right amygdala (MNI coordinates 32, -2, -12) was observed in the ss group compared with sl and ll genotypes. This study confirm the role of serotonin transporter in the regulation of neural reactivity to emotional stimuli in patients with schizophrenia. Hariri A et al Serotonin transporter genetic variation and the response of the human amygdala. Science 2002. 297, 400-403. Sanjuan, J.et al Serotonin transporter gene polymorphism (5-HTTLPR) and emotional response to auditory hallucinations in schizophrenia. Int J Neuropsychopharmacol. 2006 (1):131-3. Sanjuan, J. Emotional auditory paradigm in neuroimaging: a base for the study of psychosis. Actas Esp Psiquiatr. 2005; 33(6):383-9. Sanjuan, J (b) Emotional words induce enhanced brain reactivity in schizophrenic patients with auditory hallucinations. Psychiatry Research Neuroimaging 2006 (In press). This study was supported by Spanish Grant FIS P.I. 052332

MULTIMODAL IMAGING OF THE MISMATCH NEGATIVITY DEFICIT IN SCHIZOPHRENIA

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Reduced Mismatch Negativity (MMN) is a common finding in patients with schizophrenia. This project examines the developmental time course of the deficit as well as exploring its neurological

basis using a variety of imaging techniques. EEG, fMRI and structural MRI data were obtained from chronic patients with schizophrenia (>5 years duration), first episode patients (<2 years duration), first degree biological relatives, and age and gender matched controls. A Duration Deviant MMN paradigm was used in which participants hear an unattended random series of tones consisting of standards (92%, 50 ms duration) and deviants (8%, 100 ms duration). High resolution MMN ERPs (64 channels) were obtained as the difference between the response to deviants and standards. Cortically constrained LORETA current source density analysis was performed using Curry V4.6. Structural MRIs were used to construct Realistic Head Models and cortical surfaces for each individual for the source analysis. fMRI contrasts between deviant and standard tones can be incorporated as priors into the current source density analysis. A subset of data is presented comparing patients (N=15) to matched controls. A reduction in MMN amplitude was seen in younger patients (<40 yrs) compared to controls, but no difference was present in older participants (>40 yrs). This is consistent with our previous findings. Current source density analysis of the early phase of the MMN suggests that the major cortical generator of the MMN lies in the Superior Temporal Gyrus (STG) as expected. The latter phase of the MMN engages more anterior cortical regions including premotor cortex. Patients show reduced activity in STG but increased activity in right premotor cortex. fMRI analysis revealed differences between patients and controls. Patients have greater activation in the insula and premotor cortex, whereas controls show greater activation in middle frontal gyrus. Overall, the results are consistent with a deficit that onsets early in the disorder, that is associated with substantially reduced processing within auditory cortex, and that leads to different patterns of activation in frontal cortical regions in patients compared to controls.

REDUCED PREFRONTAL FUNCTIONING IN PRESUMED OBLIGATE CARRIERS OF SCHIZOPHRENIA: AN FMRI STUDY

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Background: Numerous cognitive functions sub-served by anatomically and functionally interconnected networks of specialized brain regions are found to be disturbed in schizophrenia. One particularly well-studied function is that of working memory where a network of parietal and frontal areas has been shown to have a different pattern of activation in normal subjects and patients with schizophrenia. This study examined whether dysfunctions in this network reflect transmission of the schizophrenia genotype. Methods: We compared the working memory network of presumed obligate carriers of schizophrenia to that of age and sex-matched healthy subjects using functional magnetic resonance imaging. Results: A network of parietal and frontal areas was activated in both groups, but there was evidence for a reduced response in obligate carriers, compared to healthy subjects, in the anterior cingulate, dorsolateral prefrontal cortex and right cerebellum with normal performance in both groups. Relative to healthy subjects, presumed obligate carriers also showed lack of correlated activity between (a) anterior cingulate and frontal regions, and (b) cerebellum and frontal regions. Conclusions: Our study demonstrates that presumed obligate carriers of schizophrenia exhibit aberrant frontal and cerebellar functioning. These functional abnormalities might be associated with inheritance of alleles modulating functions of the prefrontal-cerebellar networks and involved in transmission of schizophrenia genotype.

TACTILE STIMULATION ELICITS ANOMALOUS DESYNCHRONIZATIONS OF RIGHT CEREBELLUM IN EARLY-ONSET PSYCHOSIS

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It is well-recognized that the cerebellum plays a central role in sensorimotor processing, and recent neuroimaging and lesion-deficit studies have shown it is also involved in more purely cognitive tasks. Several groups have previously demonstrated aberrant cerebellar functioning in adults with schizophrenia, which has lead some to conclude it is the crucial node in an abnormal cortical-cerebellar-thalamic-cortical circuit. In this study, we used somatosensory stimulation to probe cortical-cerebellar circuitry in early-onset psychosis. Ten adolescents with psychosis (schizophrenia: n=4; schizoaffective: n=3; bipolar with psychotic features: n=3) and 10 matched controls completed >1000 trials of unilateral tactile stimulation (200 ms duration; 1.5 s ISI), upon the pad of each index finger, as whole-head magnetoencephalography (MEG) data were acquired. MEG data from each condition were co-registered to the participant's MRI, edited for artifacts, and source-imaged in the time-frequency domain using a linearly-constrained minimum variance beamformer. Following MEG source imaging, each participant's structural MRI was transformed into MNI space to generate a transformation matrix that could be applied to the co-registered functional output images prior to statistical analyses in SPM2. In the early-onset psychosis group, we observed significant 8-16 Hz desynchronizations in the right cerebellum during right finger stimulations from 40-65 ms and 65-90 ms post-stimulus. Interestingly, patients showed a similar decrease in 8-16 Hz activity from 40-65 ms in right cerebellar cortex during left finger stimulation, but this activity dissipated between 65-90 ms post-stimulus. In adolescent controls, stimulation of the left or right finger elicited a significant increase in 8-16 Hz activity from 40-65 ms and 65-90 ms in ipsilateral sensorimotor cortices. However, during the latter time bin, the significant increase in 8-16 Hz activity was more robust for right finger stimulations, stretching further posterior and bilaterally. In conclusion, adolescents with psychosis exhibited abnormal 8-16 Hz activity in sensorimotor cortices ipsilateral to stimulation and right cerebellar areas regardless of hand stimulated. These findings suggest aberrations in right cerebellar circuitry may disrupt connectivity between sensorimotor and cerebellar cortices, potentially degrading inhibitory processes in sensorimotor regions ipsilateral to stimulation.

COMPARING HALLUCINATION-RELATED ACTIVITY BETWEEN HEALTHY SUBJECTS WITH AUDITORY VERBAL HALLUCINATIONS AND SCHIZOPHRENIA PATIENTS; AN FMRI STUDY

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Introduction: Auditory verbal hallucinations (AVH) are highly prevalent in schizophrenia. However, AVH are also found in 5-10% of healthy subjects. It is unclear whether AVH in healthy subjects and in

schizophrenia patients are the same phenomenon. Several differences have consistently been described. For example, AVH in healthy subjects generally have a positive content, in contrast to AVH in schizophrenia patients. It has been suggested that hearing voices in healthy subjects could be viewed as vivid mental imagery, rather than as true AVH. Aim: The aim of the present study is to compare the underlying neurological basis of AVH in healthy subjects to that in schizophrenia patients. Method: 10 healthy subjects who had frequent AVH were included. They were matched to 10 schizophrenia patients who experienced AVH of a similar frequency and duration. To provide contrast, 10 healthy subjects without AVH were asked to imagine a person speaking to him at an emotional tone. All subjects were scanned in a 3T scanner for 45 minutes, during which they indicated by button press when AVH were present. Results: The schizophrenia patients and the healthy hallucinating subjects showed clear hallucination-related activation bilaterally in Wernicke's area and its right-sided homologue and, to a lesser extent, in Broca's area and its contralateral homologue. The activation pattern from the imagery-task in healthy subjects showed predominantly frontal activity, which was lateralized to the left. When contrasted to the imagery-related activation, hallucination-related activation in both schizophrenia patients and healthy subjects showed significantly more activation in the right sided homologue of Wernicke's area (including the primary auditory cortex).Conclusion: There was no difference between hallucination-related activity in healthy subjects and in schizophrenia patients. Both hallucination-related activation patterns could be distinguished from mental imagery, in that the auditory component was more pronounced in hallucination-related activity than in imagery-related activity. These data indicate that AVH in healthy subjects are a similar phenomenon as AVH in schizophrenia, which is distinct from mental imagery.

Differences (ANOVA) Number of significant voxels per ROI, P=0.05

Contrast	Broca's area	Broca's contralateral	Wernicke's area	Wernicke's contralateral
Healthy hallucinations vs imagery	1	1	4	44
Schizophrenic hallucinations vs imagery	0	1	4	43

ALTERED BRAIN ACTIVATION IN ADULTS AT GENETIC RISK FOR BIPOLAR PSYCHOSIS: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF WORKING MEMORY

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Introduction: First-degree relatives of persons with bipolar psychoses carry elevated genetic risk for the illness, and demonstrate cognitive deficits in attention and memory (possible "endophenotypes"). However, little is known about functional magnetic resonance imaging (fMRI) phenotypes. Methods: In this study we evaluated brain activity during working memory (WM). Participants were 17 adult patients with DSM-IV bipolar disorder, 17 non-psychotic, adult offspring of persons with bipolar psychosis, major depression with psychotic features, or schizoaffective disorder, bipolar type and 22 controls. We compared groups while performing a 2-back WM and control CPT-X vigilance task during fMRI. BOLD signal was measured using two whole-brain gradient echo EPI pulse acquisitions on a Siemens 1.5T MR scanner. Data were analyzed using SPM-2. Results: Normal Control (NC) and Bipolar Disorder (BP) groups were comparable on gender, handedness, parental SES, vocabulary and block design scores, but were not comparable on education, WRAT-3 reading score and ethnicity. Average age in NC and BP groups were 39.1 and 41.0 years, respectively ($p<0.02$). NC and BP Offspring (BPoff) groups were comparable on gender, ethnicity, handedness, vocabulary, block-design and reading scores, but were not comparable on parental SES or education. Average age in the BPoff group was 36.3 ($p<0.002$). BP patients and BPoff had comparable CPT-X performance, but significantly reduced 2-back performance compared to controls ($p<0.05$). In comparison to NCs, BP showed significantly less activation in the right medial frontal gryus (BA 9/10; $t=3.48$, $p<0.03$). In comparison to the NC group, BPoff showed significantly greater activation in the right inferior temporal gyrus (BA 38; $t=4.04$) and significantly less activation in the right posterior cingulate ($t=3.10$) (all $p<0.05$). BPoff also showed a trend toward greater activation in the left middle temporal gyrus (BA 37; $t=2.90$), left superior temporal gyrus (BA 22; $t=4.01$) and left putamen ($t=4.01$) (all $p<0.06$). There were no significant differences between BP and BPoff groups in a priori hypothesized regions of interest. Conclusion: These preliminary data suggest that: 1) BPoff and BP patients show different activation patterns than controls and 2) Additional analyses in larger samples adjusting for confounders such as current psychopathology are necessary to clarify the results in the non-psychotic offspring.

HIPPOCAMPAL ACTIVATION PATTERNS DURING NOVELTY DETECTION WITH SUCCESSFUL MEMORY IN SCHIZOPHRENIA

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Several lines of evidence suggest alterations of medial temporal lobe (MTL) function in schizophrenia. The MTL is involved in aspects of learning and memory performance in human cognition. Its alteration in schizophrenia may affect both the performance of these cognitive tasks and their representation during fMRI BOLD acquisitions. Novelty detection is known to activate regions of medial temporal cortex (MTC) with different stimuli showing distinct activation patterns (Preston and Wagner, 2004). We have already shown that the MTL novelty effect to complex scenes is altered in schizophrenia in the anterior, but not the posterior, aspect of the MTL, predominantly in the perirhinal cortex (PRc). Whereas MTL activations to novelty in normal volunteers (NV) were bilateral, with symmetric activations in both anterior and posterior MTL, the schizophrenia volunteers (SV) showed symmetric activations in posterior MTL, but reduced activation in the left anterior MTL. The significance of this difference was confirmed in a subtraction analysis of NV minus SV resulting in a significant area of reduced activation in the anterior aspect of left MTL in SV ({-20,-36,-26} $p=0.005$ uncorrected). Moreover, antipsychotic medication tended to correct this alteration, but did not fully reverse it. We have also examined the novelty effect with successful memory. Subsequent memory of novel scenes was evaluated directly after the fMRI scan by presenting volunteers with a series of 400 scenes (200 previous novel scenes and 200 never seen scenes); they had to identify those that they were certain they had seen before, which they did

not remember and which they were certain they had not seen. Among the normals, volunteers correctly identified 47% of the scenes as previously seen with a 20% false alarm rate, giving a d' of 89%. Among the individuals with schizophrenia, the volunteers correctly identified 35% of the scenes with a false alarm rate of 19%, giving a d' of 70%. An analysis of the successful memory activation results will be presented. These data support our initial hypothesis that in schizophrenia, dysfunction in MTL occurs in anterior regions, even using stimuli which characteristically activate the posterior MTL (e.g. scenes). We are expanding this novelty study by using additional stimuli (Scenes, Faces, and Words); we will compare normal with schizophrenia activation patterns in response to the three stimuli and examine the effects of antipsychotic medication.

INCREASED ACTIVATION OF THE HIPPOCAMPUS DURING AUDITORY GATING IN SCHIZOPHRENIA

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Introduction Auditory gating deficits are one of the most reproducible physiological endophenotypes associated with schizophrenia. Failure to inhibit evoked responses to repeated auditory stimuli may be related to inhibitory dysfunction thought to be central to disease pathophysiology. This fMRI study used a novel paired-tone paradigm to study the functional neuroanatomy of auditory sensory gating deficits in schizophrenia.**Methods** Subjects first performed a hearing test in the scanner to set the volume at 50dB above their hearing threshold. Functional images were acquired with TR=14s (clustered volume acquisition of 2s, plus 12s silence). Subjects attended to a silent movie while passively listening to the auditory task. Clustered volume acquisition was used 1) to allow 8s of silence following scanner noise for neuronal inhibitory circuitry to reset and 2) to allow auditory stimuli to be presented during silence. Eight seconds after scanner noise, subjects heard a pair of tones, separated by 500 ms, either 1) identical in pitch or 2) different in pitch. Two types of 100 ms pure tones were used, a 'high' tone, (2000 Hz), and a 'low' tone (500Hz). The expectation was that the identical tone pairs would elicit more robust sensory gating, compared to the pairs of substantially different pitch. Data from six schizophrenia subjects and six comparison subjects were realigned, normalized to MNI space, smoothed with an 8mm FWHM kernel and evaluated with a random effects analysis in SPM2. **Results** During sensory gating (identical pitch tones vs. different pitch tones) schizophrenia subjects exhibited multiple areas of greater activation than controls. The most robust observed difference was increased activation of the hippocampus. Other regions, including the parietal cortex, primary auditory cortex, thalamus, basal ganglia and prefrontal cortex also showed increased activation in schizophrenia. No areas of decreased activation in schizophrenia subjects were observed. **Conclusions** These data replicate results from our previous study of sensory gating in schizophrenia, in which we observed increased activation of the hippocampus, thalamus and prefrontal cortex. Greater activation observed in additional regions in the present study may reflect increased sensitivity of the new study design, in which stimulus energy was equivalent between conditions. These results support the hypothesis of inhibitory dysfunction of these regions in schizophrenia.

REDUCED WORKING MEMORY CAPACITY IN SCHIZOPHRENIA; AVAILABILITY VERSUS UTILIZATION OF LIMITED RESOURCES

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Practice reduces demands on working memory (WM) capacity (Jansma 2001). The extent to which WM becomes available after practice predicts one's capacity to perform an additional task simultaneously (Ramsey 2004). Schizophrenic patients inefficiently engage WM and thus reach capacity limits with lower task load (Callicott 2000; Manoach 1999; Jansma 2004). In search of a mechanism underlying reduced WM capacity in schizophrenia we tested their ability to release WM resources with practice and their capacity to perform a concurrent task. We hypothesized that patients continue to recruit WM after practice and therefore have less capacity available to simultaneously perform an additional task. First, 18 patients and 18 controls practiced a verbal WM task (WMT). During fMRI they performed WMT with novel stimuli (NT), practiced stimuli (PT) and a baseline (CT) to control for non-WM effects. Next, they performed WMT alone and simultaneously with a second task outside the scanner. The NT-CT contrast identifies WM regions. We compared PT to NT activity in this network to measure availability of capacity. The drop in performance, comparing dual and single task performance, measures one's capacity to perform a concurrent task. Patients showed elevated NT activity in left prefrontal ($F=5.04$; $p=0.03$) and parietal ($F=6.96$; $p=0.01$) cortex, corroborating inefficient WM function in schizophrenia. Practice reduced brain activity and improved performance to the same degree in patients as controls ($F=142.10$; $p<0.001$), indicating reduced demands on WM in both groups. However, patients showed significantly increased performance loss in the dual task ($F=10.53$; $p=0.003$). Practice-induced availability of WM resources was related to dual task capacity in controls ($r2=0.34$; $p<0.02$) but not in patients ($r2=0.03$; $p=0.54$). Thus, patients did not inefficiently recruit WM after practice and should therefore have sufficient capacity for a concurrent task. However greater impact of the second task on patients' performance indicates compromised utilization of their available resources when task load increases. We argue that reduced WM capacity in schizophrenia may be caused by an impairment to engage WM resources when updating information temporarily stored in WM. This impairment could explain inefficient WM recruitment during NT as well as the disproportional performance loss in a dual task, as both tasks involve storage of continuously changing WM content.

HEMISPHERIC DOMINANCE FOR LANGUAGE AND DISORGANIZATION TRAITS IN KLINEFELTER SYNDROME (47,XXY): EVIDENCE FROM FMRI

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De novo occurring genetic variations provide the opportunity to study gene-brain-behavior pathways. In this regard, Klinefelter syndrome, characterised by an XXY chromosomal pattern, is of significant interest. Language disability is a well-described cognitive feature of Klinefelter syndrome. Recently, several traits in the schizophrenia spectrum have been observed in XXY men, which is of interest as language deficits are prominent in schizophrenia. One possible neural mecha-

nism underlying these deficits is abnormal hemispheric specialization for language. As there has been no study of brain activity patterns during language processing in XXY men, we used functional Magnetic Resonance Imaging (fMRI) to reveal the contribution of both hemispheres to language. Also, we aimed to investigate the link between loss of language lateralization and mental functioning in these men, with special interest in those functions relating to organization of thought and language in the schizophrenia spectrum. Hemispheric dominance for language was assessed in 15 XXY men and 14 control men using fMRI. In each hemisphere, the following language regions were analysed: Broca's area, superior temporal gyrus, middle temporal gyrus, angular gyrus and supramarginal gyrus. Psychopathology was measured using the PANSS interview measuring schizophrenia symptoms and a schizotypal personality questionnaire. Compared to controls, the XXY group was characterized by loss of hemispheric specialization for language ($F(1,27)= 7.6$, $p=.01$). Loss of asymmetric processing of language was due to increased activity in the language areas of the right hemisphere ($F(1,27)=6.0$, $p=.02$) rather than reduced activity in the left hemisphere ($F(1,27)=1.7$, $p=.20$). Decreased functional asymmetry was most prominent in the superior temporal gyrus ($F(1,27)=8.2$, $p=.008$) and correlated with disorganized speech and thinking from the schizotypy spectrum ($r=-0.81$, $p=0.003$). These findings provide suggestive evidence for a role of the X chromosome in the development of hemispheric specialization for language, since loss of language lateralization, most prominent in the superior temporal gyrus, was observed in this X chromosomal disorder. A loss in hemispheric specialization for language processing appears to have important consequences for mental functioning, as it was associated with clinical phenomena that are observed in the schizophrenia spectrum pertaining to the organization of thought and language.

BRAIN FUNCTIONING ASSESSED BY FMRI IN SCHIZOPHRENICS AND CONTROLS USING VIRTUAL TESTS OF LEARNING AND MEMORY

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People with schizophrenia are known to have abnormalities in brain anatomy and function. These can be assessed using functional imagining and virtual tasks designed to replicate those used in animal studies, where a variety of methods can be used to confirm behavioral findings. The virtual water maze test is a computerized version of the Morris water task for rodents (Astur et al, 2004), a sensitive indicator of hippocampal functioning in rodents. In the rodent task an animal is placed into a circular pool of opaque water and must escape by climbing onto an invisible (submerged) platform. This form of spatial learning is often referred to as "place learning" and can be contrasted with "cued navigation" in which a single stimulus marks the platform location. These two forms of learning can be dissociated in rats based upon lesion, pharmacological, and behavioral studies. We have completed a pilot study of 16 controls and 16 schizophrenic patients. On two measures of performance using a simplified watermaze task, in which subjects could choose from one of 1 of 4 discrete platform locations, performance differences was small, but schizophrenics still performed more poorly than controls. In healthy subjects, performing a virtual watermaze task involved multiple brain regions, including the SMA, inferior frontal regions, basal ganglia, hippocampus, basal ganglia, parietal cortex and cerebellum. Involvement of these regions is consistent with their known functions, particularly motor planning and execution (SMA, basal ganglia, cerebellum), memory and learning (hippocampus) and understanding spatial relationships (parietal cortex). Compared to control subjects, schizophrenia subjects showed reduced activation in some, but not all of these regions (caudate, hippocampus, parietal cortex), with additional reductions in the DLPFC, thalamus, and primary visual cortex. No group differences in activation were observed in inferior prefrontal cortex and cerebellum. Because of the unexpected lack of primary hippocampal activation in this task, as compared to that in rodents, we have identified another virtual performance task recently shown in normals to produce significant hippocampal activation (Parslow et al, 2004). We will compare findings on these two tests, and also compare performance in schizophrenics vs. controls. Astur, R.S., St. Germain, S., Mathalon, D.H., et al. (2004). Cybertherapy Abstracts Parslow, Rose, Brooks et al, Neuropsycholgy, 18:3, 2004

NEURAL MECHANISMS UNDERLYING PROBABILISTIC CATEGORY LEARNING IN PATIENTS WITH SCHIZOPHRENIA

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Prior imaging studies in healthy young adults have demonstrated concurrent activation of the caudate nucleus and prefrontal (PF) and parietal (PAR) cortices during probabilistic category learning (PCL). Normal function of the striatum is believed to be critical to PCL since illnesses associated with striatal dysfunction, such as Parkinson's and Huntington's diseases, are characterized by impaired PCL rates. Prior studies have shown that while patients with schizophrenia (SC) display impaired accuracy relative to healthy controls (HC) during PCL, their rate of learning (assessed by increased accuracy over time) is similar to HC. The hypothesis of the current study posits that relative to HC, patients with SC would display preserved caudate nucleus and abnormal PF cortex activation during PCL. Forty patients with SC on stable doses of antipsychotic medication and 25 HC were assessed on interleaved blocks of PCL and perceptual-motor control tasks while they underwent BOLD fMRI. Nine patients and no controls were excluded due to excessive motion. Whole brain functional images were acquired using a GE 1.5T scanner with gradient echo EPI (3/1 mm, TR/TE = 3000/50msec). Imaging data were analyzed using SPM2. Relative to HC, patients with SC performed poorly (decreased accuracy). However, their learning rate was similar to HC. Image analysis showed a similar network of brain regions including the PF and PAR cortices and caudate nucleus in both HC and patients with SC. HC displayed greater bilateral caudate and dorsolateral PF cortex activation relative to patients in quartiles 1, 3, and 4. Conversely, patients with SC displayed greater activation of bilateral orbital frontal cortex (BA 11) and left parahippocampal gyrus (BA 34-36) relative to HC in each of the 4 quartiles. Effective connectivity within these regions and the relationship between PCL and brain activation will also be determined. These data are consistent with previous neuroimaging studies of PCL in HC. Differential activation of the caudate nucleus, parahippocampal gyrus, orbital frontal and dorsolateral PF cortices between patients with SC and HC concurrent with a similar learning rate and in conjunction with impaired accuracy in patients may reflect distinct processing strategies or altered neural function

promoting normal learning rate yet decreased accuracy in patients with SC.

CREATING LINGUISTIC CONTEXT: FAILURE TO INTEGRATE CONTEXTUAL INFORMATION IN SCHIZOPHRENIA IS REFLECTED IN REDUCED LEFT TEMPORAL AND FRONTAL LOBE ACTIVITY

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Use of linguistic context is impaired in schizophrenia. It is unclear whether this is a problem of maintenance of context, or if there are difficulties in the initial integration of information to create context. We used a word association task to investigate the brain regions recruited to support the integration of linguistic information and the creation of context. Thirteen healthy and 7 first-episode psychosis (FEP) participants were scanned in a 1.5T magnet while performing a word association task. Participants were asked to say aloud the first word that came to mind upon viewing a set of three words. Each set had a 'target' response which was either a semantic associate of the three stimulus words (semantic condition) or a word that would, along with the stimulus word set, create a single concept (context condition). Spoken responses were recorded online with custom digital recording software incorporating active noise cancellation to reduce scanner noise in the audio recording. Controls performed better (i.e. produced the target response more often) on the semantic condition than the context condition, and performed better than the FEP group for both conditions. The FEP group performed equivalently for both conditions. Controls activated the left middle temporal gyrus (MTG) more during the context condition than the semantic condition (random effects uncorrected $p<.01$). Relative to the FEP group, controls showed increased activation during the context condition in left medial and inferior frontal and middle temporal gyri (random effects uncorrected $p<.01$). The FEP group showed no increase in activation relative to the controls. Previous research suggests sentence level processing, above and beyond single word processing, involves bilateral temporal and prefrontal cortices, but this research has not addressed the creation of context. Controls showed greater left temporal lobe activation during the context condition than the semantic condition, indicating that they were integrating the word triads in the context condition into a single concept and processing them as if they were sentences. The FEP group were impaired in their ability to perform the context task, and showed reduced left frontal and temporal activation relative to controls. The impaired use of linguistic context in schizophrenia may be due to deficits in the initial integration and representation of context information.

NEURAL CORRELATES OF SOURCE MEMORY PERFORMANCE IN SCHIZOPHRENIA

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Background Remembering whether something has occurred can be accomplished based on a feeling of familiarity, while remembering the specific details of an event requires recollection of contextual information. The degree to which these two processes are impaired in patients with schizophrenia remains a matter of some debate. This study sought to tease apart the relative contribution of familiarity-based and source-based memory processes, and examine their neural basis using functional magnetic resonance imaging. Methods 18 medicated outpatients with schizophrenia and 18 controls participated. During encoding, subjects heard 26 words spoken by either a male or female and indicated the gender by button-press. At test, they indicated whether the 52 presented words (26 old and 26 new) were spoken by the male, by the female, or were new. Echoplanar images were acquired using a Siemens 1.5 Tesla scanner and analyzed using FSFast to compare activity during correct recognition of old items (with and without accurate source discrimination) with the correct rejection of new items. Results When compared with the control subjects, patients with schizophrenia recognized fewer of the presented words as being old (Hit Rate: 83% vs. 71%). There were no between-group differences in the response accuracy to new items. Of those words considered to be old (based on a "male" or "female" response), there were no significant between-group differences in source attribution. Based on initial analyses, both groups demonstrated robust activation within left prefrontal cortex (PFC) as well as left, right, and midline parietal regions, during the correct recognition of old items, regardless of source accuracy. In these contrasts, control subjects, but not patients, also demonstrated activation within the right anterolateral PFC, leading to between-group differences within this territory. Conclusions Contrary to our initial hypotheses, patients with schizophrenia demonstrated impaired familiarity-based recognition with intact source discrimination. During the correct recognition of old items both groups demonstrated activation of left prefrontal and parietal areas, regions known to be important in episodic memory. Differences within the right PFC may reflect variation in familiarity-based cerebral activity and/or discrepancies in post-retrieval monitoring. Additional planned analyses will more closely examine these possibilities.

GENDER OF HALLUCINATION-LIKE SPEECH AFFECTS AUDITORY CORTICAL RESPONSE DIFFERENTLY IN BOTH MALE AND FEMALE LISTENERS: A FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) STUDY

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Auditory verbal hallucinations (AVHs) are a key symptom of schizophrenia. The majority of patients affected by AVHs state that they perceive the most prominent voice as male. We aimed, using functional magnetic resonance imaging (fMRI), to test the hypothesis that male and female voices activate distinct but different regions of the brain. Twenty-four (12 male) healthy right-handed volunteers were studied. The stimuli used were emotionally neutral sentences spoken by male (50%) and female speakers. A total of 12 speakers were used. Half of the stimuli had their fundamental frequency pitch-shifted to the midpoint between the male and female average, whilst the other half remained at their original pitch. The pitch-shifted stimuli had all other spectral components preserved, allowing them to remain "gender-apparent". Functional MRI was performed on a 3T system at Sheffield University. In a sparse design (72 time-points, TR=12,500ms; 35×4mm slices; matrix=128×128, field of view=230mm), stimuli were presented in 48 of the time-points, with the remaining 24 being silent periods. Time-points were arranged in a pseudorandom order. In a 2 alternative forced choice identification

paradigm, subjects were asked to assign gender to each of the speakers they heard by pressing one of 2 pre-designated buttons. Images were analysed using statistical parametric mapping in SPM2. Female voices, when compared to male voices, were found to cause increased activation in the left superior temporal gyrus (Talairach co-ordinates x=-40, y= -33, z=3; peak t=6.94; p≤0.001 corrected for multiple comparisons in the whole brain volume). This could not be explained by simple pitch-perception, as the activation observed was conjointly activated by both original-pitch and pitch-matched stimuli. At the same statistical threshold, there were no auditory cortical foci more activated by male than female voices. The findings are supportive of the idea that the greater acoustical complexity of the female voice causes greater auditory activation. The male voice can therefore be thought of as the "default" voice, thus explaining its predominance in AVHs.

CORRELATIONS BETWEEN FMRI ACTIVATION AND POSITIVE SYMPTOM SEVERITY IN SUBJECTS AT HIGH GENETIC RISK OF SCHIZOPHRENIA

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As part of the Edinburgh High Risk Study young adults at high genetic risk of schizophrenia were recruited to examine the relationship between disordered neuronal activity and the development of clinical features of the illness. Subjects underwent two imaging paradigms; the Hayling sentence completion task (n=89), and a verbal memory task (n=87), the latter comprising encoding (word classification) and retrieval (old word/new word judgment). Symptom severity was assessed using the positive and negative symptom scale (PANSS). Images were pre-processed and analysed using SPM2. Contrasts were constructed for sentence completion versus rest (Hayling), a parametric contrast examining increasing activation with increasing sentence difficulty (Hayling), word classification versus baseline (encoding), correct recognition, and correct rejection versus baseline (retrieval). For the second level analysis the total score for positive symptoms was entered into a simple regression analysis. Scores for delusions, hallucinations, and persecution/suspiciousness were entered into a separate multiple regression analysis. Mean scores for the total positive score, delusions, hallucinations, and suspiciousness were 8.39 (sd 2.40), 1.51 (sd 0.85), 1.31 (sd 0.67) and 1.28 (sd 0.71) respectively. No significant correlations were seen for the total positive symptom score for any of the contrasts examined. Task specific associations were however seen in the anterior middle temporal gyrus in relation to hallucinations during the language task, and in the medial temporal lobe in association with delusions and suspiciousness in the memory task. Cerebellar activation was associated with delusions and suspiciousness across both the language task and the encoding phase of the memory task. Overall these results are consistent with the existing literature on the established illness implicating temporal cortex involvement in auditory hallucinations and limbic regions with positive psychotic symptoms, and highlight the potential role of the cerebellum in the formation of delusions. That the current results are seen in un-medicated high risk subjects indicates these associations are not specific to the established illness and are not related to medication effects. This work was funded by an MRC programme grant. HCW and SML are funded by the Sackler Foundation.

NEURAL CORRELATES OF EPISODIC ENCODING AND RECOGNITION OF UNFAMILIAR FACES IN UNMEDICATED PATIENTS DURING AN ACUTE EPISODE OF SCHIZOPHRENIA

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Event-related functional magnetic resonance imaging was used to study regional cerebral activation in 20 right-handed patients (14 males/6females) with an acute episode of schizophrenia and in a healthy control group matched for gender, age, and education, during the performance of the faces subtest of Warrington's Recognition Memory Test. During the encoding task, 40 photographs of unfamiliar faces (activation condition) and 40 scrambled images as a reference condition were presented in a pseudo-random order. Subjects were instructed to remember the faces for the subsequent recognition memory task, consisting of the 40 photographs presented during the encoding task, 40 new faces as well as 40 scrambled images. Consistent with previous findings, performance accuracy was significantly impaired in patients. Schizophrenia patients showed reduced activation in the left supramarginal gyrus compared to controls during face encoding. During correct recognition of previously presented faces, reduced activation was found in the patients' sensorimotor, anterior cingulate, and supramarginal cortices, whereas during correct rejection of distractor faces, reduced activation was found in the patients' sensorimotor, anterior cingulate, supramarginal, and middle temporal cortices. In summary, our results suggest that schizophrenia is characterized by a specific deficit of episodic encoding and recognition of unfamiliar faces, which is associated with impaired function of the anterior cingulate, sensorimotor, middle temporal, and parietal cortices. Moreover, these deficits in processing facial information may be related to the misinterpretation of social interactions or the flat effect commonly found in schizophrenia.

ABNORMAL STEADY-STATE CORTICAL RESPONSES IN ADOLESCENTS WITH PSYCHOSIS: EVIDENCE FROM MEG

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Gamma oscillations have been implicated in the temporal binding of stimulus properties across distinct cortical areas, as well as other forms of complex information processing. Several groups have reported gamma frequency-range abnormalities in schizophrenic adults, but the developmental trajectory of such observations has yet to be investigated. In the current study, we examined auditory gamma responses in adolescents with psychosis. Ten adolescent controls and 10 matched psychosis outpatients listened to

monaurally presented 40 Hz click trains. The order of ear stimulated was counterbalanced and each participant completed >200 trials (duration=500 ms; ISI=1.5 s) per ear, as whole-head magnetoencephalography data were acquired. These data were coregistered to the participant's MRI, inspected for artifacts, time-domain averaged, and bandpass filtered around the 40 Hz steady-state response. The neural generators of contralateral 40 Hz responses were then modeled with equivalent current dipoles. For each subject, these dipoles (1 per condition) were combined into a single two-source model, which was used to calculate an inverse spatial filter for deriving source waveforms for each trial of the raw MEG time series. To estimate spectral power density for contra- and ipsilateral generators, we performed time-frequency decomposition of these single-trial source waveforms using complex demodulation. Our results indicated the main effect of ear stimulated was not significant, but that both hemisphere and diagnosis effects were significant. The hemisphere effect showed greater 40 Hz power for right hemispheric generators across groups, whereas the effect of diagnosis indicated significantly reduced 40 Hz power in patients. Our three-way interaction effect also approached significance (p=0.08), and further analyses indicated the overall effect of ear stimulated on 40 Hz power differences was significantly reduced in early-onset psychosis patients. Lastly, we detected a selective increase in left-hemispheric 30 Hz power for adolescent patients relative to controls. These adolescents with early-onset psychosis exhibited significantly reduced 40 Hz activity, along with anomalous ear-of-stimulation effects. Thus, high-frequency abnormalities likely emerge early in the disease process, and aberrations in early auditory pathways may contribute to observed reductions in gamma oscillations due to altered connectivity preceding auditory cortical areas.

AFFECT RECOGNITION IN SCHIZOPHRENIA: IMPAIRMENTS AND TREATMENT APPROACHES

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Impairments in affect recognition are well known in schizophrenia. Such impairments are known to be a traitlike characteristic in schizophrenia mostly unaffected by traditional treatment. Moreover they seem to play a crucial role in patients' poor social functioning. The present study should contribute to the still open question of treatment options for these impairments. A special Training of Affect Recognition (TAR) was evaluated using a pre-post-control group design with three groups of about n=25 partly remitted schizophrenia patients each. To control for nonspecific effects of implicit cognitive training, TAR was compared with a Cognitive Remediation Training (CRT) aiming at improvement of basic neurocognitive functioning. To control for nonspecific effects the two active training groups were compared with a control group without additional training (CG). Patients under TAR showed an improvement in facial affect recognition, with recognition performance after training approaching the level of healthy controls from former studies. Patients under CRT and those without training (CG) did not show improvements in affect recognition, though patients under CRT improved in some memory functions. Improvements in disturbed facial affect recognition in schizophrenia patients is not obtainable with a traditional cognitive remediation program like CRT, but needs a functional specific training like the newly developed TAR.

INTEGRATED ERP AND FMRI ANALYSIS REVEALS ABNORMAL NEUROPHYSIOLOGICAL RESPONSES TO AN AUDITORY ODDBALL TASK IN SCHIZOPHRENIA

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Both evoked response potentials (ERPs) and functional MRI activation patterns are abnormal in schizophrenia patients performing "oddball" tasks. Target detection engages "top-down" cognitive functions known to be impaired in affected individuals, such as working memory and sustained attention, while novel distractors induce automatic "bottom-up" orienting processes thought to be hypersensitive in schizophrenia. Given their complementary advantages in temporal and spatial resolution, combined ERP and fMRI analysis may yield greater understanding of underlying neural deficits. Here we integrate both analyses within the same cohort of patients with schizophrenia and healthy controls. Subjects performed identical auditory oddball tasks in separate EEG and fMRI sessions. Task stimuli were 140 standard tones (1000 Hz), with 30 target tones (2000 Hz) and 30 novel recognizable environmental sounds, in pseudorandom sequence. 4T fMRI BOLD data and EEG data were preprocessed and analyzed with standard techniques. Analyzing novel and target conditions separately, BOLD responses within a priori regions of interest were correlated across subjects with P3 ERP amplitudes (Pz for targets, Cz for distractors). Exploratory regression analysis identified other brain regions whose BOLD activation to target or novel stimuli covaried with P3 ERP amplitude. Our results demonstrate that both patients and controls activate bilateral temporal cortex and inferior parietal regions to targets, while activity in basal ganglia and thalamus is significant only in controls. To novel distractors, both groups activate bilateral temporal regions similar to those activated by targets. In contrast to the target response, novels induce little parietal activation, but much greater frontal activation. Again, controls but not patients activate bilateral thalamus and basal ganglia; controls also exhibit stronger frontal lobe responses. P3 ERP magnitude to both novel and target stimuli was significantly decreased in the schizophrenia group. Regional fMRI-ERP correlation patterns were distinct for target and novel conditions, and for the two subject groups, and were found both inside and outside the areas showing significant task-related fMRI activity. Group differences in fMRI-ERP correlations may reflect both underactivation and compensatory overactivation in schizophrenia, as well as reduced differentiation between novel and target conditions in the patient group.

AN FMRI INVESTIGATION OF PROCEDURAL LEARNING IN UNAFFECTED SIBLINGS OF INDIVIDUALS WITH SCHIZOPHRENIA

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The search for candidate schizophrenia susceptibility genes may be aided by the identification of endophenotypes related to the disorder that have more straightforward genotype-phenotype relationships than complex behavioral symptoms or subjective diagnostic categorizations. Prior functional Magnetic Resonance Imaging (fMRI) investigations of procedural learning in patients with schizophrenia identified reduced activity in the frontal and parietal cortices and

basal ganglia during performance of the serial reaction time (SRT) task suggesting that abnormal function of these regions might be an endophenotype for schizophrenia. To determine if the abnormal responses detected in patients is related to genetic susceptibility for schizophrenia, 12 unaffected siblings of patients and 15 controls underwent fMRI during performance of the SRT task. The results confirmed that unaffected siblings' performance on the SRT task was normal but cerebral activity was abnormal. Unaffected siblings demonstrated less activity in regions of the frontal and parietal lobes and basal ganglia during procedural learning, compared to the normal controls. The findings support previous investigations suggesting that altered cerebral neurophysiology during performance of cognitive tasks may be a useful endophenotype of schizophrenia. However, further criteria, especially with respect to the heritability of SRT performance and the associated cerebral neurophysiological response to the task, remain to be fulfilled.

DLPFC MEDIATED DEFICITS IN CONTEXT PROCESSING IN FIRST EPISODE SCHIZOPHRENIA

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Background: The identification of the neural mechanisms underlying higher order cognitive deficits in schizophrenia remains a central goal in our efforts to develop effective treatments for this debilitation condition. Generalized deficits and effects of illness chronicity present significant challenges to efforts to identify specific etiologic factors. Here we present an event related fMRI study of first episode schizophrenia subjects (SZ) and controls (C) while they undergo testing with the AX-CPT task, a paradigm that reliably identifies context processing deficits in schizophrenia. Methods: 25 subjects who have been diagnosed with schizophrenia within the first year of illness onset and 25 demographically matched healthy control subjects completed this study. Subjects engaged in the AX-CPT task while undergoing fMRI in a Siemens 3T TRIO scanner. FMRI data processing followed standard procedures and included spatial normalization to an MNI template. The main fMRI dependent measure was task related changes in the BOLD signal in the DLPFC. Results: In scanner performance was consistent with previous studies and showed a differential deficit in the SZ group. In the BX condition, which requires the highest degree of context processing, SZ accuracy was significantly worse than C, $P < 0.01$. In the AY condition, which requires minimal context processing, SZ performance on accuracy was similar to that of C, $P > 0.3$. Analysis of the DLPFC ROI BOLD time series revealed a significant group x condition x scan interaction, $P < 0.05$, such that the SZ group was unable to engage the DLPFC during context processing. T-tests revealed that in the C group, DLPFC activity during B cue processing was significantly elevated compared to A cue, $P < 0.05$. In the SZ group, we did not observe this engagement of DLPFC activity during context processing. Conclusions: These results replicate prior studies showing DLPFC mediated context processing deficits early in the coarse of illness in schizophrenia. These findings strongly imply that these deficits are a core aspect of this illness and not the results of illness duration or treatment. The relationship between our fMRI results and other measures, such as prefrontal induced gamma band activity, as well as clinical measures, will be discussed.

13. Neuroimaging, Neurochemical

CORTICAL DOPAMINERGIC TRANSMISSION AT THE D1 RECEPTOR: RELATIONSHIP TO NEGATIVE SYMPTOMS

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Multiple neurotransmitter systems have been implicated in the pathophysiology of negative symptoms in schizophrenia. Among those, a deficit in cortical dopamine transmission has received indirect support from postmortem as well as imaging studies. We have used imaging of the D1 receptor with Positron Emission Tomography (PET) and the radiotracer [11C]NNC112 as an index of dopamine transmission in the cortex in patients with schizophrenia (n=28) and matched controls (n=28). [11C]NNC 112 specific to nonspecific equilibrium partition coefficient, V3", was derived with kinetic analysis using the arterial input function. No group differences were noted in plasma clearance, plasma free fraction, or nonspecific distribution volume of [11C]NNC 112. We observed an increase in receptor levels in the dorso-lateral-prefrontal cortex (DLPFC) and a correlation between D1 levels and two measures of cortical dysfunction in schizophrenia: deficits on working memory performance (r2= 0.28, p=0.006) measured with the n back task, as well as severity of negative symptoms (r2= 0.15,p=0.04) measured with the negative symptoms subscale of the Positive and Negative Symptoms Scale of Psychopathology (PANSS). No such correlation was found between D1 and severity of positive symptoms (r2= 0.02,p>0.05). To further evaluate if the increase in D1 may reflect chronic low dopamine tone, we examined the effect of the Cathecol-O-Methyl-Transferase (COMT) genotype on D1 binding. We obtained COMT genotypes in healthy controls (n=21) who had undergone PET imaging with [11C]NNC112. V3" was increased across frontal cortical regions in the val/val (n=6) group compared to the met/val and met/met group (n=15). No differences were detected in striatal regions. These results support a prominent role for COMT in determining dopamine tone in cortical but not striatal regions. Cortical D1 receptor elevations in the val/val group might represent an upregulation to compensate for lower levels of dopamine and support the model of cortical dopamine deficit in schizophrenia mediating negative symptoms and cognitive impairment. These studies suggest that D1 can be used as a biomarker for cortical dopamine transmission to guide treatment for these symptoms, by selecting the patients to treat and developing targeted therapeutic approaches aiming at enhancing cortical dopamine transmission. Supported by NIMH and Lieber Center for Schizophrenia Research.

CROSS-SENSITIZATION BETWEEN STIMULANTS AND STRESS IN HUMANS: BEHAVIORAL AND NEUROCHEMICAL CORRELATES

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Dysregulation of the stress response is a potential risk factor in the development and/or relapse of dopamine (DA) related human disorders, including psychosis. In humans, the underlying neural events that may result in a hypersensitive response to stressors are unknown. One proposed mechanism is sensitization, whereby repeated exposure to stressful events or psychostimulant drugs (PS) progresses into increased stress (or drug)-associated neurochemical activation. A key demonstration is that neuronal sensitization to PS is subject to cross-sensitization with stress in rodents (Piazza & Le Moal, 1996). We previously reported increased d-amphetamine (d-Amph)-stimulated DA release in healthy volunteers who underwent a sub-chronic d-Amph regimen, an observation interpreted as evidence of neurochemical sensitization (Boileau et al., 2006). The aim of the present study was to use the PET [11C]Raclopride method to test the hypothesis that repeated exposure to d-amphetamine, at the same dosing regimen previously shown to produce DA sensitization, would result in an enhanced DA response to a mild stressor. Six healthy male volunteers (mean age ± SD = 23.3 ± 4.9 y, TPQ high novelty seeking score: 22.3 ± 1.5) underwent 3 PET sessions. [11C]Raclopride binding to D2/3 receptors, an index of striatal synaptic DA concentration, was measured during an unstressful version of the Trier Mental Challenge Task (day 0), and during two stressful versions: prior to (day 1) and 14 days after (day 21) the repeated d-Amph regimen (3 x 0.3 mg/kg p.o. in the same test environment, on three separate days, every other day). Mood and physiological measurements were recorded at regular intervals throughout each session. Prior to sensitization, exposure to the mental challenge stress elicited the expected behavioral and physiological responses (increased heart rate, prolactin, anxiety, anger and lowered self-confidence) ($p \leq 0.05$), but failed to demonstrate a measurable change in [11C]Raclopride receptor occupancy. Conversely, stress-related DA release was detected upon re-exposure to stress 14 days after administration of the last of the 3 doses of stimulants, (right ventral striatum: t=4.85; right putamen: t=5.67), an observation consistent with cross-sensitization between stimulants and stress. Though preliminary, those results suggest increased DA responsiveness to stress in young adults previously exposed to stimulants.

GLUTAMATERGIC DYSFUNCTION IN EARLY SCHIZOPHRENIA: 4TESLA H-MRS SINGLE-VOXEL AND PROTON-ECHO PLANAR SPECTROSCOPIC IMAGING(PEPSI) STUDIES

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A glutamatergic excitotoxic effect secondary to NMDA hypofunction has been postulated in schizophrenia. The purpose of these studies was to examine glutamate-related neuronal dysfunction early in schizophrenia. In Study 1, fifteen patients with a history of minimal medication exposure (<3 wks lifetime), were scanned before antipsychotic drugs and then following treatment at 1, 6 and 12 months. Three voxels were acquired at 4T with STEAM (TR 2000ms, TE 20ms, 256 water-suppressed and 16 water-unsuppressed averages)from: ant.cingulate (AC; 8cc),thalamus (1.5cc) and prefrontal white matter(1.5cc). Ten healthy volunteers were scanned once. In Study 2, fifteen patients and 15 controls were scanned once with PEPSI at 4T (TE 15 ms, TR 2s, 32x32 spatial matrix, FOV 256 mm, slice thickness 15 mm, 8 water-suppressed, 1 non-water suppressed averages)from a supraventricular axial tissue slab (over 100, 1cc voxels). Results

from Study 1 included significant group by region interactions for NAA and glutamine/glutamate ratio(Gln/Glu) at baseline (F(2, 33)=3.48, p=0.04 and F(2, 33)=3.44, p=0.04, respectively). Hence, before treatment schizophrenia patients had lower NAA than controls (10.48 mM,SD=2.8 vs 13.31, SD=1.13, respectively; t(1,19)=-2.53, p=0.02)and increased Gln/Glu ratio(0.7, SD=0.23 vs 0.5, SD=0.08, respectively; t(1,19)=2.82, p=0.01), in the AC. None of the other metabolites differed between the groups in the other regions.Follow-up scans in the schizophrenia group failed to detect significant changes over time with treatment in any of the metabolites studied (region by visit interactions with p's 0.31 to 0.93). These findings suggest that AC neuronal dysfunction (NAA is a marker of neuronal viability) is apparent early in the illness, consistent with a recent metanalysis(Steen, 2005). Because we used a very short TE (20 ms), this result is relatively insensitive to possible changes in T2.Furthermore, increased AC Gln/Glu suggests dysfunction in the glutamate neurotrasmitter cycle (Gln is the glial metabolite of synaptic Glu), consistent with elevated Gln/Glu ratio found in cerebrospinal fluid of medication-naive schizophrenia (Hashimoto, 2005). High-field H-MRS permits the assessment of glutamate mediated excitotoxicity as postulated by the NMDA-hypofunction model of schizophrenia.

EXTRASTRIATAL DOPAMINE D2 RECEPTORS IN NEUROLEPTIC-NAïVE FIRST-EPISODE SCHIZOPHRENIC PATIENTS PREDICTS TREATMENT OUTCOME

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We have previously reported highly significant correlations between frontal D2/3-receptor binding potentials (BP) and positive schizophrenic symptoms (Glenthoj et al. 2006). The aim of the present study was to examine the relation of regional D2/3-receptor activity to treatment outcome.Twenty-three neuroleptic-naïve schizophrenic patients were examined with psychopathological ratings and single-photon emission computerized tomography (SPECT) using the D2/3-receptor ligand [123I]epidepride before and after 3 months of treatment with either risperidone or the typical antipsychotic drug, zuclopenthixol. Given, very uniform occupancies in the zuclopenthixol group we did not expect - and did not find - significant correlations between extrastriatal D2/3-receptors and treatment outcome in this group. Concerning the risperidone group and the total group of patients, the data confirmed that frontal D2/3-receptor BP in the neuroleptic-naïve state predicted treatment outcome with regard to positive schizophrenic symptoms ($p<0.01$). Additionally, we found that high D2/3-receptor BP values in the left thalamus predicted treatment outcome with regard to negative symptoms. The data further confirmed correlations between blockade of D2/3-receptors in the left thalamus and effect on positive symptoms and (negative) correlations between treatment-effect on negative symptoms and blockade of frontal as well as thalamic D2/3-receptors. The results strongly support that schizophrenic symptomathology is influenced by frontal and thalamic D2/3-receptor activity and that antipsychotic drugs not only exerts their therapeutic actions via D2 blockade in the striatum but also via frontal and thalamic D2/3-receptors.
Reference: Glenthoj BY, Mackeprang T, Svarer C, Rasmussen H, Pinborg L, Friberg L, Baaré W, Hemmingsen R, Videbæk C. Frontal dopamine D2/3 receptor binding in drug-naïve first-episode schizophrenic patients correlates with positive psychotic symptoms and gender. Biological Psychiatry 2006; in press. Mar 30; [Epub ahead of print]. PMID: 16784819 [PubMed - as supplied by publisher].

IMAGING THE D2/D3 RECEPTORS IN HUMANS USING AN AGONIST VS. AN ANTAGONIST RADIOTRACER: IMPLICATIONS FOR PSYCHOSIS

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The dopamine D2/3 receptors exist in two states –a state which has a high affinity for dopamine (D2/3-high), is linked to second messenger systems and is responsible for its functional effects; and a state which has a low affinity for dopamine, is not linked to second messenger systems and is functionally inert. The two states are interconvertible, but, it is the D2/3-high that eventually mediates dopamine action. An increase of the proportion of D2/3-high is thought to be a basis for the hyperdopaminergic state observed in psychosis. It has not been possible to measure the D2/3-high in patients because all previous studies have used antagonist radiotracers (e.g. [11C]raclopride) which cannot differentiate the high and low states. Recently, [11C]-(+)-PHNO (PHNO) a D2/D3 agonist has been standardized as a ligand in humans. The aim of this study is to compare the binding profile and distribution of PHNO vs. [11C]raclopride in healthy controls. This aim will be followed by a direct comparison of the D2/3-high in schizophrenic drug-free patients. PET-scans with PHNO and [11C]raclopride has been performed in twelve healthy controls. Time activity curves from the caudate, putamen ventral striatum (VS), globus pallidum (GP) and substantia nigra (SN) were obtained and the Binding Potentials (BP) were estimated using the SRTM with the cerebellum as reference. The BP values for PHNO ranged from 2.15 to 3.43 with a significant difference between regions ($F(4,55)=7.9$. $p<0.001$). The pairwise comparisons showed that VS and GP (mean±SE; 3.43±0.9 and 3.36±1.0) were higher than the caudate and SN (2.15±0.4 and 1.96±1.1). The BP for [11C]raclopride ranged from 1.88 to 4.32 with a significant difference between regions ($F(4,55)=103.2$ $p<0.001$). The [11C]raclopride's BPs were higher in the putamen (4.32±0.7) than in all the regions; the caudate and VS were higher than GP and SN (3.38±0.6, 3.36±0.5 vs. 1.88±0.4, 0.5±0.02); and the GP were higher than the SN. Our results in healthy controls show a preferential distribution of PHNO for the D3-rich limbic areas. On the other hand, [11C]raclopride shows a preference distribution in D2-rich motor areas. Thus, PHNO provides the first opportunity to examine the high states of the D2/3 receptors in schizophrenia, and will provide a special window ito the D3 receptors in the limbic regions. Currently, clinical investigations are in progress with drug-free schizophrenic patients and it will be discussed into this work.

SCHIZOPHRENIA IS ASSOCIATED WITH INCREASED SYNAPTIC DOPAMINE IN ASSOCIATIVE RATHER THAN LIMBIC REGIONS OF THE STRIATUM: IMPLICATIONS FOR MECHANISM OF ACTION OF ANTIPSYCHOTIC DRUGS

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Receptor imaging studies have over the past decade documented that schizophrenia is associated with increased dopamine (DA) function in the striatum. Previous studies were limited by measurement of DA function at the level of the striatum as a whole. The striatum is divided into limbic, associative and sensorimotor subregions, based on the origin of cortical projections. PET imaging with the ECAT HR+ camera permits resolution of the radioactive signal generated in these striatal subregions. The goal of this study was to apply the high resolution of this camera to determine the striatal subregional localization of DA hyperfunction in schizophrenia. In this study, we scanned 18 untreated patients with schizophrenia and 18 matched healthy control subjects. PET scans were performed using a bolus-plus-constant-infusion paradigm with [^{11}C]raclopride. Scans were acquired at baseline and again 48 hours later, following acute DA depletion induced by alpha-methyl-paratyrosine (AMPT), a reversible inhibitor of DA synthesis. The difference in D_2 receptor availability between the baseline and DA depleted scans provided an index of occupancy of D_2 receptors by DA at baseline. Five regions of interest were analyzed: ventral striatum (VST), precommissural dorsal caudate (preDCA), precommissural dorsal putamen (preDPU), postcommissural caudate (postCA) and postcommissural putamen (postPU). AMPT-induced increase in D_2 receptor availability was significantly higher in schizophrenia (SCH) compared to controls (CTR) in preDCA (SCH: 15.1 ± 8.1%; CTR: 9.0 ± 7.6%, p = 0.03), but not in the VST (SCH: 11.5 ± 9.7%; CTR: 9.8 ± 6.7%, ns) nor in other striatal subregions. This result suggests that schizophrenia is associated with increased D_2 receptor transmission in the preDCA, the area of the striatum that receives the most dense projections from the dorsolateral prefrontal cortex (DLPFC). These findings 1) question the widely accepted view that the therapeutic effects of antipsychotic drugs derive from D_2 receptor blockade in the limbic or ventral striatum while D_2 receptor blockade in the dorsal striatum is responsible only for motor side effects; and 2) suggest that while subcortical DA dysregulation in schizophrenia has historically been conceptualized as a consequence of DLPFC dysfunction, subcortical DA transmission abnormalities might in turn negatively impact DLPFC function, by impairing glutamate-mediated information flow in DPLFC-preDCA-thalamic-DLPFC loops.

DISCOVERING SELECTIVE SMALL-MOLECULE MODIFIERS OF NEUREGULIN-SIGNALING PATHWAY

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The genes encoding neuregulin1 (Nrg1) and its receptor, ErbB4, have been suggested to be risk genes for schizophrenia by a number of reports. Biological evidence consolidating the relationship between Nrg1-ErbB4 signaling and schizophrenia is also suggestive. Neither the genetics nor the biology is certain. Finding selective modulators of Nrg1-ErbB4 signaling pathway may be an important approach to further elucidate the relationship of this signaling system to the human disease. We have generated a PC12 cell line which co-expresses the ErbB4 receptor and green fluorescent protein (GFP). The cell line, allows us to quantify neurite outgrowth in a live cell imaging assay in which measurements are made on the entire population of cells in wells of a 384-well plate using automated microscopy. We have shown that we can quantify neurite outgrowth as a function of Nrg1 concentration down to low nano-gram/ml levels. This cell model provides an opportunity to characterize the neurotrophic effects of Nrg1-ErbB4 signaling pathway and compare these effects to those of the NGF-TrkA signaling pathway, which already exist and are functional in the PC12 system. Although Nrg1 and NGF both stimulate the differentiation of PC12-ErbB4-GFP cells, NGF's effect is slower than Nrg1 especially in the first two days after treatment. In addition, co-treatment of NGF dramatically increases final length of neurites in the presence of saturating amounts of Nrg1. Nrg1 treated cells also exhibits a distinct phosphor-tyrosine signature from cells treated with NGF. Therefore, it is possible to begin to define the signaling pathways that each protein uses .to produce its biological effects. We have used this screening system to screen for small molecules that would selectively inhibit or potentiate the effects of Nrg1 or NGF. We have identified several classes of compounds that can specifically affect the Nrg1-ErbB4 signaling pathway. These compounds will be extremely useful in studying the biology of Nrg1 and in potentially developing novel treatment of schizophrenia. Progress in this system will be described.

PROTON MRS IN TWINS DISCORDANT FOR SCHIZOPHRENIA

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The heritability of structural cerebral changes associated with schizophrenia is well established. However, the heritability of specific metabolite variations in schizophrenia has not been thoroughly investigated. Proton (1H) magnetic resonance spectroscopy (MRS) allows *in vivo* measurement of metabolite concentrations in specific cerebral regions of interest. Changes in metabolites such as N-acetylaspartate (NAA), creatine, and choline have already been shown in schizophrenia using MRS. This study utilized MRS in a twin sample to determine if changes in GABA, glutamate, and NAA are shared by schizophrenia patients and their co-twins compared with controls. Two monozygotic and twelve dizygotic twin pairs discordant for schizophrenia from a Finnish birth cohort were compared with four monozygotic and nine dizygotic healthy comparison twin pairs without a family history of psychosis. 3T MRS spectra were obtained in three regions of interest (frontal white matter, frontal gray matter, and hippocampus) then analyzed using LCModel. Overall, NAA concentrations were significantly higher in both frontal gray matter and hippocampus compared to frontal white matter, and both probands and their co-twins had a significantly higher concentration of NAA compared with controls, effects that were especially pronounced in the hippocampus. GABA concentration was significantly greater in frontal gray matter compared with frontal white matter and significantly greater in both co-twins and probands compared with controls. Glutamate concentration was significantly greater in frontal gray matter and hippocampus compared with frontal white matter and significantly lower in probands and their co-twins compared with

controls. Probands and co-twins did not differ significantly on any of these metabolites. This pattern suggests that MRS is sensitive to inherited changes in neurochemical metabolites among schizophrenia patients and their co-twins and encourages search for susceptibility genes that contribute to these variations.

SELECTIVE INCREASE OF THE AGONIST RADIOTRACER [11C]-(+)-PHNO UPTAKE IN D3 RICH REGIONS OF CHRONICALLY TREATED SCHIZOPHRENIC PATIENTS

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Current studies of the in vivo occupancy of antipsychotics have all used antagonist radioligands (e.g. [11C]raclopride, [11C]fallypride). These radioligands do not differentiate between the high-affinity and low-affinity states of the D2/3 receptor, and lack of any selectivity between D2 and D3. [11C]-(+)-PHNO is an agonist radioligand developed to bind to the high-affinity state of the D2/3 receptor; and as compared to the previous antagonist radioligands shows preferential selectivity for D3 over D2. The aim of this study was to compare the binding profile (% occupancy) of [11C]-(+)-PHNO vs. [11C]raclopride in schizophrenic patients chronically treated with clozapine, risperidone or olanzapine. This cross-sectional study recruited schizophrenic patients treated with stable dosages of clozapine (n=5) (300-500 mg/day), olanzapine (n=7) (5-27.5 mg/day) or risperidone (n=4) (0.75-6 mg/day). Each patient had two PET scans, [11C]-(+)-PHNO and [11C]raclopride, performed on two separate days at the time of expected peak level. Receptor occupancies were calculated using a healthy controls dataset of sixteen matched controls. The MRI-co-registered regions-of-interest were drawn on the caudate, putamen, ventral striatum (VS), globus pallidum (GP) and substantia nigra (SN). We found that the occupancies were higher with [11C]raclopride than with [11C]-(+)-PHNO in the striatum and mesencephalon with every antipsychotic ($F(1,146)=73.6$, $p<0.001$). The most striking results were in the D3 rich regions (GP and SN) wherein [11C]-raclopride reported occupancies in the range of 30-80%, but, the binding potentials (BP) as measured by [11C]-(+)-PHNO were higher (negative occupancies) in schizophrenic patients, despite drug treatment. The occupancies were in the range of -50% to -140% and -40% to -230% in the GP and SN, respectively. The differential findings between [11C]raclopride and [11C]-(+)-PHNO raise two very interesting possibilities – either schizophrenia is associated with an increase in high-affinity states or D3 receptors in the pallidal/mesencephalic regions; or, chronic antipsychotic treatment induces compensatory upregulation in the high affinity states of D2/3 or D3 in these regions. Studies are underway to differentiate between these possibilities.

CANNABIS INCREASES D2 RECEPTORS IN THE STRIATUM

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There is increasing evidence that cannabis is a risk factor for schizophrenia (1). A metanalysis of five epidemiological studies shows that adolescent cannabis misuse doubles the risk of subsequent schizophrenia (2). It has been hypothesized that the psychotogenic properties of cannabis are mediated via altered dopamine signalling (1). In support, susceptibility to cannabis is modified by a functional polymorphism in the gene for the enzyme catechol-O-methyltransferase, which metabolises dopamine (3). We investigated the effect of previous cannabis exposure on striatal D2 receptor populations in healthy controls (n=19) and in first episode, un-medicated schizophrenic subjects (n=17) using 123I-iodobenzamide single photon emission tomography (123I-IBZM SPET). Previous cannabis exposure was ascertained by structured questionnaire at the time of recruitment. Evidence of primary substance use disorder, or chronic use of psychoactive substances clearly associated with psychotic episodes were exclusion criteria. The patient group met DSM-3R criteria (American Psychiatric Association 1987) for a diagnosis of schizophrenia. Images were acquired with a SME 810 SPET brain scanner as previously described (4). In a multiway ANOVA (GLM2), age and previous cannabis use were related to striatal D2 receptor binding. In the cannabis exposed group (n=22), age-adjusted mean striatal binding was significantly higher, 70.4 (95% CI 66.2-74.6) than in the non-cannabis group (n=14), 63.1 (95% CI 57.8-68.4); (ANOVA $F1,35=4.78$, $p=0.04$). There was no effect of diagnosis ($F1,35=2.25$, $p=0.14$) and no diagnosis*cannabis interaction ($F1,35=0.84$, $p=0.36$). We conclude that exposure to cannabis increases striatal D2 receptor binding. Repeated administration of cannabis to rats induces sensitization to the psychomotor effects of amphetamine, indicative of up-regulation at post-synaptic dopamine receptors (5). Abnormalities of D2 receptors have long been hypothesised to be important in schizophrenia (6). Here we provide the first evidence that cannabis increases striatal D2 binding. This may constitute in part, the mechanism underlying the risk of cannabis for psychotic illness. 1 Hall WD. Lancet 2006; 367: 193-95. 2 Arseneault, et al. Causal. Br J Psychiatr 2004; 184: 110-117. 3 Caspi A, et al. Biol Psychiatry 2005; 57: 1117-27. 4 Pilowsky LS, et al. Lancet 1992; 340: 199-202. 5 Gorriti MA, et al. Eur J Pharmacol 1999; 365: 133-42. 6 Snyder SH, Neuron 2006: 49; 484-5.

PROTON MAGNETIC RESONANCE SPECTROSCOPY AND THOUGHT DISORDER IN CHILDHOOD SCHIZOPHRENIA

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This study examined if children with schizophrenia and normal subjects with formal thought disorder have metabolic abnormalities in frontal lobe regions involving language (i.e. inferior frontal gyrus, IFG) and short-term memory (i.e. middle frontal gyrus, MFG) using proton Magnetic Resonance SpectroscopicImaging (1H MRSI). 1H MRSI was acquired from both regions at 1.5T for 13 children diagnosed with schizophrenia and 13 age- and gender-matched healthy controls. CSF-corrected aAbsolute and CSF-corrected values of N-acetyl aspartate (NAA), creatine plus phosphocreatine (Cr), choline compounds (Cho), myo-inositol (mI), and glutamate plus glutamine (Glx) were compared between groups. Speech samples of all subjects were coded for formal thought disorder using the Kiddie Formal Thought Disorder Rating Scale1. Levels of NAA and Glx were significantly lower in the left IFG in subjects with schizophrenia. Both Glx concentration in the right MFG ($r=0.882$, $p<0.01$) and mI concentration in the left IFG ($r=0.649$, $p<0.05$) correlated positively with the frequency of illogical thinking in schizophrenia patients. Lower levels of NAA and Glx suggest that neuronal integrity and glutamate may be diminished in child-onset schizophrenia. Children

with schizophrenia may be sensitive to putative thought-disorder provoking properties of glutamate, glutamine, or mI. Elucidating a metabolic substrate for thought disorder may provide insight into the development of effective medications.

Metabolite Differences Between Patients and Controls

Region	Metabolite	% Diff.	P-Value
Right MFG	Cho/Cr	-15.2	0.044
Right MFG	Cho	-23.6	0.027
Left IFG	Cr	-16.9	0.006
Left IFG	NAA	-25.5	0.001
Left IFG	Cho	-14.0	0.042
Left IFG	Glx	-17.7	0.006
Right IFG	Cho	-15.2	0.028

*Schizophrenia - Control

ELEVATED 5-HT2A RECEPTOR BINDING IN THE CAUDATE NUCLEUS IN NEUROLEPTIC NAïVE SCHIZOPHRENIC PATIENTS

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The aim of this PET study was to investigate both cortical and subcortical 5-HT2A binding in neuroleptic-naïve schizophrenic patients and matched healthy controls using the selective 5-HT2A tracer [18F] altanserin. Post-mortem investigations and the receptor profile of atypical antipsychotics have implicated the serotonin 5-HT2A receptor in the pathophysiology of schizophrenia. In general the post-mortem investigations have reported a decreased 5-HT2A density especially in frontal areas. However the very limited number of clinical imaging studies has not confirmed this. For example no significant difference in cortical 5-HT2A binding was found between healthy controls and schizophrenic patients in three of the available imaging studies. Furthermore these studies used radiotracers with limited 5-HT2A affinity hindering the subcortical regions to be examined. The present results are based on data from the first included 15 patients and controls. We expect to be able to present data from 25 antipsychotic naïve patients and matched controls at the meeting. The schizophrenic patients had a significantly higher 5-HT2A binding in the caudate nucleus than the controls (0.7 +/- 0.1 vs. 0.5 +/-0.3, p=0.02). Between the two groups there was no significant difference in cortical 5-HT2A binding.The present data confirm previous PET studies reporting unaltered 5-HT2A binding in cortical regions. However this is the first PET study to show elevated 5-HT2A binding in the caudate nucleus. It remains to be explored whether this elevation is actually a primary pathophysiological disturbance or rather a secondary effect caused by a change in endogenous serotonin levels.

RELATIONSHIP BETWEEN PROTON METABOLITE RATIOS AND DURATION OF CANNABIS USE: IMPLICATIONS FOR SCHIZOPHRENIA

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It has been reported that exposure to cannabis is associated with both increased vulnerability for the onset of schizophrenia and poor clinical course. The in vivo changes in neural mechanisms that may be associated with cannabis use remain to be clarified. The objective of the current study was to apply proton (1H) magnetic resonance spectroscopy (MRS) to examine whether metabolite concentrations would be significantly different in adult subjects with a history of regular cannabis use compared to healthy non-smoking controls. Eleven men diagnosed with cannabis dependence (21.4 ± 3.3 yrs.) and eight healthy control men (23.1 ± 3.8 yrs.) underwent 2D J-MRSI/PRESS CSI at 4.0 Tesla. Global proton metabolite concentrations were measured using LCModel. In addition, tissue segmentation was used to examine metabolite distribution in grey and white matter. There was a significant negative relationship between duration of cannabis use and global white matter Cho/tCr levels, with longer lengths of use being associated with lower Cho/tCr levels, r=-.61, p=.024. In addition, grey and white matter GLX (glutamine + glutamate)/tCr levels were significantly correlated with duration of use, r=.53, p=.045. No significant between group differences in metabolites ratios were observed between cannabis-users and healthy controls. These findings are consistent with reports of abnormal Cho and GLX levels in schizophrenic patients. Reductions in choline levels associated with extended exposure to cannabis may reflect alterations in phospholipid membrane turnover and cellular bioenergetics. Altered levels of GLX, however, may suggest a greater change in glutamatergic function with longer cannabis use. Additional studies are needed to further elucidate the role of cannabis exposure to neurobiological changes associated with schizophrenia.

IS ANTIPSYCHOTIC EFFICACY DRIVEN BY CORTICAL DOPAMINE RECEPTOR OCCUPANCY? AN ORIGINAL PATIENT DATA META-ANALYSIS OF SPET AND PET STUDIES

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Since the finding that clozapine and other second generation antipsychotics (SGA) show preferential occupancy at cortical over striatal dopamine D2/D3 receptors, it has been hypothesized that antipsychotic efficacy could be driven by cortical D2/D3 occupancy, with striatal D2/D3 binding leading to extrapyramidal side effects (EPSE). Single photon emission tomography (SPET) and positron emission tomography (PET) permit measurement of antipsychotic occupancy at regional dopamine D2/D3 receptors, but sample sizes have been too small to determine the relationship of receptor occupancy with clinical effects. We studied these relationships using meta-analysis of original patient data from published PET and SPET studies. We selected SPET or PET studies in which a single ligand in the same patient was used to estimate D2/D3 receptor availability in both striatum and cortex. We plotted dose vs. occupancy for striatum and cortex, and calculated the dose at which 95% of receptors were occupied for each drug in each region (ED95occ). We also selected large double-blind variable dosing studies in order to calculate the dose at which drugs had 95% of their therapeutic effect (ED95eff). For each drug, we compared D2/D3 occupancy in cortex with striatum. We studied the relationship between ED95eff and ED95occ at striatal and cortical D2/D3 receptors with Pearson's correlation. We studied EPSE by dividing drugs into three groups: high dose first generation antipsychotics (FGA), low dose FGA, and SGA. We examined the relationship of group with striatal and cortical D2/D3 receptor occupancy using ANOVA with Helmert contrast of FGA vs. SGA, high FGA vs. low FGA, and post-hoc comparison of SGA vs. low dose FGA. Both FGA and SGA pro-

duced high (70-80%) D2/D3 occupancy in cortex, but only FGA produced high D2/D3 receptor occupancy in striatum ($p<0.00001$). ED95eff correlated most strongly with cortical ($r=0.99$, $df=6$, $p<0.005$), rather than striatal ($r=0.72$, $df=6$, $p<0.05$) dopamine D2/D3 receptor occupancy. There was a stronger relationship of EPSE propensity with striatal than with cortical binding ($p<0.00001$, $p=0.045$). For striatal D2/D3 occupancy high dose FGA > low dose FGA > SGA ($p<0.05$). Antipsychotic efficacy appears driven by cortical dopamine D2/D3 receptor occupancy, with striatal D2/D3 inducing EPSE.

SPECTROSCOPY AND MORPHOLOGICAL ASSESSMENT OF THALAMUS IN FIRST-EPISODE SCHIZOPHRENIA SAMPLE

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Background: Structural and histological abnormalities of thalamic nuclei are hypothesized to play a crucial role in schizophrenia pathophysiology. Whole thalamus volumetric differences have been difficult to replicate due to technical complexity of assessing thalamic nuclei both from MRI and from post-mortem tissue samples. In order to further elucidate nature of those abnormalities we conducted an MRI assessment in a cohort of first-episode schizophrenia subjects and obtained Proton Magnetic Resonance Spectroscopy (1H MRS) data in the thalamus. Subjects: 12 DSM IV subjects with schizophrenia (mean age 21.7yrs, 9 male, 3 female), with less than 8 weeks of lifetime exposure to antypsychotics and 23 healthy volunteers (mean age 20.5yrs,12 males, 11 female) were included. Methods: 1.5mm thick axial 3D-SPGR images were obtained on a GES 1.5 T MRI scanner for manual thalamic morphological tracing. Spectra from 3.24mL voxels, centered in the left thalamus were acquired on same scanner using a PRESS sequence. Metabolite signals were corrected for T1 and T2 relaxations, and CSF content. Results: Mean left thalamus volumes were similar to those reported in literature for both groups. There were no significant effects of diagnosis, gender or age, although mean left thalamic volume in patients was larger (5921,5mm3 vs 5581,7mm3; $t=1.33$, $df=33$, $p=.103$). Mean values for absolute concentration of Cho and Cre showed no difference between groups. Patients showed a reduction in mean absolute values of NAA (9.96 mM vs 11.02 mM; $t=-2.11$, $df=33$, $p=.043$). No correlation between none of absolute metabolite concentration and thalamic volume was found. Conclusions: These results are consistent with previous reports on subsample from our team as well as literature both on morphological and MRS data. Lack of correlation between thalamic volume and absolute NAA concentration (stated as an indirect biochemical neuronal marker) brings into question the nature of the relationship between morphological and neurochemical abnormalities in thalamus.

ASSESSMENT OF MICROGLIA ACTIVATION IN SCHIZOPHRENIA USING [11C](R)-PK11195 AND PET

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Schizophrenia is a brain disease that especially involves decrements in grey matter, a finding that is supported by many imaging studies. The pathophysiology of these grey matter changes has not been clarified. One possibility is that actual loss of (glia)cells occurs in schizophrenia. Microglia activation is the consequence of virtually all conditions associated with neuronal injury. The purpose of the present study was to assess microglia activation in patients with schizophrenia using [11C](R)-PK11195 and PET. Four male patients with recent onset schizophrenia and five age matched healthy male controls have been included to date. All patients were treated with atypical antipsychotics. PET scans were performed using an ECAT EXACT HR+ scanner. A dynamic 3D scan was acquired following a bolus injection of 370 MBq [11C](R)-PK11195. Arterial whole blood concentration was monitored continuously using an online detection system. In addition, discrete samples were taken in order to derive a metabolite corrected plasma input curve. Finally, for each subject a T1 weighted structural MRI scan was acquired using a 1.5 Tesla scanner. Using automated procedures, total brain segmentation was performed on the co-registered MRI scan. This whole brain ROI was used to generate a whole brain time activity curve (TAC). Tracer kinetic modelling of this TAC was performed using a two tissue reversible model with fixed K1/k2 ratio, providing volume of distribution (Vd) and Binding Potential (BP) as outcome measures. Total brain [11C](R)-PK11195 Vd was increased in patients with schizophrenia compared to controls (1.16 ± 0.11 versus 0.84 ± 0.16; $p = 0.009$). This was also the case for the K1/k2 ratio (0.42 ± 0.05 versus 0.26 ± 0.08; $p = 0.008$) and blood volume (0.09 ± 0.02 versus 0.07 ± 0.01; $p = 0.05$). However, total brain [11C](R)-PK11195 BP was not statistically different between patients with schizophrenia and controls (1.97 ± 0.43 versus 1.65 ± 0.38; $p = 0.28$). The data indicate that increased blood flow, changes in non-specific binding or changes in blood-brain barrier kinetics may determine the increased [11C](R)-PK11195 Vd in schizophrenia. The lack of change in [11C](R)-PK11195 BP in this small sample could be due to the high level of non-specific binding of this tracer. Therefore, reference tissue models, which include an inherent correction for non-specific binding, are currently being evaluated. In addition, to improve statistics, more patients will be included.

THE EFFECTS OF TOBACCO-RELATED COMPOUNDS AND CAFFEINE ON SENSORY GATING

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Tobacco smoking has been reported to improve P50 gating, albeit temporarily. Although nicotine seems to be involved, the effects of other chemicals in tobacco are unknown. In addition, as caffeine is believed to be associated with increased alertness, caffeine may modulate P50 gating. This study examined the chronic effect of nicotine, cotinine and caffeine on P50 Cz gating as well as M50 left- and right-hemisphere superior temporal gyrus (STG) gating in controls and in patients with schizophrenia. Hypotheses were that nicotine would not have an effect on P50 or M50 gating measures while cotinine and caffeine, given their longer half-lives, would. Sixty-nine patients and 58 controls (52 smokers and 75 non-smokers) participated. Smokers were asked to refrain from smoking at least 1 hour before recordings. Fagerström score, and nicotine, cotinine and caffeine serum levels were obtained prior to recording. Electroencephalography (EEG) and

whole-cortex magnetoencephalography (MEG) data were simultaneously collected while subjects were administered the standard paired-click task. 50 ms gating and amplitude measures (first click = S1, second click = S2, and S2/S1) were examined at Cz (P50) and, using single dipole source localization, at left and right STG (M50). As most non-smokers had low Fagerström scores and low nicotine and cotinine levels, analyses were performed in smokers only. Fagerström scores and nicotine and cotinine levels were not associated with P50 Cz or left M50 STG gating ratios or amplitudes. Cotinine level positively correlated with right M50 S1 and S2 amplitudes (r's = 0.31 and 0.32, p<.05). Caffeine level positively correlated with left M50 S1 STG amplitude (r = 0.35, p<.05). As predicted, there were no effects of nicotine on P50 or M50 gating measures. The lack of a nicotine effect may be due to the fact that subjects refrained from smoking for 1 hour before experiment. Contrary to our hypotheses, neither cotinine nor caffeine affected P50 gating measures. In contrast, there was an effect of cotinine on M50 STG amplitudes, suggesting a chronic rather than acute effect. As several groups have observed decreased S1 amplitudes in patients with schizophrenia compared to controls, the beneficial effect of caffeine and cotinine on S1 activity is of interest. In addition, the differential effect of cotinine and caffeine on right and left M50 amplitudes deserve attention.

$5HT_{2A}$ RECEPTOR BINDING OF ACP-104 IN SCHIZOPHRENIA

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In spite of the development of other atypical antipsychotics, clozapine remains the gold standard in antipsychotic therapy. However, clozapine is not well tolerated and has variable cognitive effects. ACP-104, or N-Desmethylclozapine, is the major active metabolite of clozapine. The receptor affinity profile of ACP-104 suggests that it may have better efficacy and tolerability than clozapine itself. In contrast to clozapine, ACP-104 is a muscarinic M_1 and a dopamine D_2 partial agonist. Moreover, as compared to clozapine, ACP-104 has lower affinity for histamine and alpha adrenergic receptors. Both clozapine and ACP-104 are high affinity $5HT_{2A}$ inverse agonists. Methods: This study used PET imaging to determine the degree of cortical $5HT_{2A}$ receptor occupancy induced by a single dose of ACP-104 in 10 subjects with DSM-IV schizophrenia. Each subject received two PET scans using [^{11}C]-MDL 100,907 bolus: a baseline scan after a 2-week washout of antipsychotics, and a post-dose scan at 3 hours after receiving a single oral dose of ACP-104 (100 to 150 mg). Each consisted of a 90-minute dynamic scan on a GE Advance scanner. Simultaneous arterial sampling and HPLC correction for radiolabeled metabolites were obtained. Measures of plasma levels of ACP-104 were obtained before and during the second scan. Binding potentials (BP) for $5HT_{2A}$ receptors in orbital frontal, prefrontal, superior frontal, temporal, cingulate, occipital and parietal cortices were obtained using a 2-tissue compartmental model (2TCM) with metabolite-corrected plasma input in 9 subjects, and the simplified reference tissue model (SRTM) in 10 subjects. Receptor occupancies were determined as the % change in BP from baseline to blocked case. Results: The occupancy (2TCM) of the above regions on average was E_{max} = 67% ± 16%, and IC_{50} = 76 ± 44 μg/mL, when fitted to a hyperbolic curve. At a 150 mg dose, receptor occupancy = 57 ± 12% (range 41 – 67%). For SRTM, E_{max} = 66 ± 48, and IC_{50} = 48 ± 33 μg/mL. Conclusions: These results indicate that, over the dose range of 100 to 150 mg, it is possible to achieve high occupancy of the $5HT_{2A}$ receptor with single doses of ACP-104. Further, this single dose study indicates the likelihood of high occupancies in tolerable doses when given at steady state. Follow up studies are planned. Acknowledgements: ACADIA Pharmaceuticals Inc., Stanley Medical Research Institute, and K24-DA00412(DFW).

PROTON MAGNETIC RESONANCE SPECTROSCOPY IN INDIVIDUALS AT HIGH GENETIC RISK FOR SCHIZOPHRENIA

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The purpose of this study was to investigate the neurochemical alterations in unaffected relatives of patients at high genetic risk of schizophrenia. In this study, spectra form the anterior cingulate cortex, left dorsolateral prefrontal cortex, and left thalamus were acquired in 19 unaffected relatives (22.42 ± 5.44 years old, 8 males) from families with two or more 1st or 2nd degree relatives with schizophrenia (n=18) or with a monozygotic schizophrenia twin (n=1) and 21 matched healthy controls (23.71 ± 4.96 years old, 7 males). Absolute levels of Glutamate/glutmine, N-acetyl-aspartate (NAA), creatine plus phosphocreatine (Cr), and choline compounds were measured in these regions and compared between the groups in each region. High genetic risk subjects showed increased levels of NAA and Cr in the thalamus. The levels of other metabolites were not significantly different between two groups in the three regions. The results of this study may suggest abnormalities of neuronal structure (e.g. reduced neuronal density or viability) or abnormalities of neuronal function in subjects with high genetic risk for schizophrenia.

14. Electrophysiology

PPI IN FIRST EPISODE, DRUG NAïVE SCHIZOPHRENIC PATIENTS AT BASELINE AND AFTER 6 MONTHS OF TREATMENT WITH QUETIAPINE. PRELIMINARY RESULTS

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Deficits in information processing appear to be core features in the pathogenesis of schizophrenia. Prepulse inhibition of the startle response (PPI) is an operational measure of sensorimotor gating. Preclinical studies have found that atypical but not typical antipsychotics have an effect on PPI. In clinical studies however, results are inconclusive: some studies showing improved PPI following treatment of schizophrenic patients with atypical antipsychotics, while others do not. These inconsistencies might be due to differences in binding characteristics of the various compounds that were used, and more specifically to their affinity for the D2 dopaminergic receptor: the higher the affinity for the D2 receptor, the less improvement in PPI seemed to be found. Alternatively, PPI deficits are stable vulnerability indicators. In order to solve this question, longitudinal studies on drug-naïve first episode schizophrenic patients are warranted. In the currently running longitudinal study the PPI of drug naïve, first episode, male schizophrenic patients is compared with that of sex matched healthy controls at baseline, and after six months of treatment with the atypical antipsychotic quetiapine. Quetiapine has a relatively higher affinity for the 5HT2A receptor than for the dopaminergic D2 receptor. The preliminary results from 13 patients at baseline and 9 healthy controls show significantly less PPI for patients than for healthy controls, which is consistent with literature. PPI from the 6 patients who completed the 6 months of treatment with quetiapine so far, did neither differ significantly from their PPI at baseline, nor from the PPI of the 9 healthy controls. Although the subject population at present is relatively small, the fact that patients at baseline show significantly reduced PPI in comparison with healthy controls, but not after six months of treatment with quetiapine, might indicate that PPI of the patients will significantly improve following six months of treatment in a larger population. We plan to present the results from the first 20 patients and age and sex matched healthy controls who according to our schedule will have completed the study before the start of the conference. This increased subject population will hopefully enlighten the issue whether deficits in PPI are sensible to treatment with an atypical antipsychotic drug like quetiapine, or represent stable vulnerability indicators.

DIFFERENTIAL RELATIONSHIP OF P50 SUBCOMPONENT ABNORMALITIES WITH CLINICAL SYMPTOMS IN DEFICIT AND NON-DEFICIT PATIENTS WITH SCHIZOPHRENIA

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P50 gating deficits in schizophrenia are linked to several symptoms including negative and disorganized symptoms and attention impairment; however, few conclusive relationships exist. We previously reported that P50 subcomponents can increase the ability to detect such relationships and that subcomponent suppression differences between deficit and non-deficit patients may exist. In this analysis we examined the relationships between symptoms and P50 subcomponent activity in groups of deficit and non-deficit schizophrenic patients. Auditory evoked potentials (AEP's) and clinical data were collected at the Mental Health Clinical Research Center at the University of Pennsylvania. AEPs were collected with at 32-channel recording array using a paired click paradigm (0.5 sec inter-click interval, 10 sec inter-pair interval). Spatial and temporal factor analyses performed on data from 37 control subjects revealed two spatial subcomponents of P50: a central midline component and a frontally bilateral component. Amplitude and suppression properties of these subcomponents were compared to BPRS, SAPS and SANS scores in a sample of 31 schizophrenics separated into demographically matched groups of deficit (n=12) and non-deficit (n=12) patients. The previously reported relationships of poor S2 suppression on the right frontal subcomponent relating to attention impairment ($\tau B=.30$, $p<.05$) and disorganization ($\tau B=.31$, $p<.05$) held in this matched sample (N=24) with no variation across deficit and non-deficit groups. However, a relationship between negative symptoms and poor frontal suppression across hemispheres did vary across sub-groups. In deficit patients poor S2 suppression robustly correlated with both BPRS ($\tau B=.60$, $p<.05$) and the SANS ($\tau B=.50$, $p<.05$) measured negative symptoms, but these relationships did not hold for the non-deficit group (BPRS, $\tau B=-.43$, $p=.05$; SANS, $\tau B=.03$, $p=.88$). Poor S1 amplitude on the midline subcomponent was interestingly associated with more negative symptoms in the deficit group ($\tau B=-.42$, $p=.06$) and more positive symptoms in the non-deficit group ($\tau B=-.39$, $p=.08$), although these effects were only trends. These findings suggest that sensory gating deficits are associated with different symptom types for different subtypes of schizophrenia. This research was supported by grants from the National Institute for Mental Health, MH43880 and MH50344, and by Scottish Rite Fellowships to S.D. All, A.M. Hartzell, B. Beenken, and S. Keedy.

ERROR-RELATED NEGATIVITY IN SCHIZOPHRENIA USING THE STROOP TASK: AN EVENT-RELATED POTENTIAL STUDY

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Introduction. Several event-related potentials (ERP) studies have identified a response-related frontocentral negative component recorded after errors called error-related negativity (ERN) and related to self- and conflict monitoring. Diminished ERN amplitude in patients with schizophrenia (SZ) has been reported. In addition, the correct response negativity (CRN) which is ERN-like activity after the correct response was reported larger in schizophrenia patients (SZ). The diminished ERN and enhanced CRN may suggest self-and conflict monitoring dysfunction in SZ. In this study, we sought to replicate those findings and investigate the correlations between ERPs and clinical symptoms. **Methods.** ***Subjects*** 10 male chronic SZ patients and 7 male healthy normal controls, age 20–55 years, all right-handed, participated in this study. Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). ***The task*** The Stroop task where the importance of speed and accuracy was emphasized was used to elicit ERN and CRN. The subjects

were instructed to identify the color of the font in which the four color words were printed. Prior to the Stroop task, the learning and practice sessions were conducted. In the actual task, congruent (e.g., RED printed in red color), incongruent (e.g., RED printed in blue color), and neutral (Xs printed in four colors) stimuli were presented in 3 blocks, each consisting of 432 stimuli (144 congruent, 144 incongruent, & 144 neutral). The stimuli appeared on the screen for 500 msec followed by the blank screen with a fixation point for 1500 msec. The errors were 133 in SZ and 85 in NC; and error trials included in the ERP were 121.3 in SZ and 80.9 in NC). ***EEG Recording*** The EEG was recorded from 64 electrodes, referenced off line to linked earlobes. Epochs of 800 msec duration, including a 400-msec pre-response interval, baseline corrected to a 100 msec period before the response onset were constructed. The ERN and CRN were measured both as the average and peak amplitude between 25 and 150 msec post-response. **Results and Discussion.** Reduced ERN and enhanced CRN was observed in SZ patients' grant averages. Statistical group differences were found for CRN ($p < 0.02$) but not ERN suggesting abnormalities in CRN but not ERN. . Significant ($p < .05$) correlations were found between ERN amplitude and hallucinatory behavior and between CRN and a lack of insight and judgment suggesting relationship to clinical symptoms.

DOPAMINERGIC-MUSCARINIC INTERPLAY IN THE REGULATION OF THE TEMPORAL CORTEX EXCITATION

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Activation of neocortical muscarinic receptors by tonically-released acetylcholine is critical for many neocortical functions including attention, short-term plasticity and long-term plasticity. At the cellular level, muscarinic receptors activation result in multiple effects, the most remarkable of which is an increase of neuronal firing due to inactivation of K+ conductances. However, the modulatory action by muscarinic receptors of synaptic transmission is less understood. Here we investigated how different muscarinic receptors regulate synaptic release of glutamate and GABA, by conducting in vitro whole-cell patch clamp recordings of pyramidal neurons in brain slices containing the temporal cortex. We found that muscarinic receptors activation decrease about 1/2 of the release of glutamate (to 53% of control), an effect mediated by M1R and PLC activation. A similar effect was observed in the release of GABA as revealed by decrease of about 2/3 of the evoked GABAR-mediated current (to 23% of control), mediated mainly by M2R through PI3K activation. These results suggest that tonic activation of the cholinergic corticopetal (Nucleus Basalis of Meynert) pathway may lead to a reduction of neocortical excitatory and inhibitory synaptic strength via M1R-PLC and M2R-PI3K pathway, respectively. Interestingly, we also observed that dopamine was able to restore the inhibitory effect of muscarinic receptors on synaptic release of glutamate and GABA. In presence of dopamine, the amplitude of the excitatory synapses was restored from 53% to almost 90% of control value whereas the synaptic inhibitory responses were brought back from 33% to about 60% of baseline. This indicates that dopamine may increase both excitatory and inhibitory synapses without disturbing the balance between inhibition and excitation in neocortical synapses. We speculate that this could be a physiological mechanism for increasing neocortical excitability and maintaining appropriate balance of inhibition and excitation. We propose that a disruption of the dopamine-muscarinic control of proper functioning of cortico-cortical excitatory-inhibitory synaptic transmission in the temporal cortex may be one of the critical neural bases underlying psychoses (more excitation) or depression (more inhibition).

ENDOGENOUS H_2O_2 MEDIATES GLUTAMATE-DOPAMINE INTERACTIONS IN STRIATUM:IMPLICATIONS FOR THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

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Oxidative stress has been implicated as a causal factor in psychiatric disorders, including schizophrenia. Importantly, recent studies have demonstrated a deficit in one of the main low molecular weight antioxidants, glutathione, in the cerebrospinal fluid and brain tissue from individuals with schizophrenia (Do et al. 2000). Moreover, striatal levels of the hydrogen peroxide (H_2O_2) metabolizing enzyme glutathione peroxidase (GSHPx) are also lower in schizophrenia (Yao et al. 2006). We have demonstrated recently that endogenous H_2O_2) generated downstream from glutamatergic AMPA-receptor (AMPAR) activation inhibits striatal dopamine (DA) release evoked by local stimulation (Avshalumov et al. 2003) under conditions mimicking the GSHPx deficits reported in schizophrenia. However, the cellular source of modulatory H_2O_2 is unknown. The apparent lack of AMPARs on striatal DA axons (Bernard and Bolam 1998) suggests that modulatory H_2O_2 must be generated by non-DA cells, most likely medium spiny neurons (MSNs) that do express AMPARs. To test this, we first examined whether H_2O_2 generation is enhanced in MSNs under conditions of GSHPx inhibition by mercaptosuccinate (MCS; 1 mM), using a combination of whole-cell recording and fluorescence imaging using the H_2O_2-sensitive dye H_2DCF. Local pulse-train stimulation (30 pulses, 10 Hz) in guinea-pig striatal slices caused a 30% increase in DCF fluorescence intensity (FI); stimulus-induced DCF FI doubled in the presence of MCS. TTX (1 μM) or the selective AMPAR antagonist GYKI-52466 (50 μM) blocked stimulus-induced action potentials and prevented the increase in DCF FI, showing that H_2O_2 generation depends on MSN activity and requires AMPARs. We then compared the effect of GSHPx inhibition by MCS on single-site DA release evoked by local vs. distal (>1.5 mm) stimulation of DA axon tracts in parasagittal slices using carbon-fiber microelectrodes and fast-scan cyclic voltammetry. MCS caused a 40% decrease in locally evoked DA release but had little effect on that evoked distally. GYKI-52466 increased DA release evoked by local but not distal stimulation. These data indicate that DA axons are not the primary source of glutamate-dependent H_2O_2 and provide new insight into DA-glutamate interactions in striatum. Moreover, given previous evidence for dysregulation of DA neurotransmission as well as oxidative stress in schizophrenia, our findings suggest novel factors that might contribute to the underlying pathophysiology.

HIPPOCAMPAL HYPERACTIVATION IN SCHIZOPHRENIA: MODULATORY ROLE OF THE PREFRONTAL CORTEX AND THE DOPAMINE SYSTEM

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A substantial amount of evidence derived from studies of amphetamine psychosis, the pharmacology of antipsychotic drugs, and imag-

ing suggest that positive schizophrenia symptoms are associated with increased subcortical DA neurotransmission, whereas negative and cognitive symptoms may be associated with impaired mesocortical DA function. The nucleus accumbens (Nac), an integral and important part of limbic and prefrontal cortico-striato-pallido-thalamic circuits, is thought to be involved in several cognitive, emotional and psychomotor functions known to be altered in schizophrenia. This nucleus integrates afferent information from area including the prefrontal cortex (PFC), and the hippocampus. Studies suggest that schizophrenia patients exhibit dysfunctions in PFC activation during tasks, and may also have hyperactivity within hippocampal circuits. The Nac also receives a high level of dopaminergic innervation from the ventral tegmental area. Based on the clinical literature and preclinical investigations, we have been examining a model of schizophrenia based on a disruption of homeostatic regulation of Nac information processing by PFC and DA systems, leading to pathophysiology within hippocampal-Nac circuits. This was explored by performing recordings from single Nac neurons in anesthetized rats and examining the response to activation of afferents from the ventral subiculum of the hippocampus. We then examined how these afferent inputs were altered following inactivation of the PFC by infusing tetrodotoxin. We found that inactivation of the PFC induced a decrease in the influence that the hippocampus exerts on activity of Nac neurons. Therefore, PFC input to the Nac is necessary for the hippocampus to exert an influence on this structure. These data are consistent with a model in which input from the PFC is required to allow normal flow of information from the hippocampus to the Nac. However, in schizophrenia, a disruption of activation within the PFC will pathologically attenuate hippocampal-Nac interactions. In this way, a deficit in PFC function could produce effects analogous to those associated with early hippocampal disruption; a method shown to model schizophrenia-related conditions in animal models

ONE YEAR STABILITY OF MISMATCH NEGATIVITY IN SCHIZOPHRENIA PATIENTS

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Schizophrenia patients have widespread deficits ranging from abnormalities in sensory processing to impairments in cognition and daily living. Mismatch Negativity (MMN) is an EEG waveform that is passively elicited by infrequent stimuli that occur during the presentation of more frequent stimuli. Previous studies have demonstrated that patients with schizophrenia have robust MMN deficits that are highly associated with level of daily functioning. The aim of the present study was to assess the 1-year longitudinal stability of MMN in both schizophrenia patients and nonpsychiatric adults. Schizophrenia patients (n=77) and nonpsychiatric comparison subjects (n=28) underwent EEG testing at baseline and after 12 months. Stability of MMN at electrode Fz was assessed using intraclass correlations (ICC). Consistent with previous studies, schizophrenia patients had robust MMN deficits at both the first and second session ($p<0.001$). No evidence of a progression of MMN deficits was observed in this chronic cohort of patients. MMN was highly reliable both for patients (ICC=0.93, $p<0.001$) and nonpsychiatric subjects (ICC=0.90, $p<0.001$). The results of the present study indicate that MMN is extremely stable over a 1 year interval in both schizophrenia patients and nonpsychiatric subjects. This high stability supports the use of MMN across multiple applications including as a biomarker associated with functioning and as an endophenotype in genetic association studies of schizophrenia.

IMPAIRMENT OF EARLY RELEVANCE PROCESSING IN SCHIZOPHRENIA: AN EVENT RELATED POTENTIAL STUDY IN VISUAL MODALITY

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Several studies have reported a visual equivalent of mismatch negativity (MMN) elicited by irrelevant stimulus during visual paradigms, our purpose is to demonstrate the impairment of an electrophysiological indicator of visual pre-attentional relevance processing in patients with schizophrenia. 10 patients suffering from an acute phase of schizophrenia and 10 healthy subjects were recruited. We recorded Event Related Potential (ERP) induced by a visual oddball task with three stimuli: standard (similar to 'O'), relevant target (to 'o') and irrelevant form (to 'X'). The subject attention is drowned to the detection task and the irrelevant stimulus appears as an unexpected variation. After classical pre-processing, we chose time windows by means of a data-driven principal component analysis which allow us to focus upon short latency windows, reflecting pre-attentional processing. The topographic areas were fixed following visual process streams. Then we compared variations between conditions and between groups. We found that during short latency windows (from 100 to 230 milliseconds) a negative wave, maximum in the occipito-temporal area, is specifically elicited by the irrelevant stimuli. This wave is well-matched with already reported characteristics of a visual equivalent MMN. As expected this wave was significantly faded for the patients. ERP components elicited by relevant and neutral stimuli did not differ between groups during the same time windows at this place. These results suggest that short latency neuronal correlates of visual processing for irrelevant stimuli differ between patients and healthy subjects. Thanks to latent inhibition behavioural studies, we know that relevance processing is disturbed in schizophrenia. What we observe can be considered as an indicator of a pre-attentional categorization process involving the detection of irrelevance of a stimulus. During early visual processing patients with schizophrenia do not manifest contextual specificity of brain activity, suggesting that early categorization deficit is involved in context processing impairment.

VULNERABILITY MARKERS IDENTIFY STABLE DEFICITS IN THE PRODROME AND FIRST EPISODE OF SCHIZOPHRENIA

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The early stages of schizophrenia are characterized by the emergence of psychotic symptoms and functional decline that are likely associated with neuropathological change. The Cognitive Assessment and Risk Evaluation (CARE) program has identified vulnerability markers for psychosis that are present in the prodromal phase and first episode of schizophrenia using neurophysiological and neurocognitive measures in hopes of improving the positive predictive power for current clinical criteria used to identify "prodromal" subjects. Vulnerability markers (prepulse inhibition - PPI, visual backward masking - VBM, P50 event related potential gating and neurocognitive measures) were chosen for this project based on documented deficits in schizophrenia spectrum populations as well as evidence of heritability and stability, suggesting a genetic basis for the endophenotypic trait. An important goal of this project is to increase understanding of

neurodevelopmental processes in schizophrenia by obtaining repeated vulnerability marker assessment in at risk (AR), first episode schizophrenia (FE) and normal (NC) subjects. A further aim is to determine whether the measures are reliable over repeated testing, potentially identifying stable, trait-related deficits in individuals at high risk for schizophrenia. Methods: 37 AR, 14 FE and 20 NC subjects received repeated testing on the neurophysiologic and neurocognitive battery at baseline and 6 month follow-up. Results: Stable group deficits were observed in the AR and FE samples in the P50 paradigm and across neurocognitive domains using repeated measures ANOVA. A significant group by time interaction was present in the VBM paradigm since FE subjects declined in performance over time while AR and NC subjects improved. Similarly, PPI deficits relative to NCs were present in the FE and AR groups at follow-up that were not evident at baseline assessment. Intraclass correlations were high across the majority of neurophysiologic and neurocognitive domains. Discussion: The vulnerability markers in the current study identify stable deficits that provide insight into the evolution of psychotic states. Importantly, some of the deficits are present at baseline and remain stable while other deficits appear to develop over time. When identifying potential markers for future psychotic illness, it is important to assess change over time as an indicator of disease progression that may assist in the prediction of future illness.

DIMENSIONALITY OF THE NEUROPHYSIOLOGY OF PSYCHOSES

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Cluster analysis and 3-dimensional source localization of abnormal features were performed on QEEG collected from 390 psychotic patients judged by 2 experts, 133 diagnosed by DSM (NYU)as schizophrenic, and 257 diagnosed by ICD-10(Berlin)as either schizophrenic (147),depressive (62), alcoholic(20),and dual diagnosis(28),including chronic depressive and alcoholic patients receiving medications. PROCEDURE: Cluster analysis was performed on a training set of 229 psychotic patients including members of each group. An independent analysis was performed on a test set of 148 psychotics using the same set of variables. QEEG source localization brain images identified anatomical generators of the abnormal QEEG patterns distinctive for each subtype of psychotic state. RESULTS: Psychotic patients with different diagnoses were in each of six clusters in separate analyses of the training and test sets. The findings supported 5 conclusions: 1)Features of the 6 subtypes of the training set replicated previous findings (John 1994).Test set results provided another independent replication. The subtyping appears robust. No clinical features were distinctive for the 6 clusters. 2)Major Affective Disorder as well as schizophrenic patients were classified into each cluster, suggesting a common physiological substrate for psychosis. It may be a conceptual error to guide treatment by symptomatology. 3)Every cluster contained medicated schizophrenic, depressive, and alcoholic psychotics, as well as after a period without medication and never-medicated patients evaluated during first acute episodes. Duration of illness or medication did not strongly influence cluster membership. 4)The QEEG profiles of the members of each cluster diagnosed by ICD or DSM were closely similar. 5)QEEG brain images of the generators of the most excessive and most deviant electrical activity in each subtype revealed that 2 different neuroantatomical systems were consistently dysfunctional in every subtype. An overactive system contained a very similar set of brain regions but displayed excessive activity at different frequencies in each cluster, suggesting 6 different patterns of neurotransmitter dysregulation. An underactive system was comprised of very different neuroanatomical structures displaying deficits at the same frequency in all subtypes. We postulate that the underactive system is inhibited by the overactive and the psychotic behavior results from this pathologic physiologic interaction.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) IN THE NEUROPHYSIOLOGY AND TREATMENT OF SCHIZOPHRENIA

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Objective: To examine the role of repetitive transcranial magnetic stimulation (rTMS) in the neurophysiology and treatment of refractory auditory hallucinations in schizophrenia (SCZ). Background: Several lines of evidence suggest that SCZ is associated with deficits in cortical inhibition (CI) that may relate to psychosis. For example, P50 suppression has been shown to be a robust marker of CI localized, in part, to the auditory cortex in SCZ that is mechanistically related to GABAB receptor mediated inhibitory neurotransmission and that has been shown to be deficient in SCZ. Design/Methods: Thirty patients with SCZ experiencing treatment resistant AH were randomized to receive low frequency (i.e., 1 Hz) (N=11), high frequency (i.e., priming or 6 Hz followed by 1 Hz rTMS) (N=8) or sham stimulation (N=11) for 4 weeks. Two types of stimulation were included due to neurophysiological evidence suggesting that higher frequency stimulation (i.e., priming) results in greater CI compared to low frequency stimulation (i.e., 1 Hz). AH treatment data, as indexed by the hallucinations subscale of the Psychotic Symptoms Rating Scale (PSYRATS), and P50 suppression were measured before and after 4 weeks of rTMS treatment. Results: Our data to date demonstrates that priming stimulation resulted in a 24 percent decrease in AH (Cohen's d=0.84) and 1 Hz stimulation resulted in a 18 percent decrease in AH (Cohen's d=0.84) compared to baseline. When data from active treatment groups were pooled there was a significant reduction in AH compared to sham stimulation ($p<0.05$). Vis à vis P50 suppression, priming stimulation resulted in a 47.3 percent increase (effect size: Cohen's d=0.87) that was significantly different compared to sham stimulation ($p<0.05$) while 1 Hz stimulation resulted in an 3.3 percent increase in P50 suppression. Conclusions: These findings provide compelling initial evidence that rTMS is effective for treatment refractory AH in SCZ and that such reductions may be associated with enhanced P50 suppression as a result of potentiation of GABAB receptor mediated inhibitory neurotransmission.

ELECTROPHYSIOLOGICAL EFFECTS OF FARAMPATOR (ORG 24448), A NOVEL ALLOSTERIC MODULATOR OF AMPA RECEPTORS, IN RAT HIPPOCAMPAL NEURONES

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Pharmacological enhancement of glutamatergic neurotransmission through AMPA receptors may have potential for therapeutic utility

in the treatment of psychiatric disorders. This study describes the in vitro pharmacological activity of farampator, a novel positive allosteric modulator of AMPA receptors, and compares its activity to CX516, another AMPA positive modulator reported to potentiate the beneficial effects of atypical antipsychotics, particularly in relation to cognitive symptoms. Whole-cell patch-clamp recordings were performed in rat cultured hippocampal neurons at room temperature. Glutamate (0.5 mM) was applied for 1s either alone or with the test compound using a semi-rapid drug application system. Effects of compounds on the synaptic transmission were studied in submerged hippocampal slices from rats at room temperature. Field excitatory postsynaptic potentials (fEPSPs) were recorded from stratum radiatum of CA1 area in response to Schaffer-commissural pathway stimulation. Co-application of farampator (3-300μM) or CX516 (10μM-1mM) with glutamate decreased desensitisation leading to increases in steady-state current in a reversible and concentration dependent manner: maximum increases were 19±4% (n=9) and 29±1% (n=3), respectively. EC50 values for farampator and CX516 were 14 μM (5μM to 40μM) and 95 μM (46μM to 195μM), respectively (values in brackets indicate 95% confidence intervals). In the absence of glutamate, the compounds were without effects. Bath applications of farampator (300 μM, n=7) increased the slope of fEPSPs by 46±9% (mean±S.E.M) ($p<0.05$, Student's t test). At 300 μM concentration CX516 also enhanced the fEPSP slope but this effect was smaller and not statistically significant (24±6%, n=3). At 1mM however, CX516 produced larger and statistically significant enhancement of synaptic responses (84±16%, n=9, $p<0.05$). NBQX (20μM) completely abolished the synaptic response indicating that fEPSPs are mainly AMPA receptor mediated (n=2). The selectivity profile of farampator was studied by measuring the binding affinity of farampator to several receptor and neurotransmitter sites at 10 and 100 μM. No significant interaction was observed. These results indicate that farampator is an allosteric modulator of AMPA receptor function in hippocampal neurones. It was more potent than CX516. Thus it represents an interesting tool for investigating the therapeutic potential of glutamatergic enhancement in psychiatric disorders.

INVESTIGATING THE TEST-RETEST RELIABILITY OF 50 MS PAIRED-CLICK AUDITORY GATING USING MAGNETOENCEPHALOGRAPHY SOURCE MODELING IN SUBJECTS WITH SCHIZOPHRENIA

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Abstract Introduction: Extensively used to study stimulus filtering abnormalities in schizophrenia, the EEG-recorded auditory paired-click 50 ms (P50) gating paradigm suffers from poor test-retest reliability of testing-to-conditioning gating ratios. Our group had recently observed that reliability can be increased by assessing 50 ms (M50) gating at primary auditory cortices (PAC) via magnetoencephalographic (MEG) source modeling in control subjects. In contrast to Cz P50, M50 gating ratios at bilateral PACs achieved an intraclass coefficient (ICC) of .8 or greater, a level considered sufficient for studies of individual differences. Variability of gating ratio within the same subject across sessions was also significantly smaller at bilateral PACs. The present study seeks to examine whether increased reliability due to MEG source modeling is also evident among subjects with schizophrenia. It is hypothesized that the test-retest reliability of various gating measures in schizophrenia may be lower than values observed in controls due to greater fluctuations in environmental stress, medication differences, and the varying nature of neuroanatomical insults in patients. Methods: We have begun recruiting patients with schizophrenia (target n = 10) for three sessions (at least one week apart) of simultaneous EEG and MEG obtained during the paired-click paradigm (S1 = first click and S2 = second click). Their mood profile at these sessions was also assessed. Gating ratios were calculated as S2/S1. Reliability measures were obtained using both ICC and variability measures. Results: Of the subjects analyzed (n=3), gating at left PAC M50 was poor. Whereas S1 and S2 latency ICCs were significant at around 0.7, ICCs were not significant for either left gating ratios or individual amplitudes. On the contrary, the ICC for right M50 was high and significant not only for S1 and S2 latencies (around 0.9), but also for amplitudes and gating ratio (S1: 0.7, S2: 0.9, gating ratio: 0.8). Conclusions: Preliminary findings indicated a hemispheric difference of the paired-click reliability measures in patients with schizophrenia. Hemispheric differences may be related to the putative lateralized pathology of the illness. We are currently recruiting more subjects to extend these findings and to assess the effect of other factors, such as changes in mood, on reliability measures in patients with schizophrenia.

OUT-OF-SYNCH AT A MOST BASIC LEVEL: APATHY AND AMOTIVATION

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Objective. We performed time-frequency decomposition of response-locked EEG to examine phase synchronization of oscillations across trials (inter-trial phase coherence; ITC) to self-paced button presses. Pre-press, we assessed motor intention/preparation (efference copy). Post-press, we assessed somatosensory activity (re-afference). In controls, we predicted greater phase synchrony contralateral to the press, consistent with an efference copy forward model. In patients, we predicted less evidence of a pre-press efference copy, resulting in less dampening of post-press sensory re-afference and therefore, more post-press phase synchrony. Design. EEG was collected while participants pressed a button every 1-2s. Neural phase synchronization (ITC) preceding and following button presses was calculated from single-trial EEG; averaging single trials yielded response-locked event-related potentials. Participants. Twenty-three patients (20 schizophrenia; 3 schizoaffective) recruited from community and VA hospitals; 25 age-matched healthy controls. Outcome measures and results. Consistent with forward model/efference copy sensorimotor communication preceding execution of motor plans, an increase in theta (4-7 Hz) and alpha (8-12 Hz) band ITC was evident 75ms prior to button presses over contra-lateral sensorimotor cortex. Consistent with phase synchronization evoked by sensory re-afference resulting from button pressing, broadband (theta, alpha, beta) ITC increased contra-laterally about 60 ms following the press. Pre-press ITC was greater in controls than patients, and post-press ITC was greater in patients than controls. Pre-movement ITC was especially reduced in patients with avolition and delusions of being controlled. ERP amplitude preceding presses was contra-lateralized, but did not distinguish groups or correlate with symptoms. Conclusion. Theta and alpha phase synchrony precedes self-initiated movements, perhaps reflecting forward model communication between motor and sensory cortex that transmits efference copies of motor commands and generates corollary discharges

in sensory cortex. Pre-response phase synchrony is reduced in schizophrenic patients, especially those with avolition/apathy and feelings of being controlled by outside forces, consistent with dysfunction of forward model circuitry.

DEVELOPMENTAL DISRUPTION USING MAM ADMINISTRATION: ALTERATION OF PREFRONTAL CORTICAL-HIPPOCAMPAL-ACCUMBENS INFORMATION PROCESSING

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There is increasing evidence that schizophrenia is a disorder related to development, and several animal models have investigated specific system disruptions during the prenatal/neonatal period as a means to mimic this condition. We have employed a gestational insult in rats in which the mitotoxin methylazoxymethanol acetate is administered to pregnant rats at gestational day 17, and the rats assessed as adults. These rats exhibit disorders consistent with what one would predict for an animal model of schizophrenia, including decreased cortical thickness with increase cell packing density, disruption of prepulse inhibition of startle, disrupted reversal learning, hyper-sensitivity to phencyclidine, and hyper-responsivity to amphetamine postpubertally but not prepubertally. We then used this validated model to examine interactions within the corticolimbic system. Using in vivo electrophysiological recordings, we found that these rats exhibited a loss of gating-related up-down states within the prefrontal cortex and nucleus accumbens, and furthermore the amygdala appears to compete with the prefrontal cortex for control of information flow within the accumbens. Information integration within the prefrontal cortex is also altered, in that there is a loss of gamma frequencies and altered synaptic plasticity that is exacerbated by stress. We have also found that there is an alteration in tonic-phasic dopamine neuron regulation, and that restoration of normal dopamine neuron drive will reverse the abnormally heightened behavioral response to amphetamine. Therefore, as with schizophrenia, there are likely a number of pathologies that can result in similar pathophysiologies within distinct animal models. In this model, we have found a deficit in corticolimbic system interactions, which result in abnormal potentiation of the dopamine system. As such, this will likely serve as an effective model to examine novel treatment strategies.

DIFFERENTIAL MODULATION OF FUNCTIONALLY DISTINCT SETS OF NMDA RECEPTORS IN CA1 HIPPOCAMPAL PYRAMIDAL NEURONS BY D1 DOPAMINE RECEPTORS

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Temporoamonic (TA) and Schaffer collateral (SC) axons activate pyramidal neurons in the CA1 region of hippocampus via synapses comprised of different NMDA receptors. These different NMDA receptor subtypes are pharmacologically distinct. The two inputs terminate on the apical dendrites of CA1 neurons in different locations, with TA synapses synapsing more distally. Using the in vitro hippocampal brain slice preparation, input-specific stimulation is achievable via electrical stimulation of the stratum radiatum (SC) or the stratum lacunosum moleculare (TA). Previous reports show that dopamine preferentially inhibits excitatory neurotransmission at the TA synapse. Such an effect could be consistent with a selective physical interaction of the D1 dopamine receptor with NMDARs that contain the NR2A subunit. To test the hypothesis that D1 dopamine receptor activation differentially modulates functionally distinct sets of NMDARs at TA vs. SC synapses through different mechanisms, we used the whole-cell patch-clamp technique in the in vitro hippocampal brain slice preparation to record synapse-specific NMDAR-EPSCs in CA1 pyramidal neurons. NMDAR-EPSCs were isolated in Mg2+-free Ringer solution containing picrotoxin and NBQX. SKF 81297 caused a reduction of amplitude of a subset of responses by 40%, the same D1/5 agonist administration produced an enhancement of SC responses by 82%, sometimes on the same neuron, to either the SC or TA inputs. To dissociate the D1-dependent effects, we show that pre-exposure to ifenprodil, antagonizing primarily NR2B-containing NMDARs always produced a SKF-dependent decrease in NMDAR-EPSC amplitude at both TA and SC synapses. Similar results are obtained in recordings conducted using GTP(gamma)S or GDP(beta)S, suggesting a G-protein mechanism is needed for potentiation. Application of a peptide that interferes with the NMDAR (NR2A)- D1 interaction blocks the SKF-inhibition. Further, both calcium and NMDAR activation are required for the SC potentiation and TA inhibition. Conclusion: 1. D1/5 mediated inhibition of NMDAR synaptic potentials is mediated by a protein-protein interaction with the NR2A subunit of the NMDAR. 2. D1/5 enhancement of NMDAR synaptic potentials is mediated by a G-protein dependent and NR2B dependent mechanism. Thus DA mediated post-synaptic modulation of NMDARs may be determined by specific NMDAR subunit expression.

FURTHER EVIDENCE FOR SHARED GENETIC EFFECTS BETWEEN PSYCHOTIC BIPOLAR ILLNESS AND P50 SUPPRESSION—-A COMBINED TWIN AND FAMILY STUDY

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Background: Diminished suppression of the P50 auditory evoked potential response, a robust finding in schizophrenia, has also been reported in patients with psychotic bipolar disorder. The non-specificity of impaired P50 suppression may reflect the impact of shared psychosis susceptibility genes. In our previous report on twin pairs concordant and discordant for bipolar disorder, genetic model fitting analyses showed substantial heritability for P50 suppression and significant genetic overlap between bipolar disorder and P50 sensory gating. However, the sample size was relatively small. Another report, the Maudsley bipolar family study, reported diminished P50 gating in unaffected relatives of psychotic bipolar patients from multiply affected families. However, genetic and environmental influences are confounded in family studies due to lack of monozygotic (MZ) twin pairs. The current study combined the twin sample and the Maudsley family sample to: 1) substantiate the association between psychotic bipolar disorder and P50 suppression, and 2) verify the genetic overlap between the two traits found in the twin sample. We also assessed the relationship between bipolar disorder and other P50 components (i.e., condition [S1] amplitude and latency, test [S2] amplitude and latency). Method: The twin sample comprises 94 twin pairs (10 discordant, 6 concordant MZ bipolar twins

and 46 MZ and 32 DZ control twin pairs) and the bipolar family sample comprises 41 patients with bipolar I disorder with psychotic features, 44 of their clinically unaffected first-degree relatives and 45 unrelated psychiatrically healthy controls. Identical P50 recording and analysis methods were used in both samples. Statistical analyses were based on structural equation modelling. Results: Bipolar disorder was significantly associated with diminished P50 suppression, greater S2 amplitude and longer S1 and S2 latency. Shared genetic factors were the main source of these associations, estimated to be 0.43 for P50 ratio, 0.39 for S2 amplitude, 0.26 for S1 latency and 0.23 for S2 latency. Significant heritabilities were also found for these variables. Conclusions: The results provide further evidence that P50 suppression ratio is a valid endophenotype for psychotic bipolar disorder.

LOW FREQUENCY CONTRIBUTIONS TO P50 SUBCOMPONENT ABNORMALITIES IN SCHIZOPHRENIA: PHENOMENOLOGICAL CORRELATES AND DEFICIT SYNDROME

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Background:Studies examining impaired sensory gating of the P50 component of the auditory evoked potential (AEP) in patients with schizophrenia (SZ) have typically used a 10Hz high pass filter to remove slow activity that may obscure P50. However, some have suggested that contributions below 10Hz may be important to P50 expression. Few studies have examined the relationship between P50 subcomponents in the lower frequencies (LF) and SZ symptoms. We previously demonstrated meaningful relationships between P50 subcomponents derived from the typical frequency band and SZ symptoms as well as a meaningful trend towards greater gating disruption in deficit patients. This study examined the relationship between P50 subcomponents and clinical ratings including the deficit syndrome using a 1-20Hz bandpass. Methods:AEP data were collected on 42 healthy adults and 39 SZ patients using a 32-channel recording array with a paired click protocol (0.5sec ISI, 10sec ITI). Amplitudes derived from a spatial PCA analysis of the data were correlated with available BPRS, SAPS and SANS scores in a sample of 32 SZ. Analysis of variance compared stimulus response and suppression patterns between deficit (n=12)and non-deficit (n=12) patients and controls (n=12) in a balanced sub-sample. Results:Temporal and spatial PCA analyses of control data revealed a frontotemporal subcomponent within the baseline adjusted 41-56 msec latency timeband on LF data. Comparison of these LF subcomponents to clinical symptoms did not reveal any meaningful relationships. The only significant correlation was a relationship between SZ subjects with greater disorganized symptoms having lower S2 amplitudes, implying better gating, in both the left (τB=-.31, $p<.05$) and right (τB=-.35, $p<.05$) hemispheres. This is not an expected effect and may be due to LF contributions that are not present in the traditionally filtered AEP. Despite a previous trend indicating poorer suppression in the deficit patients in the right hemisphere subcomponent no effects were found in the LF analysis. Conclusions: These findings suggest that while use of a 1-20Hz filter does allow for expressions of abnormalities in gating in SZ, some information regarding the nature of these abnormalities is not resolved with this approach and may further cloud the ability to examine the relationship between the abnormalities and clinical and symptomatic expressions of SZ.

PREPULSE INHIBITION OF STARTLE IS REDUCED IN FAMILY MEMBERS OF SCHIZOPHRENIA PATIENTS

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Inhibition of the acoustic startle response by a smaller preliminary nonstartling stimulus is termed prepulse inhibition (PPI), and is a paradigm that has been used as an operational measure of sensorimotor gating. Many patients with schizophrenia have impairments in PPI compared to healthy controls; these deficits may contribute to thought disorder and sensory overload experienced by these patients. Our prior work and work from other labs suggests that PPI impairment in schizophrenia persists despite treatment and hence may be a trait-related abnormality. Recently, researchers in the field of schizophrenia have attempted to identify distinct phenotypes, called endophenotypes, which are heritable and can be detected with a biological test. Identification of endophenotypes in schizophrenia will help to narrow the defined phenotype of this disorder, making genetic studies of this complex polygenic disease more fruitful. Based on several lines of evidence, it has been suggested that PPI may represent a heritable endophenotype in schizophrenia. We examined PPI in 85 schizophrenic patients, 41 unaffected first degree relatives of schizophrenia patients, and 82 healthy controls. We tested acoustic startle on pulse alone trials and in three prepulse + pulse trials with interstimulus intervals of 30, 60 and 120 ms. ANOVA on percent PPI failed to detect differences between groups in any trial type. We subsequently categorized all subjects into two groups: inhibitors, who exhibited lower startle amplitudes during prepulse + pulse trials compared to pulse alone trials, and non-inhibitors, who did not. We then used repeated measures logistic regression, solved using GEE, to determine if the percentage of inhibitors differed across groups. We found that there were significantly fewer inhibitors in the schizophrenia group (78.1%, p=0.009) and families (82.8%, p=0.018) compared to the control group (84.7%) during the 60 ms prepulse + pulse trials. There was no significant difference between the schizophrenia and family groups. These results confirm our hypothesis that impairments in PPI are seen not only in schizophrenia patients, but also in their unaffected family members, suggesting that PPI deficits have a genetic component. We are currently extending our investigation with a heritability analysis of PPI in families. If impaired PPI emerges as a heritable endophenotype in schizophrenia, a future direction will be to use PPI to inform genetic studies in this disease.

DIFFERENTIAL EFFECTS OF PRENATAL NICOTINE EXPOSURE ON AUDITORY SENSORY GATING IN INFANTS BASED UPON PARENTAL HISTORY OF SCHIZOPHRENIA OR BIPOLAR DISORDER

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The purpose of this study was to explore the effects of prenatal nicotine exposure and parental history of schizophrenia or bipolar disorder on auditory sensory gating in young infants. Auditory sensory gating was measured in infants from 0-6 months of age using a paired-click paradigm. Evoked potential component P1 (i.e., P50) was measured during REM sleep in four groups of infants: (1) infants with no prenatal exposure to nicotine and with no parental history of major mental illness (No Exposure/Negative History, N=57); (2)

infants prenatally exposed to nicotine with no parental history (Exposed/ Negative History, N=15); (3) infants with no prenatal exposure to nicotine with a parental history (No Exposure/ Positive History, N=10); and, (4) infants prenatally exposed to nicotine with a parental history (Exposed/Positive History, N=7). Infants in the No Exposure/No History group showed the greatest degree of response suppression to the test stimulus (indicative of intact sensory gating). Infants in the No Exposure/Positive History and the Exposed/Negative History groups showed less response suppression to the test stimulus than those in the No Exposure/Negative History group. However, infants in the Exposed/Positive History group showed little, if any, response suppression to the test stimulus (failed auditory sensory gating). Prenatal exposure to nicotine may interfere with the development of the neural circuitry responsible for auditory sensory gating and yields similar results as that found in infants in the No Exposure/Positive history group. However, smoking during pregnancy by mothers with a history of psychosis may have a greater detrimental effect on the developing brain than either factor alone. This work was supported by: NIMH (RENEWAL) 04/01/04-03/31/09 2R01 MH56539-06 "Childhood Physiology and Risk for Schizophrenia", NIMH (Freedman, P.I.) 09/15/04-06/30/09 1P50MH068582 "Molecular Neurobiology of Schizophrenia"

ELECTROPHYSIOLOGICAL COMPONENTS OF CONTEXT PROCESSING DEFICITS IN SCHIZOPHRENIA

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In a variety of cognitive tasks, patients with schizophrenia experience difficulty overriding a habitual response when signaled by a preceding cue. To elucidate neural anomalies that give rise to such context processing deficits, we used EEG to evaluate schizophrenia patients and control participants during a task designed to measure the difficulty of overriding one's prepotent reflex. In this task, participants viewed a green or red square presented in the center of the screen. Each square was followed by a probe, either the word 'left' or 'right'. The green square indicated the participant should respond to the subsequent probe by pressing a button with the hand that corresponded with the word. The red square indicated the participant should respond to the subsequent probe with the hand opposite to the word. Both groups of participants showed slower response times to the red probe. A trend toward a cue by diagnosis interaction suggested that the schizophrenia patients experienced greater slowing than the control participants in the red condition, which required context processing. EEG data will be used to aid in identifying neural mechanisms that result in a specific context processing deficit in schizophrenia.

EFFECTS OF QUETIAPINE ON P50 AUDITORY GATING IN SCHIZOPHRENIA PATIENTS

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Most schizophrenia patients have a deficit in early auditory inhibitory processes (ie auditory P50) that is not improved with conventional antipsychotic treatment (Shagass, 1964; Friedman 1983). Some atypical antipsychotics may have a normalizing effect (Adler 2004), measured as % reduced response of the test stimulus versus conditioning stimulus. Interim results of this study examined the effects of quetiapine on P50 auditory evoked potential. The two-group, randomized, single-blind, 12-week study compared the effects of ongoing risperidone (n=10) or switching to quetiapine monotherapy (n=10) on auditory P50 sensory gating in schizophrenic patients. All subjects ("heavy smokers") had an adequate treatment of risperidone monotherapy (≥6 mg total daily for ≥ 3 months) prior to enrollment. Fifty percent of patients were cross-titrated to quetiapine (up to 800 mg/day) over a two-week period, for 12 weeks. Auditory evoked potentials were recorded at baseline, weeks 6 and12. Additional assessments of clinical efficacy and side effects (e.g. PANSS, CGI, SANS, NRS, Barnes) were regularly collected. Group mean (n=20) auditory P50 sensory gating at baseline was 74.2%±56.7. Switching to quetiapine was associated with greater improvement in sensory gating (65.3%±53.3) compared with those who remained on risperidone (71.4%±54.8). On measures of clinical efficacy (PANSS and CGI), modest improvement from baseline was observed, with no significant difference between groups. These interim results suggest that quetiapine monotherapy may be associated with modest P50 sensory gating improvement as compared to risperidone monotherapy. If maintained at the end of this ongoing study (n=40), the results will suggest that quetiapine has a beneficial effect on early auditory inhibitory processes. Supported (in part) by an Investigator Initiated Grant IRUSQUET0329) from AstraZeneca Pharmaceuticals LP. References Shagass C., Schwartz M., 1964. Evoked potential studies in psychiatric patients. Ann. N. Y. Acad. Sci. 112:526-42. Freedman R., Adler L.E., Waldo M.C., et al, 1983. Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. Biol. Psychiatry. 18:537-51. Adler L.E., Olincy A., Cawthra E.M., et al, 2004. Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. Am J Psychiatry. 161:1822-8.

P300 ERP GENERATION IS AFFECTED BY DISTINCT PSYCHOPHYSIOLOGICAL PROCESSES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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The P300 event-related potential (ERP) generated to an infrequent "oddball" stimulus is considered a psychophysiological index of context updating and integration of novel events in the sensory scene. Evidence for abnormally small and late P300 peak amplitudes in schizophrenia and bipolar illness has lead to postulation regarding diagnostic overlap in neuropathology affecting these processes. The present study examined the possibility that diagnosis-specific disruption of early information processing may similarly impact later P300 generation in these disorders. Fifty-two age-matched schizophrenia (SZ), bipolar (BP), and healthy comparison (HC) subjects completed an auditory oddball procedure. N100, P300, and spectral power of early (0-256 ms) low frequency (1-20 Hz) and gamma-band (20-50 Hz) responses to standard and target (p = 0.15) stimuli were analyzed at midline electrode sites. Initial group comparisons confirmed that P300 amplitude and peak latency, as conventionally measured at electrode Pz, were deviant in SZ and BP relative to HC. Linear regression analyses were conducted for each group separately to identify early ERP components that most strongly predict P300 amplitude. Low frequency and gamma

power to standard stimuli at electrode Cz accounted for 25% of variance in target trial P300 amplitude in the HC sample, gamma power to standard stimuli and N100 amplitude change (N100 to target stimuli - N100 to standard stimuli) at Cz accounted for 19% of the variance in the BP sample, and low frequency power to target stimuli at Pz accounted for 34% of the variance in the SZ sample. SZ, but not BP, produced significantly smaller values than HC on each of these predictor variables. SZ and BP differed only in the gamma response to standard stimuli. Including this variable as a covariate in comparisons of P300 amplitude did not reduce the strength of differences between BP and HC groups, but eliminated the significant difference initially observed between SZ and HC. These results are interpreted to suggest that the early gamma response, functionally associated with sensory registration, plays an important role in the brain's ability to detect and attribute salience to novel sensory input. However, while dysfunctional gamma activation may contribute to P300 amplitude reduction in schizophrenia, similar abnormalities in bipolar disorder appear to reflect distinct, and inferentially later occurring (i.e., > 256 ms), information processing deficits.

EFFECTS OF PRENATAL EXPOSURE TO NICOTINE ON MISMATCH NEGATIVITY IN INFANTS

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While prenatal exposure to nicotine has been found to be linked to a constellation of negative cognitive and behavioral outcomes in children and adults, it is unclear whether there are similar nicotine-related effects in early infancy. In this study, auditory temporal processing in young infants who had been exposed to nicotine in utero was compared to that of unexposed infants; it was hypothesized that the nicotine-exposed group would exhibit a diminished mismatch negativity (MMN) response. 142 infants (47 of whose mothers smoked and 95 of whose mothers did not smoke during their pregnancy) heard two series of tones in which a standard-interval series was randomly interrupted by tones at deviant intervals, either "easy-to-detect" (50% temporal deviance) or "hard-to-detect" (15% temporal deviance). Evoked response potentials for the deviant tones were analyzed using the MMN paradigm. For the "easy-to-detect" deviant, the mean MMN amplitude at Pz was significantly smaller for infants who had been exposed to nicotine in utero than for those who had not. These results likely reflect effects of fetal exposure to nicotine on the central nervous system leading to impairment of auditory processing in young infants, but might also be due to post-natal nicotine exposure.

ABERRANT HIPPOCAMPAL REGULATION OF DOPAMINE NEURON RESPONSIVITY IN AN ANIMAL MODEL OF SCHIZOPHRENIA

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Aberrant dopamine (DA) signaling is believed to play a major role in the pathophysiology of several psychiatric conditions including schizophrenia. Given that there is no evidence of a primary pathology within the dopamine system itself, it has been suggested that altered DA signaling results from aberrant regulation of dopamine transmission secondary to disruption in one or more afferent inputs to the VTA. As such understanding the role of DA system dysregulation in these conditions requires a more complete delineation of the primary factors that regulate DA system responsivity. We have demonstrated previously that DA neuron activity states are independently regulated by distinct afferent pathways, and moreover that these pathways interact to control the population of DA neurons that are phasically activated. Given the central role of the ventral hippocampus (vHipp) in this regulation, and evidence for hippocampal dysfunction in schizophrenia, the aim of this study was to examine the regulation of DA neuron activity states in a developmental disruption model of schizophrenia. In this model, the mitotoxin methylazoxymethanol acetate (MAM) is administered to pregnant dams on embryonic day 17, which results in adult offspring displaying behavioral and anatomical disturbances analogous to those observed in schizophrenia patients. Using in vivo extracellular recordings from identified VTA DA neurons in chloral hydrate anaesthetized rats, we report that MAM rats display a selective increase in DA neuron population activity (the number of spontaneously active DA neurons observed per electrode track) with no significant changes in average firing rate or percent burst firing. Furthermore, although afferent (pedunculopontine tegmentum) stimulation-induced burst firing remains intact, the ability of vHipp activation to increase DA neuron population activity is absent in MAM animals. In addition, hippocampal inactivation by tetrodotoxin normalized the increased DA neuron population activity observed in MAM rats while having no significant effect on any parameter of DA neuron activity in control animals. Taken as a whole these data suggest that the altered DA neuron activity observed in MAM rats is associated with increased hippocampal output and hence may be a site of pathological regulation underlying aberrant DA signaling.

SEROTONIN TRANSPORTER GENE (5-HTTLPR) L/S POLYMORPHISM INTERACTS WITH SMOKING STATUS AND SCHIZOPHRENIA DIAGNOSIS IN DETERMINING THE DEGREE OF PAIRED-CLICK P50 CZ GATING

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The 5-HTT serotonin transporter gene has been implicated in depression and anxiety, with L allele individuals (longer promoter region resulting in greater transcription) at smaller risk than those with the S (short) allele. Several reports suggest that the effect of the 5-HTTLPR gene is sensitive to the serotonin-modulating properties of smoking. In turn, a proposed neurophysiological effect of smoking is improved information filtering, a phenomenon assessed via the paired-click P50 paradigm. A P50 gating deficit predicts increased anxiety and is regarded as an endophenotype of schizophrenia. In the present study, it was hypothesized that smoking status (zero Fagerstrom score vs a positive Fagerstrom score) and 5-HTT H/L polymorphism modulate P50 Cz gating in controls and in patients with schizophrenia. Thus

far, over 30 controls and 50 patients with schizophrenia have undergone P50 Cz gating measurement and 5-HTTLPR genotyping. Smokers were overly represented in the schizophrenia group ($p<0.01$). 5HTTLPR genotypic distribution was similar among the two groups. Using hierarchical regression analysis, a main effect of diagnosis (better gating in controls than patients) but not smoking status or 5HTTLPR genotype was observed. A significant genotype X smoking status interaction was observed ($p=0.04$), as well as a trend toward a genotype X diagnosis interaction ($p=0.08$). Whereas improved P50 gating (i.e., smaller gating ratios) was observed in smokers as a function of the number of L allele ($r=-0.34$), nonsmokers exhibited a reversed effect ($r=0.26$, $p=0.01$ per R-Z transformation). In addition, whereas gating improved in patients as a function of the number of the L allele ($r=-0.29$), controls showed the opposite effect ($r=0.34$, $p<0.01$ per R-Z transformation). Present data suggest that both smokers and patients with schizophrenia benefit from increased 5HTTLPR activity in optimizing P50 gating, and the opposite pattern was observed in non-smokers and controls. To our knowledge, our data offer the first genetic evidence of a role of serotonin transmission in P50 gating and also suggests a mechanistic process to account for the putative effect of smoking on sensory gating.

DISCRIMINATION OF BIPOLAR DISORDER AND SCHIZOPHRENIA BY PHYSIOLOGICAL MEASURES

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The use of endophenotypes has been proposed as a strategy to identify the genetic and biologic underpinnings of complex disorders. Three of the biological markers characterized as inhibitory endophenotypes in schizophrenia include suppression of the P50 auditory evoked response, inhibition of intrusive saccade generation (leading saccades) into smooth pursuit eye movements and cancellation of reflexive saccade generation in the antisaccade eye movement task. The aim of this study was to determine if any endophenotype, or a composite inhibitory endophenotype, could be used to classify persons with schizophrenia and bipolar disorder. Second, we sought to determine whether subjects with schizoaffective disorder, bipolar type, were physiologically more similar to subjects with schizophrenia or bipolar disorder. These endophenotypes were recorded in 29 subjects with schizophrenia and 58 subjects with bipolar disorder or schizoaffective disorder, bipolar type. To establish normal levels of performance, data from 42 normal control subjects for the P50 paradigm, 42 control subjects for the smooth pursuit paradigm, and 40 controls for the antisaccade paradigm were used. The schizophrenia group was impaired on all 3 measures; the bipolar group was impaired on the P50 and antisaccade paradigms. Logistic regression determined that P50 ratio and frequency of leading saccades significantly contributed to the discrimination between subjects with schizophrenia and bipolar disorder with a sensitivity of 95% and a specificity of 83%. The schizoaffective group was split, with 6 physiologically classified as schizophrenia and 12 as bipolar disorder. A combination endophenotype of P50 suppression and the frequency of leading saccades supports the current nosology of schizophrenia and bipolar disorder. This work was supported by the Veterans Affairs Medical Research Service and MH 38321

ELECTROPHYSIOLOGICAL EVIDENCE OF AUDITORY PROCESSING DEFICITS DURING THE PSYCHOSIS PRODROME AND RECENT ONSET SCHIZOPHRENIA: MISMATCH NEGATIVITY AND EVOKED GAMMA OSCILLATIONS

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Schizophrenia is associated with auditory processing deficits as revealed by electroencephalographic (EEG) methods including event-related potentials (ERP) and event-related synchronization of neural oscillations. While such deficits have been demonstrated in chronic patients, their presence at illness onset, or even during the prodromal phase preceding illness onset, remains controversial. Accordingly, we examined two distinct EEG-based measures of auditory sensory processing in patients with prodromal symptoms who are at ultra-high risk (UHR) for conversion to psychosis (n=38), as well as in early illness schizophrenic (EIS) patients who were within five years of their first hospitalization (n=22), and age-matched healthy control subjects (HC) (n=44). Auditory processing measures were: 1) evoked (i.e., phase synchronized) bursts of gamma band (36-44 Hz) oscillations occurring 50 msec following auditory tones, and 2) the mismatch negativity (MMN) component of the ERP elicited automatically by auditory deviance, including pitch deviant, duration deviant, and combined pitch/duration double-deviant paradigms. UHR patients where identified based on the Structured Interview for Prodromal Syndromes (SIPS), and EIS patients met DSM-IV criteria for schizophrenia based on a SCID interview. Results showed that evoked gamma was diminished in power due to poor phase synchronization in both EIS and UHR patients, relative to HC. MMN amplitude was also significantly reduced in EIS and UHR patients, relative to HC, particularly in the pitch/duration double-deviant paradigm, suggesting that patients did not continue to process duration deviance once pitch deviance was detected. One year clinical follow-ups from 13 UHR patients identified 6 converters to psychosis. Relative to non-converters, converters had significant baseline reductions in MMN amplitude, but not in evoked gamma power or synchrony. Thus, automatically elicited auditory processing deficits are present early in the course of schizophrenia and are also evident in individuals exhibiting prodromal symptoms. These deficits reflect compromise in auditory sensory echoic memory (MMN) and in auditory stimulus-evoked synchronization of gamma band EEG oscillations. In addition, MMN deficits may be a neurophysiological marker of risk for psychosis among prodromal patients, supporting its status as a candidate endophenotype, and potentially enhancing the predictive validity of clinically-based prodromal criteria.

MMN EVIDENCE OF A PERVASIVE TEMPORAL PROCESSING DEFICIT IN SCHIZOPHRENIA

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Previous research has suggested that mismatch negativity (MMN) to sounds that are deviant in duration (relative to background sounds)

is a particularly sensitive index of auditory system abnormalities in schizophrenia, leading to the suggestion that these findings may be indicative of more pervasive impairments in temporal processing. The purpose of the two experiments reported here was to provide further evidence of a selective deficit in temporal processing and determine whether there are impairments across a range of time scales (from μs to tens of ms). In the first experiment, MMN was generated to a change in sound lateralization created by interaural cues based on either temporal cues (differences in arrival time, ITD, or phase, IPD, of the sound at the two ears) or a non-temporal cue (differences in loudness, ILD). In the second experiment, MMN was utilized to determine if impairment can be demonstrated over a range of temporal processing tasks: encoding of the duration (or extent) or sounds, gap detection and interaural differences in onset (ITD) The amplitude of MMN was measured in individuals with schizophrenia (N=18 and 20 in Exp 1 and 2) and in healthy comparison (N = 19 and 19 in Exp 1 and Exp 2) subjects. In Exp 1, MMN to changes in sound lateralization produced by interaural temporal cues (ITD and IPD) and interaural loudness cues (ILD) were compared. In Exp 2, MMN responses to a duration increment of 50 ms, a gap of 17 ms in a white noise burst and a change in sound lateralization induced by an ITD of 700 μs, were obtained. Individuals with schizophrenia had reduced MMN amplitudes to changes in sound lateralization, when deviants were created by interaural temporal cues (both onset and phase), but not when loudness cues were used. Furthermore, MMN was reduced to all categories of deviants in experiment 2 and therefore provided evidence of impairments in the encoding of temporal properties of sounds across a range of time constants. MMN amplitudes to the three types of temporal deviants were correlated but discriminant function analysis suggested that the reduction in the gap MMN was the best discriminator between patients and controls. Gap detection is one of the most widely used measures of temporal resolution in the auditory system and the MMN results are consistent with patients having difficulties in resolving rapid temporal fluctuations in sound over time.

THE RELATIONSHIP BETWEEN SENSORIMOTOR GATING AND CLINICAL IMPROVEMENT IN ACUTELY ILL SCHIZOPHRENIA PATIENTS

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Sensorimotor gating deficits, as indexed by prepulse inhibition (PPI) of the acoustic startle reflex, have been described as an endophenotypic marker of psychotic conditions such as schizophrenia (SCZ). In the present study we 1) examined PPI in SCZ patients who are hospitalized for decompensation and are treated with antipsychotic medications for two weeks, and tested non-patient comparison subjects (NCS) over the same time course, and 2) determined the relationship between PPI and changes in symptoms over the course of treatment. By comparing PPI changes in SCZ patients who were initially unmedicated to patients initially medicated, we also sought to address whether treatment with antipsychotic medications is directly related to an amelioration of sensorimotor gating deficits. PPI was assessed at three interstimulus intervals (30, 60, and 120 msec) in 23 SCID-diagnosed SCZ patients shortly after admission to an inpatient psychiatric hospital. Eight patients were initially tested in a medication-free state, and all were re-tested approximately two weeks later after initiation or increase/change of antipsychotic medications. Symptom ratings on the Positive and Negative Syndrome Scale (PANSS) were collected at both sessions. SCZ patients showed lower PPI at the first session than NCS, after two weeks of treatment, however, their PPI increased to levels similar to those of NCS while the PPI of NCS remained unchanged over a two-week period. SCZ patients' medication status at baseline did not differentially influence PPI following two weeks of treatment. For SCZ patients, increase in PPI was correlated with a decrease in symptom scores, primarily for negative symptoms (see Table). To our knowledge this is the first report showing a systematic relationship between symptom improvement and increase in PPI. Results suggest that PPI levels in acutely decompensated SCZ patients were impaired at baseline and improved following two weeks of treatment, and that improvement in PPI was related to a decrease in symptoms of the disease.

Pearson R correlations between PPI change and PANSS change for SCZ patients (n=23)

PANSS scales	Overall PPI change	30 msec PPI change	60 msec PPI change	120 msec PPI change
Positive Scale Change	-.30	-.02	-.52**	-.11
Negative Scale Change	-.55*	-.54**	-.47*	-.27
General Scale Change	-.29	-.18	-.41	-.03
Total PANSS score change	-.48*	-.35	-.57**	-.17

*p<.05, **p<.01

PREFRONTAL CORTICAL INTERNEURONS ARE CRITICALLY AFFECTED IN ANIMALS WITH A NEONATAL VENTRAL HIPPOCAMPAL LESION

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Animals with a neonatal ventral hippocampal lesion (NVHL) exhibit a variety of behavioral deficit resembling phenomena observed in schizophrenia. These animals present hyperlocomotion, intolerance to stress, exaggerated responses to amphetamine, and sensorimotor gating deficits. We have recently characterized a variety of electrophysiological deficits in NVHL animals, primarily in the responses to mesocortical/mesolimbic activation, and the medial prefrontal cortex appears to be a central location for the expression of all these deficits. All these are evident in young adult, but not prepubertal animals. Here we explored cellular and synaptic mechanisms that may become altered in these animals, focusing on the effects of dopamine agonists on interneurons and pyramidal neurons in acute slices containing the medial prefrontal cortex. In naive and sham-treated animals, fast-spiking interneurons acquire a modulation by D2 agonists during adolescence; at that late developmental stage, D2 agonist become capable of increasing fast-spikin interneuron excitability. In NVHL animals, on the other hand, this D2 action is not observed. The data suggest that affecting hippocampal projections to the PFC at a critical early postnatal age may cause an abnormal maturation of local prefrontal circuits that becomes evident after adolescence, the period during which cortical circuits acquire adult physiological properties.

THE CONSORTIUM ON THE GENETICS OF SCHIZOPHRENIA (COGS): P50 AUDITORY EVOKED POTENTIAL-CONFOUNDERS,SENSITIVITY AND SPECIFICITY

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The COGS is a seven site consortium studying the genetics of schizophrenia using six different endophenotypes including the P50 auditory evoked potential. This study examined the effects of group (schizophrenia probands, first degree relatives or community comparison subjects), site (Washington, Colorado, Pennsylvania, UCSD, UCLA, Harvard, Mt. Sinai), education, age, and substance use or mood disorders on the P50 auditory evoked potential. The sensitivity and specificity of the P50 ratio in determining diagnosis was examined. The P50 was recorded using the LEA 2003. Five trials containing contained 20 acceptable sweeps were collected and sweeps were rejected they contained large muscle artifact or eye blinks. Averages with conditioning P50 waves <0.5 mV or with the EOG>EEG at the same latency as the P50 were excluded. To retain data, rejected data was replayed by the Q/A site. Trials with less than 12 sweeps were excluded. A single trial was then selected as representing the P50 with the least artifact. Analysis was MANOVA with the P50 T/C ratio as the outcome variable and groups, sites, education, mood disorder or substance use as independent variables and a random effect of family relationship. The P50 was fitted to a ROC curve to determine the sensitivity and specificity of the P50 ratio as a predictor of diagnosis. Data from 149 community comparison subjects, 119 probands and 259 first degree relatives were analyzed. The three groups had P50 ratios that were significantly different from each other ($F=14.20$, d.f.=2, $p<.0001$). The P50 ratio of community comparison subjects was significantly differently different from probands ($t=-5.03$, d.f.-338, $p<0.0001$). The P50 ratio of community comparison subjects was significantly different from first degree relatives ($t=-3.17$, d.f.=338, $p=0.0016$). The P50 ratio of probands was significantly different from first degree relatives ($t=2.87$, d.f.=338, $p<0.0043$). The sensitivity of using the P50 for diagnosis was determined to be 0.67 and the specificity was 0.39. The P50 auditory evoked potential is a difficult endophenotype to record, however, in this multisite study, the COGS collaboration was able to distinguish normals from probands. However, this endophenotype may not be valuable in determining clinical diagnosis. Funded by NIMH 5R01MH065588

THE EFFECTS OF INCREASED SEROTONERGIC ACTIVITY ON P50 SUPPRESSION AND ITS NEURAL GENERATORS

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Schizophrenia is a disabling mental illness with deficits in core mental functions such as sensory gating. The P50 amplitude is an evoked brain potential which in a double-click paradigm is believed to quantify sensory gating. Reports on serotonergic modulation of P50 suppression are sparse. Therefore, in the current study, the effects of increased serotonergic activity on P50 suppression and its neural generators were investigated in healthy volunteers. In a double-blind placebo controlled cross-over design twenty-one healthy male volunteers received either placebo or a dose of 10 mg of escitalopram (SSRI), after which they were tested in a P50 suppression paradigm. Escitalopram did not affect P50 suppression, but did increase P50 amplitude to the first (or conditioning) stimulus. Two bilateral sources located in the temporal cortex, two bilaterally located near the eyes, and one in a fronto-central location were identified, with only the last one correlating positively with the P50 amplitude. In the current study, escitalopram did not affect P50 suppression in healthy male volunteers, which indicates that human sensory gating is not affected by an a-specific increase in serotonergic activity. Future research should focus on the effects of specific serotonergic subtype receptors on sensory gating. Furthermore, a generator with a fronto-central location in the brain (possibly the anterior cingulate) was found to be the primary source of the P50 evoked potential.

P50 SENSORY GATING AND REPORTS OF PERCEPTUAL ANOMALIES IN SCHIZOPHRENIA

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A hypothesis proposed to account for the deficits in information processing and attention deficits commonly seen in schizophrenia is that these individuals cannot inhibit, or "gate," irrelevant sensory input, leading to sensory inundation and an overload of information reaching consciousness, possibly due to neuronal hyper-excitability stemming from a defect in sub-cortical and cortical neuronal inhibitory pathways. In their classic article, McGhie and Chapman (1961) described a defect in a central filter which, in normal control individuals, can screen out irrelevant stimuli. Schizophrenic patients reported experiences such as "I can't shut things out," and other statements that have face validity as descriptors of an impaired internal gating mechanism. Systematic analyses of the phenomenology of these perceptual experiences as well as their physiological substrates could provide convergent validation of the sensory gating deficit hypothesis in schizophrenia. A physiological procedure used to investigate gating has been to record an evoked brain potential (EP) derived from the EEG using an auditory dual-click procedure. The EP to each of 2 paired clicks separated by 500ms (10 sec inter-pair interval) is recorded, and the amplitude reduction in a response occurring at about 50 ms (P50) to the second click (S2) compared to the first (S1) is quantified using the sensory gating ratio (S2/S1). In this study the relationship between reports of perceptual anomalies, using our Structured Interview to Assess Perceptual Anomalies (SIAPA) and P50 sensory gating was examined. Age-equivalent control (n=37), chronic paranoid schizophrenia (SCPT,n=67), and schizoaffective (SAD,n=57) groups were tested. The SIAPA has 15 items tapping anomalies of external sensory perception and attention (hypersensitivity, flooding, selective attention) on a 5-point Likert scale in each of 5 sensory modalities (auditory, visual, tactile, olfactory, gustatory). Analysis of variance (ANOVA) for the total SIAPA rating showed that the SAD and SCPT groups reported significantly more anomalies than the controls ($p<.01$). There were significant differences among the groups for each modality ($p<.01$). Results showed that for both SAD and SCPT groups, the P50 ratio was signi-

ficantly larger when the total SIAPA score was above the median SIAPA score (0.80 and 0.81) compared to below the median (0.68 and 0.55). These findings provide convergent validity for a sensory gating deficit in schizophrenia.

PRONENESS TO DELUSIONS AND SEMANTIC PROCESSES: AN ERP STUDY

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In a previous study, we used a particular semantic categorisation task designed to reduce the impact of the context-processing deficit found in schizophrenia patients. More delusional schizophrenia patients were found to have smaller N400 potentials than less delusional patients, suggesting a deficit in semantic processes. In the present study, we examined whether delusion proneness could predict N400 amplitude reduction in healthy subjects performing this task. The schizotypal personality questionnaire (Raine, 1991) was used to sort our participants into a subgroup of 24 subjects more prone to delusions (MPD) and a subgroup of 22 subjects less prone to delusions (LPD). They had to perform the categorisation task, which was made of two serially presented words, a category word (ANIMAL?) and a target word that either belonged to that category (match condition) or did not belong to it (mismatch condition). To make sure the target word was fully processed and to avoid habituation, the category word was sometimes replaced by the word INACTION. In this condition, subjects had no decision to make. ERPs elicited by target words were less negative in the N400 time window in the MPD than in the LPD subgroup in the match condition suggesting less effort at integrating semantic information.. In the P600 time window ERPs were found to be more positive for the MPD than for the LPD subgroup indicating that MPD subjects could have extracted more information from a stimulus presentation. However the information may be of poorer quality due to MPD's deficient semantic information integration.

MEG GAMMA ACTIVITY IN PSYCHOSIS

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High frequency gamma band activity has been implicated as a metric indexing information transfer in the cortex and possibly an indirect measure of GABAergic activity. Several EEG based studies have found evidence of abnormalities in gamma band activity in major mental illnesses, including schizophrenia and bipolar disorder. Our laboratory has been studying the generality of such abnormalities to psychotic disorders more broadly defined. We have used the auditory steady state response (SSR) generated by 40Hz auditory stimuli. MEG has been recorded with both 37 channel and 248 channel whole head MEG systems. Averaging, equivalent current dipole modeling and source space projection/time frequency transform (TFT) analysis techniques have been used for analyzing the resulting 40 Hz MEG SSR. Subject populations have included adults with schizophrenia and bipolar disorder, adolescents with a psychotic diagnosis, and children with autism. Studies using 37 channel instruments and analyzing the magnetic extrema for auditory SSR demonstrated abnormalities/deficiencies in gamma band production in subjects with schizophrenia (Teale et al 2003) and bipolar disorder (Abrams et al, unpublished). Deficient gamma band activity appears to characterize bipolar disorder independent of the history of psychosis (Abrams et al, unpublished), childhood autism (Wilson et al in press) and adolescents with a psychotic diagnosis (Maharajh et al, unpublished). Data from a 248 channel MEG system using TFT analysis demonstrate deficient gamma band production in adolescents with a psychotic disorder independent of diagnostic subtype (Wilson et al, under review). MEG gamma alterations in children were interpreted in the context of expected developmental differences (Rojas et al, 2006). Deficient MEG gamma band activity appears to accompany a broad range of serious mental disorders in populations ranging from childhood through adolescence and adulthood. To the extent that deficient gamma band activity in SSR type paradigms index impaired GABAergic mechanisms, such mechanisms appear to be involved in a relatively wide range of serious mental dysfunction across the age span. References: Rojas et al, Clin. Neurophysiol. 117:110, 2006 Teale et al, Biol. Psychiat. 54:1149, 2003 Wilson et al, Biol. Psychiat, in press, 2006

THE CORRELATION BETWEEN P300 ASYMMETRY AND POSITIVE SYMPTOMS SEVERITY IN SCHIZOPHRENIA EXISTS BEFORE AN ABNORMAL P300 AMPLITUDE ASYMMETRY CAN BE OBSERVED

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The amplitude of the P300 event-related potential (ERP) has been reported to be reduced over left compared to right temporal sites in schizophrenia patients. This left-temporal P300 reduction has been associated with positive symptoms' severity and gray matter reduction in the left superior temporal gyrus. Moreover, P300 asymmetry and related anatomical changes seem to increase with the evolution of the disease. The first aim of the present study was to investigate a group of young first episode psychosis (FEP) patients (mean age: 22.6) to see if left temporal P300 asymmetry already exists in persons who just began suffering from psychotic symptoms in early adulthood (median duration of untreated psychosis: 15 weeks). A second aim was to study the correlations between the amplitude of left-temporal P300 and the severity of positive symptoms in our population sample, as to the best of our knowledge no FEP studies reported these correlations. Thirdly, we intended to further test whether the P300 asymmetry index and its relation to positive symptoms' severity are specific to the schizophrenia spectrum diagnosis or can be found in FEP patients with other diagnoses. Relative to normal control subjects, no asymmetry was found in FEP patients possibly because of the quite recent onset of their symptoms and their young age. Nevertheless, a correlation between P300 asymmetry itself (the subtraction of the amplitude of the P300 at the left temporal site from the amplitude of the P300 at the right temporal site) and positive symptoms severity was already present in the schizophrenia spectrum FEP group. On the other hand, P300 asymmetry was correlated with worse global functioning scores (GAF) in the schizophrenia spectrum FEP patients, a good predictor of poor outcome. Globally, these results strengthen both the specificity of the P300 asymmetry index to schizophrenia and its sensitivity to the disease progression.

PITCH DEVIANCE ELICITED N40 AUGMENTATION AND MMN ARE ATTENUATED BY KETAMINE IN MICE

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Background: People with schizophrenia exhibit reduced ability to detect change in the auditory environment, which has been linked to abnormalities in NMDA receptor mediated glutamate transmission. This ability to detect changes in stimulus qualities can be measured with EEG using auditory event related potentials (ERPs). For example, reductions in the N100 and mismatch negativity (MMN) in response to pitch deviance have been proposed as endophenotypes of schizophrenia. Therefore, we examined a novel mouse model of impaired pitch deviance detection in mice using the NMDA receptor antagonist ketamine. Methods: We recorded ERPs from awake mice during a pitch deviance paradigm prior to and following ketamine. First, N40 amplitude was evaluated using stimuli between 4-10 kHz to assess frequency dependent auditory threshold. The N40 and subsequent temporal region, hypothesized to correspond to the mouse MMN, was then analyzed following standard (7 kHz) and deviant (5-9 kHz) stimuli. All protocols were approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. Results: Mice display increased amplitude of the N40 following deviant stimuli, which is attenuated by ketamine. The MMN to deviant stimuli is also eliminated by ketamine. Conclusions: The mouse N40 demonstrates deviance response properties similar to the human N100. Both the increased N40 and MMN to deviant pitch were blocked by ketamine, suggesting that NMDA receptor antagonism in mice mimics N100-MMN deficits in schizophrenia. Both N40 and MMN alterations following ketamine support the hypothesis that NMDA hypofunction leads to a reduction in the ability to establish cortical echoic memory for standards that is needed for subsequent deviance detection. Acknowledgements: This work was supported by the NIH/NIDA 5-R21-DA-017082-02 (SJS) and P50 MH064045 (RE Gur, PI).

CORTICAL CIRCUITRY AND HALLUCINATIONS IN SCHIZOPHRENIA: INSIGHTS FROM STUDIES OF GAMMA OSCILLATIONS

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The precise synchronization of neuronal activity mediated by oscillations in the gamma band (30-100 Hz) may play a key role in conscious perception by linking together features coded by individual neurons into coherent objects, and enhancing the downstream impact of these cell assemblies coding task-relevant, attended objects. Thus, abnormal gamma oscillations in the electroencephalograms (EEGs) of schizophrenia patients (SZ) could be related to these patients' hallucinations, in which they perceive auditory and visual objects which are not physically present. We will present findings from previously-published and new studies that support this hypothesis. 1) The phase locking of the early visual-evoked gamma oscillation (VGO) was reduced in SZ compared to healthy controls (HC) in a Gestalt perception task. 2) We also found another gamma oscillation (RLO) that was phase-locked to subjects' reaction times for perceived Gestalts. In SZ the RLO occurred at a lower frequency range than in HC and was positively correlated with visual hallucination symptom scores. In contrast, visual evoked potential amplitude was reduced in SZ with vs. without a history of visual hallucinations. 3) The phase-locking aspect of the auditory 40 Hz steady-state response to right ear (left hemisphere) stimulation was negatively correlated with auditory hallucination scores. 4) The reduction of the VGO in SZ overall was actually due to this oscillation being reduced in patients with a history of visual hallucinations. 5) The early auditory-evoked gamma oscillation was reduced in SZ with low vs. high auditory hallucination symptom scores. In sum, hallucination symptoms were associated with reduced sensory-evoked activity but enhanced perception-related activity. These data support the hypothesis that hallucinations are related to gamma oscillations in schizophrenia. Our findings are consistent with evidence for hyperexcitability in the sensory cortex of hallucinators from transcranial magnetic stimulation and functional neuroimaging studies, which suggest that the cortex's response to external input is decreased but its intrinsic activity is increased. Animal models suggest that cortical hyperexcitability could be due to NMDA receptor hypofunction and impaired function of inhibitory interneurons, both of which have been implicated in schizophrenia and are crucial for the generation of gamma oscillations.

ASSOCIATION OF SUSCEPTIBILITY GENES FOR SCHIZOPHRENIA WITH GAMMA FREQUENCY ANOMALIES DURING SUSTAINED ATTENTION

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Candidate susceptibility genes for schizophrenia (NRG1, DTNBP1, and COMT) appear to affect frontal glutamate and dopamine systems. It may be productive to study neural phenotypes in schizophrenia that are dependent on glutamatergic and dopaminergic transmission. Evidence indicates that disruption of high frequency activity in electrophysiological recordings (i.e., gamma band activity) can be induced through alteration of the glutamate kinetics of interneurons. Several studies have revealed gamma activity abnormalities in schizophrenia patients during visual stimulation. We recently found diminished high frequency responses in unaffected first-degree relatives of schizophrenia patients, thus providing evidence for a gamma oscillation endophenotype in the disorder. Prefrontal dopamanergic influence on gamma activity has largely gone unexamined. We carried out analyses to test whether COMT val allele (Val108/158Met) in schizophrenia patients and first-degree biological relatives of schizophrenia patients is associated with diminished gamma oscillations to target stimuli during a sustained visual attention task (the degraded-stimulus continuous performance task [DS-CPT]). Preliminary results support the association of the COMT val allele with a gamma oscillation endophenotype in schizophrenia. Although specific functional polymorphisms related to the pathophysiology of schizophrenia have yet to be identified for NRG1 and DTNBP1 genes, single nucleotide polymorphisms (SNPs) of NRG1 and DTNBP1 will be tested for association with gamma frequency anomalies in schizophrenia patients and their relatives.

DOPAMINE D2 INHIBITION OF PREFRONTAL CORTEX EXCITATORY TRANSMISSION IS COMPROMISED IN A DEVELOPMENTAL ANIMAL MODEL OF SCHIZOPHRENIA

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Animals with a bilateral neonatal ventral hippocampal lesion (NVHL) have been proposed as a developmental model of cortical deficits in schizophrenia. Recent studies have indicated that the mesolimbic/mesocortical system is compromised in these animals. Activation of the mesocortical pathway typically elicits a hyperactive response in the PFC of NVHL animals, but only after puberty. This suggests that dopamine (DA) modulation of PFC neuronal activity is developmentally compromised in these animals. Indeed, we have recently observed that bath application of the D2 agonist quinpirole induced a concentration-dependent excitability decrease in the PFC of both NVHL and sham animals. However, this effect was significantly attenuated in the PFC of lesioned animals, with its dose-response curve shifted to the right. Here we investigated how the D2 attenuation of excitatory transmission in deep-layer pyramidal neurons is affected in the PFC of NVHL animals by conducting whole-cell patch clamp recordings in brain slices obtained from adult sham and lesioned rats. Electrical stimulation of layers I-II at a site ~1 mm lateral to the recorded cell resulted in a typical non-NMDA fast excitatory postsynaptic potential (EPSP) that lasted ~100 ms. Bath application of quinpirole (2 uM) reduced EPSP amplitude by ~20 % in both post-pubertal sham (n=6) and NVHL (n=7) animals. This effect was completely blocked with eticlopride (n=7) confirming that the inhibition is mediated by D2 receptors. Interestingly, pyramidal neurons recorded from NVHL rats recovered to baseline amplitude by ~10 min after quinpirole was removed from the bath. In contrast, a period of at least 20 min was required to partially washout the effect of quinpirole in the sham PFC. Only in presence of the GABA-A antagonist picrotoxin (10 uM), the duration of this long post-quinpirole effect could be reduced in sham animals (n=6) to a degree comparable to that observed in the PFC of lesioned rats. These results indicate that part of the inhibitory action of D2 receptors on pyramidal neuron excitatory transmission involves activation of local GABAergic interneurons, an interaction that becomes compromised in the PFC of NVHL animals. These changes could lead to the abnormal mesocortical response observed in NVHL animals. It is possible that a similar mesocortical pathophysiological alteration may underlie some of the cortical deficits observed in schizophrenia, a disorder characterized by hypofrontality.

THE PROFILE OF AUDITORY INFORMATION PROCESSING DEFICITS IN SCHIZOPHRENIA

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Abnormalities in auditory ERP measures of information processing have been widely reported in schizophrenia. Impairments commonly associated with illness extend from very early pre-attentive to late cognitive processes. Although the evidence supporting each individual deficit is substantial, the question of how the different physiological abnormalities relate to each other remains unaddressed, since multiple measures have only rarely been acquired contemporaneously in the same sample. This study was therefore designed to address two questions: 1)Do specific auditory ERP measures show evidence of differential impairment in schizophrenia? 2)Do different auditory ERP abnormalities co-aggregate within the same patients or within different patient subsets? Nine individual measures - acoustic startle magnitude, pre-pulse inhibition of startle, P50 amplitude, P50 gating, N100 amplitude, pitch deviant and duration deviant mismatch negativity, P3a and P3b subcomponents of the P300 - were acquired within the same testing session from 23 schizophrenia patients and 22 healthy comparison subjects. Two statistical procedures - profile analysis and hierarchical oblique factor analysis - were employed to answer the two questions of interest. Four individual measures - N100, pitch MMN, P3a, P3b - were abnormal in patients. Profile analysis indicated that 3 of these - N100, MMN, P3b - constituted a selective or differential deficit. The hierarchical oblique factor analysis revealed that the 9 auditory ERP measures aggregated into 4 unique primary factor and one secondary or general factor containing shared variance, with each measure loading primarily on a single factor. N100, pitch MMN and duration MMN constituted 1 factor. P50 gating was an isolated factor. P50 amplitude, startle magnitude and PPI were a 3rd factor. P3a and P3b comprised factor 4. Analysis of factor scores indicated patient deficits for factors 1 and 4. Patients who were abnormality on factor 1 also had greater deficits on SANS alogia and SAPS formal thought disorder subscales. We conclude, in part, that deficits in ERP measures of early sensory processing at the level of the primary and secondary auditory cortex co-occur within individual patients, that these represent a single common differential deficit, and that this may be an index of the physiological abnormality underlying clinical symptoms of impaired language and verbal processing.

NEURAL SYNCHRONY AS A PATHOPHYSIOLOGICAL MECHANISM IN SCHIZOPHRENIA?

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Schizophrenia is a neurodevelopmental disorder that is associated with neurocognitive deficits and an onset of psychotic symptoms typically during late adolescence. Current theories converge on the notion that cognitive deficits and the symptoms of the disorder may reflect an impairment in the precise temporal coordination of distributed neural activity. Synchronization of neural responses in the beta- (15-30 Hz) and gamma- (30-80 Hz) band is a possible mechanism to coordinate distributed neural activity and has been implicated in perceptual organization, working memory and attention (Singer, 1999). Anatomically, neural synchronization is mainly mediated by cortico-cortical connections that mature relatively late during development. In the current study, we explored the role of neural synchrony in the pathophysiology of schizophrenia by examining EEG-activity in schizophrenia patients (N=25), bipolar patients (N=20) and age-matched controls (N=25) during a Gestalt perception task. In addition, we examined the development of neural synchronization in the beta- and gamma-band in a sample of children and adolescents (N=75). EEG-data were analysed for induced and evoked spectral power as well as for phase-synchrony. The results showed that: 1) patients with schizophrenia are characterized by a deficit in long-range synchronization in the beta-band and dysfunctional Gestalt perception (Uhlhaas et al., 2006). Dysfunctions in long-range synchronization were also present in bipolar patients but less pronounced than in schizophrenia. 2) patients with schizophrenia showed reductions in evoked beta- and induced gamma-band

oscillations 3) evoked and induced high-frequency oscillations, especially in the gamma-band, increased strongly during adolescence. In addition, changes in the topography of phase-synchrony were indicative of widespread network reorganization. These data suggest that patients with schizophrenia are characterized by deficits in long-range and local neural synchronization that may be related to cognitive deficits associated with the disorder. The pronounced changes of synchronous, oscillatory activity in the beta- and gamma-frequency during adolescence highlight that aberrant maturation of cortical networks may have a role in the development of schizophrenia. Together these findings indicate that dysfunctional neural synchronization may be an important target for further research aimed at elucidating the pathophysiology of schizophrenia.

MISMATCH NEGATIVITY (MMN), EXECUTIVE FUNCTION AND SYMPTOM SEVERITY IN 1ST EPISODE AND CHRONIC SCHIZOPHRENIA

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Aims/Background: As part of a multi-site collaborative study, we examined the clinical and neuropsychological correlates of mismatch negativity (MMN), an ERP index of auditory sensory memory in patients with schizophrenia with either a short duration of illness, or a more chronic illness. We tested subjects using both the classic 'oddball' paradigm, and a novel paradigm in which the number of standards preceding a deviant varied systematically. Methods We tested patients meeting DSM-IV criteria for schizophrenia with a short duration of illness (DOI) (< 2 years) and with a long DOI (> 5 years) and age and gender matched healthy volunteers. Assessment of executive functions included the Hayling (Sentence Completion) and Brixton (Spatial Anticipation) Battery. EEG data were recorded from 64 scalp electrodes whilst subjects watched a silent movie, and tones were presented via headphones. The paradigm consisted of standard duration (50ms) tones interspersed with deviant duration tones (100ms) at a rate of 8%. MMN amplitudes at F3, Fz and F4 (fronto-central left, midline and right) were analysed using RMANCOVA, (within-subject factors of deviant probability and electrode, between-subject factor of group [1st episode schizophrenia, chronic schizophrenia, and healthy control]. Relationships between MMN amplitude, neuropsychological test results and symptom severity scores were analysed using Spearman's correlations. Results There was a significant group effect for the MMN amplitude ($p < 0.05$) indicating lower MMN amplitudes for the long DOI patient group. A significant group by electrode interaction ($p < 0.05$) reflected that patients with long DOI, but not short DOI, showed smaller MMN amplitudes in the left hemisphere whereas in healthy controls amplitudes were greater in the right hemisphere. In the short DOI patient group, reduced frontal MMN amplitude was significantly correlated with lower GAF scores ($p < 0.05$), and greater attentional impairment ($p < 0.01$). In the long DOI patients, reduced frontal MMN amplitudes were significantly correlated with greater affective flattening ($p < 0.01$) on the SANS. Conclusions MNN amplitude reduction differs according to duration of illness in patients with schizophrenia, and there is evidence of different patterns of correlation with clinical ratings. Supported by the National Health and Medical Research Council of Australia

GAMMA-PHASE SYNCHRONY AND GREY-MATTER VOLUME: A LONGITUDINAL STUDY OF FIRST EPISODE SCHIZOPHRENIA

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From an integrative neuroscience perspective, schizophrenia is characterized by a breakdown in the fundamental neural mechanisms for binding multiple sources of information. High frequency (40Hz) Gamma synchrony, which is dependent on both inhibitory GABAergic and excitatory glutamatergic actions, has been proposed as a mechanism for neural binding. We examined whether the progressive grey matter reductions exhibited by patients with first episode schizophrenia (FES)[1] were associated with corresponding changes in Gamma synchrony,**Methods:** 25 FES patients underwent a structural MRI scan (T1-weighted, MPRAGE sequence) within 3 months of their first presentation to mental health services (baseline), and again 2-3 years later (follow-up). EEG recordings were also undertaken at baseline and follow up in response to an auditory oddball task. An automated masking procedure was employed in order to calculate patients' GM volumes in the L/R frontal, parietal and temporal lobes. Gamma phase synchrony was extracted from the EEG for analogous cortical regions using customized software. Repeated-measures ANOVAs were used for statistical analysis, with brain 'region' and 'time' (i.e. baseline vs follow-up) entered as within-subjects factors. **Results:** An inverse relationship between progressive grey matter loss and Gamma synchrony was revealed. While FES patients lost significant frontal and parietal GM volume over the 2-3 years, there were corresponding increases in parietal Gamma synchrony. **Discussion:** The results suggest that grey matter loss disturbs the inhibitory-excitatory neural mechanisms of Gamma synchrony, producing an excessive level of neural binding even in the relatively early stages of schizophrenia. Given the role that Gamma synchrony has been proposed to play in binding diverse information into a coherent percept, these findings provide support for an integrative neuroscience model of schizophrenia as a disorder of neural binding[2]. **References** 1. Whitford TJ et al. (2006). Progressive grey matter atrophy over the first 2-3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. Neuroimage, 32, 511-519. 2. Williams LM (2006). An integrative neuroscience model of 'significance' processing. Journal of Integrative Neuroscience, 5, 1-47. **Acknowledgment:** Pfizer senior research fellowship (LMW). Support from the Brain Resource International Database (www.brainresource.com), coordinated by BRAINnet (www.brainnet.org.au).

15. Eye Movement Physiology

SCHIZOPHRENIA AND THE MAGNOCELLULAR PATHWAY: A VISUAL BACKWARD MASKING STUDY

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This study seeks to discover the functionality of the Magnocellular (M) Pathway in schizophrenia patients. It has been shown that schizophrenia patients have a hyperactive M pathway when compared to non-psychiatric controls. Previous research has shown that this pathway can be suppressed using red light. This study uses a Visual Backward Masking paradigm to manipulate M pathway functioning. Participants are shown stimuli presented on either a red or green background and are asked to accurately locate the position of the stimulus on the screen. The stimuli and mask are separated by varying intervals of time. Results will be analyzed using a one-way ANOVA looking for differences in percent accuracy by background color for each inter-stimulus interval. It is hypothesized that in the red background condition, where the M pathway is suppressed, that schizophrenia patients will show an accuracy rate similar to non-psychiatric controls on a green background.

A CLOSER LOOK AT NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: A SACCADIC EYE MOVEMENT STUDY

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The negative symptoms of schizophrenia are perhaps the most unremitting and burdensome features of the disorder. Negative symptoms have been associated with distinct motor, cognitive and neuropathological impairments, possibly stemming from frontostriatal dysfunction. Ocular motor research is a particularly advantageous means of evaluating cognitive and motor functioning. Therefore, this study examined the ability of patients with schizophrenia, with and without prominent negative symptoms, to perform a variety of eye movement paradigms to investigate basic sensorimotor functions, inhibitory control and spatial working memory. Twenty-one patients meeting DSM-IV criteria for schizophrenia (10 with high and 11 with low ratings of negative symptoms) and 14 controls participated. Tasks explored suppression of reflexive saccades during qualitatively different tasks, the generation of express and anticipatory saccades, and the ability to respond to occasional, unpredictable ("oddball") targets that occurred during a sequence of well-learned, reciprocating saccades between horizontal targets. Spatial working memory was assessed using a single and a two-step memory-guided task (involving a visually guided saccade during the delay period). Results indicated significant increases in response suppression errors, as well as increased response selection impairments, during the oddball task, in schizophrenia patients with prominent negative symptoms. Schizophrenia patients with increased negative symptoms scores were also more variable in their performance and generated saccades with increased peak velocities. Collectively, these findings provide further support for the proposed association between frontostriatal dysfunction and negative symptoms.

SACCADIC EYE MOVEMENT DEFICITS ACROSS TREATMENT-NAïVE FIRST-EPISODE PSYCHOTIC DISORDERS: ENDOPHENOTYPE SPECIFICITY

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Recent investigations of genotypic risks for psychosis have established several common features across disorders. Some commonalities in endophenotypes have also been reported. Antisaccade deficits are a promising endophenotype of genetic risk for schizophrenia, but their specificity to schizophrenia is not well established. In the current study, antipsychotic-naïve, first-episode psychosis patients with diagnoses of schizophrenia (n=59), bipolar disorder (n=9) or non-bipolar major depression (n=15) performed oculomotor tasks (antisaccade and visually-guided saccade) during the acute phase of illness and were compared to matched groups of non-psychotic patients with major depression (n=40) and healthy individuals (n=106). Compared to healthy individuals, schizophrenia patients showed higher rates of antisaccade errors. All other patient groups also displayed increased error rates. Only schizophrenia patients showed prolonged antisaccade latencies. No impairment was evident for visually-guided, or reflexive, saccades to targets, with the exception of hypometric saccades in the non-bipolar psychotic depressed group. The results suggest that the reduced ability to suppress context inappropriate behavior, reflected in increased antisaccade error rates, may not be a specific biomarker for schizophrenia, and thus might be an endophenotype related to psychosis across major psychiatric disorders. The differential pattern of performance in psychotic patient groups across oculomotor tasks is consistent with other observations indicating that considering profiles of deficits across paradigms may be a promising approach for identifying disorder-specific phenotypes. Supported by NIH MH62134, MH45156, MH01433 and NIH/NCRR/GCRC M01 RR00056.

FURTHER REFINING THE EYE-TRACKING ENDOPHENOTYPE OF SCHIZOPHRENIA: RESPONSE TO FOVEALLY STABILIZED MOVING OBJECT

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Context: Smooth pursuit eye movement abnormality is thought to mark schizophrenia liability. However, the precise nature of the abnormality is unknown. Previous work suggests that reduced predictive pursuit response to a briefly removed moving object observed in schizophrenia patients and their relatives may be the underlying deficit. However, the awareness of target removal may have affected pursuit performance. Foveal stabilization is used to experimentally stabilize the image of the moving object on the fovea during smooth pursuit and effectively sets the visual feedback to zero in order to isolate the responses from the brain's internal representation of the object motion. Objective: To confirm earlier findings of predictive pursuit abnormality in schizophrenia; and to determine whether the abnormality is in the internal representation of motion or in the motor feedback. Design: A new covert stabilization approach was developed to digitally stabilize the image of a moving object on the fovea

during smooth pursuit when the eyes had momentarily stopped. Performance was compared among schizophrenia patients, their relatives, and comparison subjects. Setting: Outpatient clinics. Participants: Schizophrenia patients (n=45), non-schizophrenia first-degree relatives (n=42), and an epidemiologically matched healthy comparison group (n=22). Main Outcome Measures: Predictive acceleration and predictive pursuit gain. Results: Schizophrenia patients (p= 0.004) and non-schizophrenia relatives (p= 0.04) had reduced predictive acceleration during the initial phase of predictive pursuit as compared to the healthy controls. Similarly, schizophrenia patients (p= 0.01) and relatives (p= 0.05) had reduced predictive pursuit gain compared to healthy controls during steady state foveally stabilized pursuit. Conclusions: This study confirms the finding of abnormal predictive pursuit in schizophrenia using a novel covert foveal stabilization technique during smooth pursuit. Reduced predictive acceleration suggests that this abnormality is not a motor-feedback problem, but rather a deficit in the internal representation or discharge of the anticipated motion.

UNPREDICTABILITY AND SACCADIC COMPONENT OF OCULAR PURSUIT IS INFLUENCED BY THE TARGET MOTION IN SCHIZOPHRENICS

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Oculomotor abnormalities are useful markers of genetic liability to schizophrenia. Smooth pursuit eye movements use three systems: the smooth pursuit component, the saccadic component and the prediction based on internal representation of target movement. The predictive component of smooth pursuit has been studied by comparing the gain, i.e. the ratio of eye velocity to target velocity, during predictable (pure sinusoid) and unpredictable (pseudo-random stimuli composed of a mixture of sinusoids of different frequencies) target motions. The aim of this experiment was to study those components and pursuit performances in schizophrenics as compared with controls. 51 schizophrenics (DSM IV, categorized into deficit and non-deficit subgroups) and 21 controls were studied. During a predictable task, subjects were asked to track a target which moved in horizontal sinusoidal waveform at 0.4 Hz. The smooth pursuit gain was the ratio of the amplitude of eye velocity to target velocity. For the unpredictable task, the target motion was composed of five sinusoidal waveforms moving at respectively 0.1, 0.2, 0.4, 0.6 and 0.8 Hz. The pseudo-random pursuit gain was calculated for each subject and each frequency. The combination of smooth and saccadic eye position gains was called "pseudo-random eye position", it was calculated for each subject and for each frequency as the ratio of the amplitude of the eye position to the amplitude of the target position. The mean smooth pursuit gain was significantly decreased in schizophrenics as compared to healthy controls with no significant differences between patient's groups. During pseudo-random task at 0.4 Hz, the gain was similar in all groups. The gain was higher during predictable target as compared to pseudo-random stimulus at 0.4 Hz. However the difference between the mean gains of the two paradigms was significantly lower in schizophrenics as compared to controls. The mean pseudo-random eye position gain was higher in schizophrenics as compared with controls, especially at the highest frequency (0.8 Hz). No correlations were found between the gain and any of the clinical variables. The predictive mechanisms involved in the eye pursuit of an unpredictable target were impaired in schizophrenic patients. At 0.8 Hz, deficit schizophrenics had the highest pseudo-random eye position gain and the lowest pseudo-random pursuit gain, indicating that the saccadic system was used to compensate for low smooth pursuit gain.

16. Therapeutics: Treatment Trials

CLOZAPINE FOR FIRST-EPISODE SCHIZOPHRENIA PATIENTS WITH PERSISTING POSITIVE SYMPTOMS

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Early and appropriate treatment with antipsychotics is an important strategy for patients with first-episode schizophrenia. The large majority of patients treated for their first episode of schizophrenia will experience considerable improvement with initial antipsychotic treatment; however, many patients will experience significant ongoing positive symptoms. While clozapine has unique efficacy in improving treatment-refractory patients with chronic schizophrenia, its role in the treatment of first episode patients remains unclear. We have implemented a treatment algorithm in our First Episode Psychosis Program to standardize medication treatment. Patients are treated according to a 7-step algorithm, which includes an atypical antipsychotic at low, medium and high doses (Stage 1, 2 and 3), a second trial of a different atypical antipsychotic at low, medium and high doses (Stage 4, 5, and 6) and then a trial of clozapine. Patients progress along the algorithm according to the CGI and BPRS rating scales. This analysis was carried out to determine how many patients fail to respond to initial trials of atypical antipsychotic treatment, and to characterize their response to clozapine. To date, 115 patients with a first episode of schizophrenia have been treated according to the algorithm. Of these, 97 (84.3%) responded to the first trial of an antipsychotic. Only 6 patients responded to the second antipsychotic trial. Twelve patients who failed to respond to a second antipsychotic agreed to a trial of clozapine; another 7 patients who had been treated according to the algorithm did not agree to a trial of clozapine but were nonetheless followed over time. As a result, we are able to compare the 12 patients who accepted a trial of clozapine with the 7 patients who did not. The patients treated with clozapine experienced a mean BPRS change of 25.4 points (from 58.9 to 33.5) and a change in the CGI severity rating from 5.7 to 3.1 (from severely ill to mildly ill); those who refused clozapine had only a 0.4 change in mean BPRS (from 58.0 to 57.6) and only a 0.2 change in CGI-S from 5.7 to 5.5 (remaining markedly to severely ill). The results suggest that if patients with first episode fail a high dose of their first antipsychotic the chance that a second non-clozapine antipsychotic will help is low; but clozapine does show remarkable efficacy in those who are willing to take it. Should clozapine be considered as a second-line treatment?

LIPID PROFILE AMONG PATIENTS WITH SCHIZOPHRENIA RANDOMIZED TO BIFEPRUNOX, PLACEBO, OR OLANZAPINE: A COMPARISON OF RESULTS

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(a) To examine lipid changes in patients with an acute exacerbation of schizophrenia treated with bifeprunox. (b) A 6-week randomized, double-blind, placebo-controlled, olanzapine-referenced, parallel-group, multi-center study of bifeprunox was conducted. Patients with acutely exacerbated schizophrenia (DSM-IV-TR) were randomized to once-daily treatment with bifeprunox 20 mg (n=154), 30 mg (n=150), placebo (n=150) or olanzapine 15 mg (n=150). Bifeprunox doses were titrated, beginning with a dose of 0.25 mg on day 1 and approximately doubled every day until 20 mg (day 7) or 30 mg (day 8) was reached; olanzapine was dosed at 10 mg for the first 7 days, and then maintained at 15 mg for the remainder of the study. Lipid measures at baseline and endpoint included fasting and non-fasting patients: total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL). (c) In this study, bifeprunox 20 and 30 mg trended towards an improved lipid profile compared to olanzapine (Table 1). In addition, bifeprunox 30 mg significantly improved TG levels from baseline compared with placebo. (d) These results suggest that bifeprunox may be associated with a favorable lipid profile in patients with schizophrenia.

Table 1

	Treatment Group			
Lipid Parameter	Bifeprunox 20 mg (N=154)	Bifeprunox 30 mg (N=150)	Placebo (N=149)	Olanzapine 15 mg (N=150)
Total Cholesterol, n	132	128	127	127
Baseline Mean	190.5	195.8	198.4	194.0
Mean Change from Baseline (SD)	-16.3 (30.5)	-16.5 (35.1)	-12.7 (31.7)	-2.1 (37.4)
Triglycerides, n	132	128	127	127
Baseline Mean	155.1	179.3	175.9	172.2
Mean Change from Baseline (SD)	-24.1 (81.4)	-50.7 (92.5)	-27.1 (106.7)	0.5 (98.4)
VLDL, n	107	108	109	112
Baseline Mean	29.4	32.8	32.9	32.6
Mean Change from Baseline (SD)	-4.0 (14.7)	-7.4 (13.6)	-4.6 (17.0)	0.3 (16.3)
LDL, n	125	119	119	116
Baseline Mean	112.0	113.7	119.4	109.4
Mean Change from Baseline (SD)	-9.7 (28.5)	-9.1 (29.6)	-10.3 (30.5)	1.6 (31.5)
HDL, n	132	128	127	127
Baseline Mean	48.3	47.8	46.8	48.1
Mean Change from Baseline (SD)	-1.5 (10.7)	0.4 (12.4)	0.2 (15.0)	-2.7 (13.6)

PROGRESS IN TREATMENT OF AUDITORY HALLUCINATIONS WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

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Slow repetitive transcranial magnetic stimulation (rTMS), at 1 Hz, has been proposed as a treatment for auditory hallucinations. Several studies have now been reported regarding the efficacy of TMS treatment. Although some results have been inconsistent, significant reductions in hallucination frequency have been reported by a number of studies. This symposium will discuss the newest findings utilizing rTMS in clinical trials of patients with auditory hallucinations highlighting prospects as a clinical intervention, predictors of clinical response, safety, novel strategies for positioning using functional and structural MRI, and different stimulation frequencies. In addition, we will address how novel investigative approaches (e.g., fMRI and EEG) may be used help identify mechanisms through which treatment effects are optimized.

SIMILAR RATES OF AGITATION, ANXIETY AND INSOMNIA IN SEDATING AND NON-SEDATING ANTIPSYCHOTICS: EVALUATING CLINICAL TRIAL RESULTS WITH ARIPIPRAZOLE, HALOPERIDOL AND OLANZAPINE

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Calming rather than sedation is the goal when managing agitation. However, calming and sedation have not been well described and their relationship is obscure. Aripiprazole (Ari) is an atypical antipsychotic (AA) with a unique mode of action and a receptor signature substantially different from other AAs. Although it has demonstrated calming properties, patients initiating Ari may experience symptoms such as agitation, anxiety and insomnia, particularly when switching from full D2 antagonists with sedative and anticholinergic properties. Agitation, anxiety and insomnia were assessed in schizophrenia patients receiving Ari, haloperidol, (Hal) or olanzapine (Olz) in 3 trials: a 52-week study, comparing Ari 30mg/d (n=859) and Hal 10mg/d (n=431) and 2 trials (26- and 52-week) comparing Ari 15-30mg/d (n=504) and Olz 10-20mg/d (n=505). Incidence, time to onset, duration and severity of symptoms, discontinuation rates and concomitant use of benzodiazepine (BZD) associated with these AEs were assessed. The analysis focused on the first 12 weeks of these trials, since these AEs are most commonly reported in the initial phase of treatment. At endpoint, patients reported comparable rates of anxiety in the Ari and Hal groups (Ari: 11.8%; Hal: 10.4%), agitation (Ari: 5.7%; Hal: 7.2%) and insomnia (Ari: 20.5%; Hal: 18.8%). Similarly, Ari and Olz patients reported comparable rates of anxiety (Ari: 14.3%; Olz: 13.7%), agitation (Ari: 6.4%; Olz: 8.3%) and insomnia (Ari: 24.8%; Olz: 20%). Most patients (≥75%) reported these AEs during the first 12 weeks of the trials. In the Hal trial, the median duration of the AEs was of 1-2 weeks and similar in both groups. In the Olz trials, the median duration was much shorter (≤ 3 days) in both Ari and Olz. Most AE cases (≥80%) were reported as mild or moderate and rarely led to discontinuation. BZD use was similar for all groups, varying from 55 to 61% among patients not reporting AEs and from 87 to 91% for those reporting the AEs. Under double-blind conditions, some aspects of anxiety, agitation and insomnia appear similar for Ari and Hal, two non-sedating antipsychotics. These AEs were also similar for Ari and Olz, contrary to assumptions about Olz sedative effects. High BZD use may have masked the course and severity but should not do so differentially. These results suggest that agitation, anxiety and insomnia are not directly related to sedation; however, more data are warranted to support this preliminary conclusion.

EFFECT OF REGRESSION TO THE MEAN ON DRUG-INDUCED WEIGHT CHANGE

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Background: The misconception that antipsychotic drugs cause less weight gain among obese subjects than among non-obese subjects may be due to regression to the mean (RTM). The principle of RTM predicts that a mean weight loss (or gain) will tend to occur in a group selected on the basis of high (or low) baseline values, even in the absence of real causal differences in the effects of the drugs by baseline weight. The objective of this post-hoc analysis is to assess the effect of RTM on determining weight change induced by antipsychotic treatments. Methods: We analyzed two long-term, randomized, placebo or active-controlled schizophrenia patient cohorts. Patient Cohort 1 consisted of a total of 1649 subjects in 11 studies of ziprasidone and several antipsychotic agents (olanzapine, risperidone, and haloperidol). All subjects with weight data collected for the treatment durations of 6 months (150-210 days, N=450) and 12 months (330-390 days, N=470) were included in the analysis. Patient Cohort 2 consisted of 294 stable, chronic subjects with schizophrenia in a randomized, double-blind, placebo-controlled, 1-year study of ziprasidone. Subjects were classified according to their baseline BMI: underweight or normal (<25); overweight (25-29.9); and obese (>30). We performed regression analyses to evaluate the effect of RTM on weight change. ANCOVA model was used to estimate the placebo-corrected antipsychotic effects on weight change, and its interaction with baseline BMI value. Results: Evaluations of weight changes in the placebo group showed the greatest weight loss, on average, in those with the highest baseline BMI in Patient Cohort 1 ($r=0.87$ at 6 months; $r=0.76$ at 1 year; $p<0.001$). Similar RTM effect was observed among placebo-treated subjects in Patient Cohort 2. Tellingly, there were no significant interactions between baseline BMI range and antipsychotic treatment effect on weight change for ziprasidone, haloperidol, risperidone, and olanzapine ($p=0.47$). Conclusions: These results suggest that the weight-gain inducing properties of antipsychotic drugs are independent of baseline BMI. Correction for RTM is necessary for the accurate assessment of antipsychotic-induced weight change. The omission of appropriate correction for RTM bias has likely resulted in a systematic underestimation of the weight gain induced by atypical antipsychotic treatment among subjects with high baseline weight.

OMEGA-3 FATTY ACIDS REDUCE THE RISK OF EARLY TRANSITION TO PSYCHOSIS IN ULTRA-HIGH RISK INDIVIDUALS: A DOUBLE-BLIND RANDOMIZED, PLACEBO-CONTROLLED TREATMENT STUDY

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Evidence that fatty acid deficiencies or imbalances may contribute to neurodevelopmental disorders warrants investigation on the therapeutic efficacy of omega-3 fatty acids in prodromal schizophrenia and other psychoses (Berger et al, 2006). We conducted a randomized, double-blind, placebo-controlled trial testing the effects of 1.5 g/day omega-3 fatty acids (0.84 g/day eicosapentaenoic acid, EPA; 0.7 g/day docosahexaenoic acid, DHA) administered as a supplement in 81 adolescents (mean age=16.4, SD=2.1, range=13-24 years) with subthreshold symptoms at incipient risk for progression to a first-episode psychosis. This "at-risk-mental-state" was classified by the criteria of Yung et al (2005). Psychiatric measures included PANSS, MADRS, and GAF. Supplementation was administered for 12 weeks. Side effects were recorded using the UKU. Transition to psychosis was operationally defined, based on Yung et al.'s criteria, using cut-off points on PANSS subscales, (4 or more on hallucinations, 4 or more on delusions, and 5 or more on conceptual disorganization), and the frequency of symptoms (at least several times a week) and their duration (more than one week). Chi-square test and

t-test were used for group comparisons. Statistical tests were two-tailed. P values of 0.05 or less were considered significant. At 12-week follow up 1 (2.6%) of 38 individuals in the EPA/DHA group and 8 (21.1%) of 38 in the placebo group met exit criteria for psychotic disorder. A Chi-square exact test indicated a significant group difference (exact p=0.028). The change from baseline on the PANSS positive symptom score (p=0.014), the PANSS global symptom score (p=0.006), and the GAF score (p=0.025) also differed between treatment groups showing a statistically significant and clinically relevant advantage of EPA/DHA over placebo. No serious side effects, or other adverse events, were observed. The positive findings of this first RCT indicate a potentially important role for omega-3 fatty acids as treatment in subthreshold states. The findings, however, need replication and warrant longer term observation. Berger GE, Smesny S, Amminger GP. Bioactive lipids in schizophrenia. Int Rev Psychiatry 2006 18:85-98 Yung AR, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005 39:964-71

LONG-TERM EFFECTS OF ARIPIPRAZOLE ON THE LIPID PROFILES OF PATIENTS WITH SCHIZOPHRENIA IN A 26-WEEK PLACEBO-CONTROLLED TRIAL

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Serum lipid level changes in patients with stabilized chronic schizophrenia treated with aripiprazole in a 26-week, randomized, double-blind, placebo-controlled trial were analyzed in response to an FDA request. Incidences of treatment-emergent abnormal lipid levels associated with aripiprazole 15mg/d (n=153) or placebo (n=153) were assessed at Weeks 6, 18, and 26. Statistical differences were compared using the Fisher's Exact Test. The FDA requested that thresholds for abnormal lipid values (total cholesterol [TC] ≥240mg/dL, low-density lipoprotein [LDL] ≥160mg/dL, high-density lipoprotein [HDL] <40mg/dL, or triglycerides ≥200mg/dL) be based on guidelines from the NCEP ATP III. Mean changes (baseline-to-endpoint) in lipid levels were analyzed by ANCOVA. Total pooled incidences of abnormal fasting and nonfasting lipid levels did not differ significantly between aripiprazole- and placebo-treated patients: TC = 20/142 (14.1%) aripiprazole, 10/138 (7.2%) placebo; LDL = 12/139 (8.6%) aripiprazole, 10/137 (7.3%) placebo; HDL = 47/142 (33.1%) aripiprazole, 53/138 (38.4%) placebo; triglycerides = 33/142 (23.2%) aripiprazole, 32/138 (23.2%) placebo. Mean changes (baseline-to-endpoint) in lipid levels were also not significantly different between aripiprazole- and placebo-treated patients: TC (mean [SE]) = -11.8mg/dL (2.9) aripiprazole, -1.4mg/dL (2.5) placebo; LDL = -7.5mg/dL (2.6) aripiprazole, -2.0mg/dL (2.2) placebo; HDL = -0.4mg/dL (1.2) aripiprazole, 0.0mg/dL (0.9) placebo; triglycerides = -24.1mg/dL (10.3) aripiprazole, 2.2mg/dL (6.5) placebo. When fasting and nonfasting labs was looked at separately, incidences of abnormal lipid levels remained nonsignificant between aripiprazole and placebo. Significantly reduced TC and LDL levels were observed in nonfasting patients on aripiprazole, compared with placebo (P<0.05). No other significant differences in lipid levels were observed between aripiprazole and placebo for fasting or nonfasting groups. Patients with schizophrenia who received long-term treatment with aripiprazole had similar lipid profiles to those receiving placebo.

EFFICACY AND METABOLIC PROFILE OF BIFEPRUNOX IN PATIENTS WITH SCHIZOPHRENIA

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(a) Examine efficacy and metabolic effects of bifeprunox in patients with acute and stable schizophrenia. (b) A 6-month randomized, double-blind, placebo (PBO)-controlled study of bifeprunox (20 mg: n=158; 30 mg: n=172; PBO: n=166) evaluated patients with stable schizophrenia (n=166). Time to deterioration was the primary efficacy endpoint. Efficacy and metabolic data were assessed in four 6-week randomized, double-blind, PBO-controlled, active-referenced studies in patients with an acutely exacerbated schizophrenia. Treatment groups were: bifeprunox (1, 5, 10, 20, 30, and 40 mg, n=1080), PBO (n=454), haloperidol 10 mg (n=50), risperidone 6 mg (n=267) and olanzapine 15 mg (n=146). Efficacy was defined as change from baseline in PANSS total score at endpoint versus PBO. Additional evaluations included body weight and fasting plasma lipids. (c) The 6-month study indicated a significantly longer time to deterioration with bifeprunox (20 mg: P=0.008, 30 mg: P=0.006) versus PBO. Bifeprunox 20 mg and 30 mg also demonstrated efficacy versus PBO on PANSS total in 6-week trials (P=0.031 and P=0.02, respectively). Results from various metabolic measures are listed in Table 1. (d) The favorable short- and long-term metabolic profile of bifeprunox, coupled with efficacy in short-term trials and in maintenance of stability, suggests that this agent could be used to address significant unmet needs in the long-term care of patients with schizophrenia.

Table 1

Treatment Group	Bifeprunox 20 mg (N=159)	Bifeprunox 30 mg (N=172)	Placebo (N=166)	Bifeprunox Total (N=1050)	Placebo (N=469)	Risperidone 6 mg (N=274)	Olanzapine 15 mg (N=15)	Haloperidol 10 mg (N=52)
Study Length	6 months			6 weeks				
Body Weight, n	143	149	150	909	414	234	139	50
Baseline Mean (kg)	70.7	71.9	71.3	80.5	80.1	83.0	79.5	69.3
Mean Change from Baseline	-1.0	-1.2	-0.4	-0.8	-0.1	1.7	2.4	-0.1
Total Cholesterol*, n	120	135	127	873	384	235	115	49
Baseline Mean (mmol/L)	4.764	4.929	4.849	4.995	5.056	4.996	5.061	4.955
Mean Change from Baseline	-0.246	-0.323	-0.084	-0.34	-0.285	-0.067	-0.073	0.003
Triglycerides*, n	121	135	127	8739	385	235	115	49
Baseline Mean (mmol/L)	1.654	1.561	1.559	2.042	2.178	2.205	1.960	1.461
Mean Change from Baseline	-0.218	-0.271	-0.128	-0.438	-0.316	-0.084	0.032	-0.031
Fasting LDL, n	71	72	73	124	60	0	69	0
Baseline Mean (mmol/L)	2.875	2.966	2.953	3.024	3.217	-	2.976	-
Mean Change from Baseline	-0.224	-0.278	-0.080	-0.222	-0.248	-	-0.008	-
Fasting HDL, n	72	74	74	130	66	0	74	0
Baseline Mean (mmol/L)	1.203	1.180	1.270	1.246	1.221	-	1.239	-
Mean Change from Baseline	0.093	0.055	0.030	-0.012	-0.027	-	-0.036	-
Triglyceride:HDL ratio, n	72	74	74	130	66	0	74	0
Baseline Mean	1.501	1.539	1.408	1.688	1.808	-	1.828	-
Mean Change from Baseline	-0.257	-0.441	-0.051	-0.402	-0.308	-	-0.027	-

*Fasting or nonfasting

NICOTINE REDUCES IMPULSIVITY IN NONSMOKERS WITH SCHIZOPHRENIA

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Converging lines of evidence suggest that dysregulation of the nicotinic receptor system contributes to the pathophysiology of schizophrenia. There is a high prevalence of smoking in schizophrenia and nicotine improves auditory sensory gating, attention, working memory and oculomotor function, suggesting a possible therapeutic role for cognitive deficits. This study investigated the effects of nicotine on attention and memory in nonsmokers with schizophrenia and nonpsychiatric controls. Nonsmokers with schizophrenia (n=28) and controls (n=32) received 14 mg transdermal nicotine and identical placebo in a double-blind fashion one week apart. Cognitive tasks were conducted before and 3 hrs after patch application. Change scores were calculated for each variable (pre minus post dose) and entered into a mixed model analysis of variance with treatment (nicotine, placebo) as within group and diagnosis (schizophrenia, control) as between group factors. There was a main effect of nicotine treatment on the Continuous Performance Test Identical Pairs Version (CPT-IP) for reaction time (RT) ($F(1,58)=20.35$, $p=<0.0001$), standard deviation of reaction time (SDRT) ($F(1,58)=8.233$, $p=0.006$) and random errors (RE) ($F(1,58)=7.9$, $p=0.007$). There was a significant diagnosis x treatment interaction for CPT-IP RE ($F(1,58)=5.95$, $p=0.018$) and false alarms (FA) ($F(1,58)=7.576$, $p=0.008$), and the 3-card Stroop Interference T-score (ITS) ($F(1,55)=4.87$, $p=0.03$). Nicotine caused a greater reduction in FA and RE and improvement in ITS in schizophrenia (mean change on nicotine RE: 1.26+2.5, FA:0.82 +1.99, ITS:-2.07+4.4) versus controls (mean change RE:0.19+0.49, FA:-0.14 +1.02, ITS:-0.3+5.5). Nicotine also significantly reduced false alarm rate on an episodic memory task (main effect: $F(1,18)=9.14$, $p=0.007$) with a trend-level diagnosis x treatment interaction ($F(1,18)=3.29$; $p=0.086$), as nicotine reduced false alarms to a greater extent in patients (mean change on nicotine = 8.7 + 11.0) than controls (mean change = 2.1 + 3.8). Nicotine improved attention and memory in both groups. Greater benefits were seen in patients with schizophrenia on four separate measures of response inhibition or impulsivity. By including only nonsmokers, the results are not confounded by nicotine withdrawal/reinstatement effects. These results confirm that nicotine improves attention and suggest that nicotine may specifically improve response inhibition in patients with schizophrenia.

THE EFFECTIVENESS OF INTRAMUSCULAR BIPERIDEN IN ACUTE AKATHISIA: A DOUBLE BLIND, RANDOMIZED, PLACEBO - CONTROLLED STUDY

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Neuroleptic-induced acute akathisia (NIA) is an important clinical problem, since it is associated with exacerbation of psychopathology, suicidal or impulsive behavior, and noncompliance. Anticholinergics are among the treatment options, however, a review of the literature fails to identify a randomized, placebo-controlled study of these medications in NIA. We randomized 30 patients with DSM-IV NIA to im biperiden (n=15) or isotonic saline (n=15) injections, repeated 1-3 times unless akathisia was completely treated (scored zero for global akathisia with the Barnes Akathisia Rating Scale, BARS). Patients were assessed for akathisia, other movement disorders and psychiatric symptoms at baseline and 3 times after the first injection at two hour intervals. Response was defined as at least a 2-point decline in the global akathisia score. The number of responders in the two groups (7 in the biperiden group and 5 in the placebo group) were not significantly different. The course of the individual items on the BARS, other movement disorders and general psychopathology were also similar. Side effects were minimal in both groups. Although the response rate to biperiden was in line with the previous open clinical trials, our results suggest that, when compared to placebo, biperiden should not be considered as a first line treatment for acute akathisia.

The course of the individual BARS items in the biperiden and placebo groups

	Baseline	2 hr	4 hr	6 hr	
BARS Objective Biperiden	1.53	1.27	1.00	0.93	F=0.15 df=1 p=0.69
BARS Objective Placebo	2.20	1.93	1.53	1.67	
BARS Awareness Biperiden	2.67	1.73	1.53	1.53	F=2.56 df=1 p=0.12
BARS Awareness Placebo	2.40	1.93	1.87	1.93	
BARS Distress Biperiden	2.33	1.20	1.13	1.07	F=2.47 df=1 p=0.13
BARS Distress Placebo	2.47	1.67	1.80	1.73	
BARS Global Biperiden	3.33	2.40	2.07	1.93	F=0.64 df=1 p=0.43
BARS Global Placebo	3.67	2.93	2.67	2.60	

Baseline values are covaiates for the objective akathisia scores.

AN RCT OF NEUROCOGNITIVE ENHANCEMENT THERAPY WITH SUPPORTED EMPLOYMENTL: EMPLOYMENT OUTCOMES AT 24 MONTHS

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This study was a randomized clinical trial to determine whether supported employment (SE) outcomes for people with schizophrenia or schizoaffective disorder were enhanced by adding neurocognitive enhancement therapy (NET). 72 stable outpatients with schizophrenia recruited from an urban community mental health center were randomly assigned to a 12 month program of NET+SE, or SE alone with 12 month follow-up, for a total of 24 months of employment records. SE alone was based on the IPS model and include job development, job coaching, transitional funds when appropriate, and two weekly support groups. NET+SE augmented vocational services with progressive computer-based cognitive training exercises, a social information processing group and a work feedback and goal setting group. Almost all participants worked for at least one week regardless of condition. There were no significant differences in average hours worked or rates of employment during the 12-months of active intervention. However, significant differences ($p < .05$) emerged during the 12 months of follow-up, with participants in the NET+SE condition significantly increasing their rates of competitive employment while participants in the SE only condition declined in their rates of competitive employment. Participants in the NET+SE condition worked significantly more hours ($p < .0001$) over the 24 month period of the study, and they worked significantly more hours of competitive employment

during the 12 month follow-up period ($p < .05$). Logistic regressions indicated that participants with low community function scores at intake who were in the NET+SE condition were nine times more likely to be competitively employed than participants with low community function who were in the SE only condition. Transitional funds made it possible for almost all participants to obtain a job in a competitive setting. Supported employment enhanced by multifaceted cognitive training produced better work outcomes than supported employment alone, but these differences only emerged during the 12-month follow-up period, after the rehabilitation phase was completed. This suggests that cognitive training may need to be intensive and sustained over time before it affects functional outcomes. Cognitive training was especially beneficial for patients with poor initial community functioning, who were unlikely to obtain competitive employment if they received SE alone.

TREATMENT OF ALCOHOL USE DISORDERS IN PEOPLE WITH SEVERE MENTAL ILLNESS

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Alcohol use disorders in people with schizophrenia and other forms of severe mental illness (SMI) is a critical public health problem that is associated with poor treatment compliance, increased relapse and levels of violence, and poor overall functioning. Treatment is especially difficult due to symptoms and deficits that make it difficult for SMI patients to engage in the higher level cognitive processes or the self-directed behaviors generally required to reduce drinking. This poster will present results from a recently completed treatment development project funded by the National Institute on Alcohol Abuse and Alcoholism to develop and pilot tested a behavioral intervention for SMI patients with alcohol use disorders. The intervention, Behavioral Treatment of Alcohol Abuse in SMI, incorporates strategies that have been found to be effective in reducing drinking, but tailors them to meet the needs of this population: (1) pre-treatment motivational enhancement to increase motivation to change; (2) short-term goal setting at each session; (3) social skills and alcohol refusal skills training; (4) education and coping skills training for managing negative affect; (5) relapse prevention training; (6) intensive case management to enhance treatment engagement. Participants had DSM-IV diagnoses of severe mental illness (schizophrenia, schizoaffective disorder, recurrent major depression, bipolar disorder) and concurrent diagnosis of primary current Alcohol Abuse or Dependence, and were randomly assigned to attend twice weekly meetings of BTAAS or a supportive comparison group for six months. Participants completed baseline and post-treatment assessments of drinking severity, social functioning, and motivation to change, and were monitored at each session for self-reported drinking, self-reported drug use, and objective testing of use (saliva tests; urinalysis). This poster will present preliminary findings for 47 participants (29 randomized to BTAAS and 18 randomized to comparison group) on: Descriptive characteristics of the sample; (2) Differences by treatment group in engagement and attendance; (3) Differences by treatment group in rates of completion and drop out; and (4) Differences by treatment group in post-treatment severity of drinking and drinking-related consequences. Implications of the findings for developing and implementing interventions to decrease drinking in patients with SMI will be provided.

THE OPUS TRIAL: RESULTS FROM THE FIVE-YEARS FOLLOW-UP

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Objective: Effective treatment in the early phases of schizophrenia and schizophrenia spectrum disorders need investigation in order to improve short-term and long-term outcome. One- and two year follow-up of patients included in the OPUS trial showed significant positive effects on psychotic and negative symptoms, substance abuse, use of bed days, housing situation, client satisfaction and maintenance of the treatment for the IT group compared to the ST group. The positive effects retain as long as the experimental treatment is active, but it is unknown whether the positive effects last after the treatment has finished. This study investigates whether the positive effects from the integrated OPUS team treatment last up to five years after inclusion. Method: During the years 1998-2000 we randomised 578 first-episode psychosis patients to integrated treatment or standard treatment. The integrated treatment lasted for two years and consisted of assertive community treatment with programmes for family-involvement and social skills training. Standard treatment offered contact with a community mental health centre. Patients have been assessed comprehensively at baseline, at 1 and 2 years and now at 5 years. Additional register informations are obtained in the 5 years follow-up. Results concerning, positive and negative symptoms, substance abuse, use of bed days, mortality, work situation and housing situation will be presented.

CHANGES IN PROLACTIN LEVELS AND ARIZONA SEXUAL EXPERIENCE SCALE (ASEX) SCORES AMONG PATIENTS SWITCHED FROM RISPERIDONE TO ARIPIPRAZOLE IN THE SCHIZOPHRENIA TRIAL OF ARIPIPRAZOLE (STAR) STUDY

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Purpose: The large, open-label, naturalistic Schizophrenia Trial of Aripiprazole (STAR) assessed sexual function in ambulatory patients with schizophrenia receiving community-based therapy who were switched from risperidone to either the atypical antipsychotic aripiprazole or standard of care (SoC) agents. Methods: Enrolled patients were considered eligible for a change in medication owing to tolerability issues and/or suboptimal control of clinical symptoms. Patients (n=555) were randomized 1:1 to aripiprazole (10-30 mg/day) or SoC agents. Investigators selected the SoC agent (olanzapine 5-20 mg/day, quetiapine 100-800 mg/day or risperidone 2-8 mg/day) according to treatment history; patients were not to receive the agent prescribed just prior to study entry, or one not previously tolerated/effective. In this exploratory subanalysis, previously risperidone-treated patients could not be switched to risperidone SoC therapy; thus, SoC was olanzapine/quetiapine. Sexual dysfunction was assessed by the validated Arizona Sexual Dysfunction Scale (ASEX), which measures 5 items for males and

females separately: sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Each item is rated from 1-6 (higher score=more dysfunction), with total scores 5-30. Serum prolactin levels, which may be correlated with sexual dysfunction, were measured concurrently. Mean changes from baseline in ASEX scores were analysed by analysis of covariance (ANCOVA) with treatment group and gender as main effects, and baseline score as a covariate. Mean changes in prolactin levels were analysed by ANCOVA with treatment group and fasting status as main effects, and baseline value as a covariate. Results: In total, 103 patients switched from risperidone to aripiprazole (n=49) or SoC agents (n=54). Mean ± standard error (SE) change from baseline at Week 26 in ASEX total score was -1.64±0.52 with aripiprazole (n=42) and -0.21±0.59 with SoC agents (n=43; last observation carried forward [LOCF]), showing a statistically significant improvement in sexual functioning with aripiprazole vs. SoC agents (p=0.038). Mean ± SE change at Week 26 in prolactin levels was -41.5±3.9 with aripiprazole (n=47) and -32.9±3.7 with SoC agents (n=47; LOCF; p=0.091). Conclusions: Patients switched from risperidone showed a greater improvement in sexual function (ASEX scores) with aripiprazole vs. SoC agents. Prolactin levels improved with both treatments.

GALANTAMINE DOES NOT SIGNIFICANTLY EFFECT POSITIVE OR NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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Galantamine is an acetylcholinesterase inhibitor, and an allosteric modulator of the $\alpha4\beta2$ and $\alpha7$ nicotinic receptors. Several case reports have been published describing potential benefits of galantamine for the negative symptoms of schizophrenia. To date no randomized placebo controlled studies have been conducted with galantamine for the treatment of negative or positive symptoms in people with schizophrenia. We report a 12-week, placebo-controlled, parallel group, RCT in which the effect of galantamine on positive and negative symptoms was evaluated using the Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS). Seventy-nine patients with either DSM-III-R/DSM-IV schizophrenia or schizoaffective disorder were randomized to study drug (galantamine: 39/placebo: 40); 72 subjects completed the study (galantamine: 35/placebo: 37). Statistical analysis for clinical improvement was conducted on the BPRS psychosis and BPRS anxiety/depression subscales along with the BPRS total score and SANS total score. No significant change was found with any of the scales. There was a slightly larger decrease in mean score per item on the SANS with galantamine compared to placebo (chi-square= 3.18, df=1, p=0.075). The study results do not exclude a potential benefit of galantamine for negative symptoms. The lack of significant effect of galantamine on negative, and other symptom domains, may be due to the relatively low baseline level of these symptoms. Future studies are required that are specifically designed to address the issue of the efficacy of galantamine for negative symptoms through the inclusion of subjects with sufficient symptom severity to detect therapeutic effects. Supported by the Stanley Medical Research Institute and P30 068580. Ortho-McNeil Neurologics, Inc. provided study medication.

ONSET OF RESPONSE WITH ORAL PALIPERIDONE EXTENDED-RELEASE TABLETS IN PATIENTS WITH ACUTE SCHIZOPHRENIA

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Rapid and adequate control of symptoms is the primary goal of treatment in the management of acute schizophrenia. Paliperidone extended-release (ER) is an investigational psychotropic delivered using OROS® technology that results in minimal plasma fluctuations and allows treatment to begin at an efficacious dose without initial titration. We assessed time to onset of response with paliperidone ER in patients with acute schizophrenia using a stringent composite definition for response to maximize the clinical relevance of the findings. This post-hoc analysis examined pooled data from three 6-week, double-blind, fixed-dose, placebo-controlled studies of paliperidone ER in adults with acute schizophrenia. Efficacy assessments included PANSS and CGI-S scores. A composite response was defined as ≥30% reduction in PANSS total score from baseline, plus CGI-S score of 1-2 (or improvement of 2 levels at endpoint). Paliperidone ER (3-12 mg/day; n=842) was compared to placebo (n=351) by ANCOVA for change from baseline in PANSS scores and by the Cochran-Mantel-Haenszel test for responder rates. Demographic and baseline characteristics were similar for both arms. Composite response rates for paliperidone ER 3-12 mg were significantly higher than placebo from day 8 (6.3% vs 3.4%; P=0.025) through endpoint (23.6% vs 11.1%; P<0.001). Criteria of ≥20% reduction in PANSS total score showed a significantly greater response rate with paliperidone ER compared to placebo from day 4 (16.7% vs 12.1%; P=0.012) through endpoint (62.8% vs 35.6%; P<0.001). There was a significant improvement in mean (±SD) PANSS total change score with paliperidone ER vs placebo at day 4 (–5.4±9.0 vs –2.8±9.7; P<0.001], with improvement continuing to endpoint (–17.6±20.5 vs –4.8±22.0; P<0.001]. There were significant differences at baseline in patients who met vs those who did not meet composite response for the following variables: gender, race, duration in trial, schizophrenia subtype, and baseline PANSS total and CGI-S scores (P<0.05). Adverse events (≥10% of patients) were (paliperidone ER vs placebo: headache (13.3% vs 11.7%) and insomnia (12.4% vs 14.2%). Definitions for response in schizophrenia should reflect a clinically meaningful level of improvement. Using a stringent composite definition of response, these data suggest that paliperidone ER was associated with a rapid and clinically meaningful response in patients with acute schizophrenia. Supported by funding from Janssen, L.P.

BIFEPRUNOX IS SAFE AND EFFECTIVE IN PREVENTING DETERIORATION IN PATIENTS WITH STABLE SCHIZOPHRENIA: RESULTS FROM A 6-MONTH, PLACEBO-CONTROLLED STUDY

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(a) Determine the efficacy, safety and tolerability of bifeprunox in stable patients with schizophrenia by assessing time to deterioration at 6 months and PANSS total score at 6 weeks. (b) In this 6 month

randomized, double-blind, study of bifeprunox, 497 patients with diagnosis of schizophrenia (DSM-IV-TR) and stable symptomatology were randomly assigned to receive once-daily, fixed dose of bifeprunox 20 mg, 30 mg or placebo. Bifeprunox doses were titrated, beginning with a dose of 0.25 mg on day 1 and approximately doubled every day until 20 mg (day 7) or 30 mg (day 8) were reached. Primary efficacy variable was time to deterioration from randomization, defined as fulfillment of one or more of the following: CGI-Improvement (CGI-I) score ≥5, PANSS item P7 (hostility) and/or G8 (uncooperativeness) score ≥5 for 2 consecutive days, or ≥20% increase in PANSS total score from baseline. Key secondary measure was change in PANSS total score at week 6. Safety evaluations included adverse events (AEs), EPS, weight/BMI, laboratory tests (including fasting and non-fasting lipid and glucose), serum prolactin and vital signs. (c) Treatment with bifeprunox resulted in significantly longer time to deterioration of schizophrenia (20 mg: P=0.008 and 30 mg: P=0.006) versus placebo. Rates of deterioration were: 59% in the placebo group, 41% in the bifeprunox 20 mg group, and 38% in the 30 mg group. Bifeprunox showed statistically significant improvement for PANSS total score at week 6. Statistically significant improvement was seen in PANSS total, PANSS positive, negative and GPP subscales, BPRS totals, and BPRS psychosis cluster versus placebo, at most time points. The most common AEs (incidence ≥5% and twice placebo) included: nausea, vomiting, decreased appetite, dizziness and akathisia. Prolactin levels decreased in all treatment groups. Bifeprunox-treated patients demonstrated reduction in triglycerides and increase in HDL, irrespective of fasting/non-fasting condition. Weight decrease was also observed in patients taking 30 mg bifeprunox (P<0.05) compared with placebo (LOCF). (d) In this study, bifeprunox 20 and 30 mg/day were effective in preventing deterioration over 6 months and significantly improved PANSS total score at week 6 in patients with stable schizophrenia. Bifeprunox may be beneficial for long-term treatment and offers a favorable metabolic profile in stable patients with schizophrenia.

DIFFERENTIAL EFFECTS OF QUETIAPINE, OLANZAPINE AND RISPERIDONE ON GLUCOSE METABOLISM: A 24-WEEK STUDY IN SCHIZOPHRENIA

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Introduction: This study compared the effects of quetiapine, olanzapine or risperidone on glucose metabolism in non-diabetic patients with schizophrenia. Methods: This multicenter, randomized, 24 week, open-label, flexible dose, parallel-group study used a primary endpoint of baseline to Week 24 change in AUC 0-2h plasma glucose during an oral glucose tolerance test (OGTT); the primary analysis compared quetiapine and olanzapine. Secondary analyses included change in fasting and 2-h glucose, insulin parameters (fasting levels, AUC 0-2h, ISI), HbA_{1c}, weight and fasting lipids. Results: 395 patients (quetiapine 115, olanzapine 146, risperidone 134) had data at baseline and ≥20 weeks of treatment (mean mg/day: quetiapine, 607; olanzapine, 15.2; risperidone, 5.2). A significant (p=0.048) difference was observed between quetiapine and olanzapine in the primary endpoint, the change from baseline in AUC 0-2h plasma glucose (mg/dL×h), with significant increases during treatment with olanzapine (+21.9, 95% CI 11.5, 32.4) and risperidone (+18.8, CI 8.1, 29.4), but not quetiapine (mean +9.1, CI -2.3, 20.5). There were no significant between-treatment group differences in fasting glucose, HbA_{1c}, insulin parameters or weight. LDL-C increased significantly in quetiapine and olanzapine groups (olanzapine vs risperidone statistically significantly different). Post hoc analysis indicated triglyceride/HDL and total cholesterol/HDL ratios increased significantly from baseline during treatment with olanzapine, but not quetiapine or risperidone. Conclusion: In this 24-week study, significant reductions in glucose tolerance were observed during treatment with olanzapine and risperidone but not quetiapine, with a statistically significant difference between olanzapine and quetiapine.

EXPERIENCE OF AN OCCUPATIONAL THERAPY GROUP, DEVELOPED IN THE SCHIZOPHRENIA PROGRAM OF THE FEDERAL UNIVERSITY OF SãO PAULO (UNIFESP), BRAZIL

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The objective of this presentation is to tell about an experience of an Occupational Therapy group, developed in the Schizophrenia Program of the Federal University of São Paulo (UNIFESP), Brazil. The group was considered and carried by occupational therapists who were inserted in the Mental Health Specialization Program of UNIFESP. The initial criteria for participation had been: patients inserted in the service; maximum age 25 years; short history of illness and sent by the respective psychiatrists after team discussion. The group was initiated in 2005. Seven patients were sent, but five of them have adhered the proposal. In the evaluation period was observed that the difficulties most related were: social isolation, apathy, difficulty to be in touch with the others participants and daily activities missed because of the damage pragmatism. Initially the interactions with each others mainly happened through the therapists and the activities, what showed the necessity of an active and directive position of the therapists. All of them had to be stimulated so they would participate actively in a way that the group could be established. Among several activities presented, it was clear that the music was a common element, emerging more interactions and offering others expression possibilities. Such therapeutic resource promoted the construction of a common language. This observation enabled to plot objectives and organize activities that made easier the active participation of the patients, as individual or group tasks, inside and outside the therapeutic setting. During this time the music activity was happening concomitantly with the others activities, turned into a group code. It was possible to find ways of expression and organize several activities of the occupational repertoire (individual and group), healthy living situations, trying and elaborating the owners situations of this life period, many times damaged by the dynamics established at rupture moments (disease, stigma). The Occupational Therapy group has promoted a routine experience in a protect way and it was extended for the daily situation. Since the current necessities are located in the most pragmatic questions and in the social insertion, the initial difficulties were minimized and the objectives were reviewed.

CLINICAL PREDICTORS OF OLANZAPINE AND RISPERIDONE TREATMENT RESPONSE DEPEND ON TREATMENT RESPONSE DEFINITIONS

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Clinical schizophrenia studies frequently use the Positive and Negative Symptoms Scale (PANSS) for rating symptoms of schizophrenia and define treatment response. In these studies a reduction of at least 20%, 30%, 40%, or 50% of the initial PANSS score have been used as a cut-off to define "response". Moreover, the Clinical Global Impression Scale seems to be more intuitive and informative. The aims of this study was to determine if initial descriptive clinical assessment based on the evaluation of the PANSS can predict the short term drug response at J42 using several criteria for response definitions based on the reduction of PANSS or CGI-severity (CGI-S). 95 schizophrenics' patients, according to DSMIV criteria, were prospectively assessed with the PANSS and CGI-S at day 0 and day 42 of an open label trial with olanzapine (56) and risperidone (39). Several propositions (A, B, C, D, E) for response at day 42 were proposed: diminution of 20% at the PANSS and a score less than 35 at the BPRS (A), reduction of at least 30% (B), 40% (C), or 50% (D) of the initial PANSS score, decrease in the CGI-S rating: 1-point (base line assessment between 1 and 3) or 2-point (base line assessment between 4 and 6) (E). The average positive, negative, general and total PANSS scores, the average of the five dimensions structure of the PANSS (negative, positive, excitation, cognitive, and anxiety/depression) were compared between non responders and responders for each group using a non parametric Man Whitney test. For response A: total (110.3 vs 95.4**), general (52.0 vs 44.6**), positive (29.2 vs 25.5*) score of the PANSS and positive (41.3 vs 38.3 **) and excitation (20.5 vs 16.0**) factors of the five dimensions factors of the PANSS were statistically different between non responders and responders at day 0. For respectively response B and D: cognitive (17.6 vs 12.7*) and depression (11.8 vs 9.3*) factors of the five dimension model were statistically different at J0. For response E: Total (112.0 vs 95.4***), general (53.4 vs 43.8***), negative (29.8 vs 25.7**) score of the PANSS and cognitive (17.7 vs 15.0***) and excitation (20.9 vs 16.3**) and negative (33.4 vs 26.6**) factors of the five dimensions factors of the PANSS were statistically different between non responders and responders at day 0. Clinical predictors of short term olanzapine and risperidone treatment response are inflicted by response definition. * P<0.05; ** P<0.01; *** P<0.05

GALANTAMINE FOR THE TREATMENT OF COGNITIVE IMPAIRMENTS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Patients with schizophrenia are characterized by a broad range of cognitive impairments. Despite appropriate antipsychotics treatment, patients continue to exhibit pronounced cognitive impairments. This has led to the investigation of adjunctive agents for the treatment of these impairments. The cholinergic system has been implicated in multiple cognitive processes. Cognitive effects may be mediated through the muscarinic or nicotinic receptor systems. Galantamine is an acetylcholinesterase inhibitor, which also acts as an allosteric modulator at the $\alpha4\beta2$ and $\alpha7$ nicotinic receptors. Previous small-N studies have reported potential benefits of galantamine for cognition. Methods: In the current 12-week, placebo-controlled, parallel group, RCT, the efficacy of galantamine for cognitive impairments was evaluated using paper and computerized assessments of attention, manual dexterity, processing speed, simple and complex reaction time, verbal and visual memory, visual recognition, and working memory. Results: Seventy-nine patients with either DSM-III-R/DSM-IV schizophrenia or schizoaffective disorder were randomized to study drug (galantamine: 39/placebo: 40); 72 subjects completed the study (galantamine: 35/placebo: 37); and 62 subjects had valid cognitive assessments at baseline and 12 weeks (galantamine: 32/placebo: 30). The treatment effect for the overall composite cognitive summary score was not significant, but the analysis examining whether there was a heterogeneity of treatment effect was significant (chi-square=10.65, df=4, p=0.031). Follow-up analyses revealed that galantamine, compared to placebo, was associated with a significant improvement in verbal memory (chi-square=4.79, df=1, p=0.029), with a trend for improvement in processing speed (chi-square=3.81, df=1, p=0.074). In contrast, patients randomized to placebo, compared to galantamine, showed a significant improvement on the vigilance measure (chi-square=6.26, df=1, p=0.012). There were no significant between group differences in manual dexterity or working memory. The effects of galantamine on computerized simple and complex reaction time and visual recognition measures will be presented. Discussion: Study results will provide a comprehensive evaluation of the efficacy of galantamine for cognitive impairments in patients with schizophrenia. Supported by the Stanley Medical Research Institute and P30 068580. Ortho-McNeil Neurologics, Inc. provided study medication.

EFFECTS OF PALIPERIDONE ER IN PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY TREATED WITH RISPERIDONE

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Paliperidone extended-release (ER) tablets, an investigational psychotropic, may be efficacious in patients with acute symptoms of schizophrenia who received prior treatment with risperidone. This is a post-hoc analysis of pooled data from patients in the ITT population of three 6-week, double-blind, parallel-group, placebo-controlled trials. Patients included in this exploratory analysis were randomized to fixed doses of paliperidone ER 3-12 mg/day or placebo and had received treatment with oral risperidone within 2 weeks prior to randomization. Assessments included PANSS, PSP, and CGI scores, and adverse event reports. An ANCOVA model was used to compare between-treatment differences for continuous variables. A total of 285 patients (paliperidone ER 3-12 mg/day, n=207; placebo, n=78) met the inclusion criteria. In the active treatment group, patients had a mean age of 37.5±11.5 years and a mean length of illness of 11.2±9.8 years. The mean baseline total PANSS score was 92.7±12.2. Patient characteristics were similar in the placebo group and in the pooled ITT population. The median duration of prior risperidone treatment was 95 days in the paliperidone ER group and 104 days for placebo. The median risperidone dose in both groups was 4.0 mg/day. The study completion rate was 59.9% for paliperidone ER vs 41.0% for placebo. At endpoint, significant improve-

ment was observed in mean PANSS total score (paliperidone ER, –15.1±19.9; placebo, –4.7±23.5; $P<0.001$). There was a significantly greater improvement with paliperidone ER than placebo in all mean PANSS factor change scores at endpoint ($P\leq0.01$). Mean scores improved significantly at endpoint (paliperidone ER vs placebo) on PSP (+8.0±14.2 vs –2.2±16.1; $P<0.001$) and CGI (–0.8±1.1 vs –0.2±1.2; $P<0.001$). There was no significant difference in mean SAS change scores at endpoint (paliperidone ER, 0.01±0.2; placebo, –0.05±0.2; $P=0.226$). Adverse events noted in ≥10% of patients were (paliperidone ER vs placebo): headache (13.0% vs 14.1%), agitation (6.8% vs 11.5%), insomnia (11.6% vs 15.4%), and anxiety (6.3% vs 11.5%). Results suggest that in patients with acute symptoms of schizophrenia who received prior treatment with risperidone, paliperidone ER was significantly superior to placebo for improving symptoms and functioning, with no unexpected tolerability findings. Supported by funding from Janssen, L.P.

RESULTS OF A BIFEPRUNOX DOSE-FINDING STUDY IN PATIENTS WITH ACUTELY EXACERBATED SCHIZOPHRENIA

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(a) Evaluate efficacy and safety of bifeprunox in patients with acute exacerbations of schizophrenia. (b) A 6-week randomized, placebo-controlled, risperidone-referenced dose-finding study was conducted in patients with an acute exacerbation of schizophrenia (DSM-IV-TR) assigned to once-daily doses of bifeprunox 5 mg (n=115), 10 mg (n=120), 20 mg (n=115), placebo (n=119) or risperidone 6 mg (n=120). Bifeprunox doses were titrated, beginning with a dose of 0.125 mg on day 1 and approximately doubled every day until 10 mg (day 7) or 20 mg (day 8) were reached; risperidone was titrated over 3 days. Primary efficacy measure was change in PANSS total score from baseline to endpoint at week 6. Secondary efficacy measures included: PANSS positive, negative, and general psychopathology (GPP) score, PANSS-derived BPRS score, Clinical Global Impressions-Severity of Illness (CGI-S), CGI-Improvement (CGI-I) scores, and responder rates. Safety assessments included extrapyramidal symptoms (EPS), weight gain, non-fasting lipids and serum prolactin. (c) Treatment with bifeprunox 20 mg was associated with a statistically significant (P<0.05) decrease in PANSS total score at week 3 and endpoint compared to placebo. Improvements with bifeprunox 20 mg were also observed in PANSS positive, negative, GPP subscales, BPRS, and responder rates. Risperidone was statistically different from placebo for the primary endpoint and thus provided proof of assay sensitivity. The most common adverse events observed in the bifeprunox group (incidence >5% and twice placebo) included: dyspepsia, nausea, vomiting, and constipation; however, a dose relationship was not evident for any of these events. Bifeprunox was associated with reduction in prolactin levels and rates of EPS that were comparable to placebo. Compared to placebo, subjects receiving bifeprunox experienced statistically significant (5 mg, -0.45 kg; 10 mg, -0.59 kg; 20 mg, -0.27 kg; P<0.05) weight decreases, and improvements in plasma triglycerides (P<0.005) and total cholesterol (P<0.005). (d) Patients treated with bifeprunox 20 mg experienced statistically significant reduction in symptoms, decrease in weight and improvement in their lipid profile. Given these findings, bifeprunox may have clinically important advantages in the treatment of schizophrenia.

SELECTIVE BENEFIT OF ESTROGEN AUGMENTATION IN PERSISTENTLY SYMPTOMATIC SCHIZOPHRENIC WOMEN: OCCURS IN TREATMENT WITH SECOND GENERATION ANTIPSYCHOTICS, BUT NOT WITH FIRST GENERATION ANTIPSYCHOTICS

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Background: We have previously reported a benefit of ERT in reducing positive symptoms in persistently ill schizophrenic women despite adequate dose and duration of treatment with an antipsychotic medication. We now have further evaluated the data and are reporting that the benefits of estrogen augmentation are selectively seen in patients treated with second generation antipsychotics and not seen in those treated with first generation antipsychotics. In addition, the reductions in positive symptom scores were more pronounced in post-menopausal women. Methods: The study is an eleven-week, double blind, randomized trial comparing ERT to placebo augmentation of antipsychotic medications that assesses the effects of ERT on symptomatology and neurocognitive functioning. 22 female subjects between the ages of 18 and 50 were recruited for study participation. All subjects were on a stable regimen of antipsychotic medication for at least one month, but were still experiencing persistent psychotic symptoms. Subjects were not taking oral contraceptives. Results: ANCOVA analyses were performed with treatment, menopausal status, and type of antipsychotic (typical vs atypical) as between subject variables, PANSS subscores as the dependent variables, and baseline scores as covariates. In the analysis of PANSS positive symptom scores, there was a group by time interaction, with patients on ERT showing greater improvement in their positive symptom scores over time than those on adjunctive placebo (p=0.048). There was also a time by treatment by type of antipsychotic interaction, with the reduction in positive symptoms in the ERT group greatest in patients on atypical antipsychotic medications (p=0.030). There was also a time by treatment by menopausal status interaction, with the reduction in positive symptoms in the ERT group greater in post-menopausal women (p=0.043). Significance. This 11-week trial suggests that even in the "stabilized phase" of illness, there is a selective benefit of ERT reducing positive psychotic symptoms in female patients with schizophrenia who are been treated with atypical antipsychotic medications. Due to possible risks of chronic ERT, it is important to delineate groups of schizophrenic women who can most benefit from this intervention so an appropriate risk-benefits assessment can be made.

ACUTE PHASE MANAGEMENT OF SCHIZOPHRENIA WITH ARIPIPRAZOLE: A 8-WEEK OPEN-LABEL PROSPECTIVE STUDY IN KOREA

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OBJECTIVE: To investigate acute phase efficacy and safety of aripiprazole in patients with schizophrenia or schizoaffective disorder in Korea. METHOD: This study is multicenter, single group, 8-week period aripiprazole treatment in patients with schizophrenia or schizoaffective disorder. Three hundred patients participated and two hundred and one patients completed an 8-week acute phase aripiprazole treatment. Patients' symptoms severity were assessed by the

PANSS. Clinical Global Impression (CGI) was also measured. All patients showed acute episodes and their initial PANSS scores were over 60 points. Tolerability of aripiprazole was evaluated by recording treatment-emergent adverse events and measuring vital signs, weight, and laboratory tests. RESULTS: Two hundred and one patients completed an 8-week aripiprazole treatment. Total one hundred and fifty nine patients showed more than a 30% improvement in PANSS score after an 8-week aripiprazole treatment. The incidence of adverse effects was low during the 8-week period and the most common adverse effects were GI symptoms, insomnia, and akathisia. Mean body weight was increased from 62.02kg to 63.25kg. In addition there were no significant abnormalities of glucose and prolactin level as well as lipid profile after acute phase treatment. At the end of treatment, above one half of the patients were medicated with aripiprazole only. CONCLUSION: Our result showed that aripiprazole is a clinically effective antipsychotic medication for acute phase management of schizophrenic patients without serious adverse effects.

NUMBER NEEDED TO TREAT AND NUMBER NEEDED TO HARM: MAKING SENSE OF CATIE

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Objective: The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) will be used to demonstrate the concepts of Evidence-Based Medicine, namely Number Needed to Treat (NNT) and Number Needed to Harm (NNH). Method: NNT (NNH) can describe how many patients one needs to treat on Drug A versus Drug B to see one extra success (or adverse event). Effectiveness and safety outcome data was extracted from the three principal publications that documented the results of Phases 1 and 2 of the CATIE schizophrenia study. NNT and NNH were calculated from the categorical results. The formula used was NNT=1/AR, where AR is the Attributable Risk. AR is calculated by subtracting the frequency of the outcome of interest for one drug from the frequency of the outcome for the other medication being compared. Results: Olanzapine and clozapine demonstrated advantages over comparators in terms of all-cause discontinuation, largely driven by efficacy advantages. NNT for olanzapine compared to perphenazine, quetiapine, risperidone, and ziprasidone ranged from 5.5 to 10.1 in Phase 1. NNT for clozapine compared to risperidone or quetiapine was approximately 3 in Phase 2. There were marked differences in association with weight gain and metabolic effects, with olanzapine demonstrating a NNH ranging from 12.4 to 17.7 in terms of discontinuation of treatment in Phase 1 because of these effects. Results from Phase 2 reflect Phase 1 in this regard, and demonstrated an advantage for ziprasidone in terms of discontinuation because of weight gain or metabolic effects, with NNT ranging from 10.6 to 20.8. However, these notable differences in association with weight gain and metabolic effects did not seem to drive the differences in overall time to all cause discontinuation. The absolute magnitudes of the NNT that are reported here are not dissimilar to other examples in the psychiatric literature, where a comparison of antipsychotic versus placebo for the treatment of schizophrenia results in a range of NNT of 2 to 5 for the outcome of a 40 percent reduction in the Brief Psychiatric Rating Scale score or a rating of "much improved" on Clinical Global Impression, and of family intervention versus usual care for patients with schizophrenia which nets a NNT of 7 for the outcome of relapse. Conclusions: NNT and NNH can help place the wide array of CATIE results into clinical context, and permits quantification of the differences observed between the antipsychotics.

CLINICAL INSIGHT MODERATES TREATMENT OUTCOME IN COGNITIVE BEHAVIORAL SOCIAL SKILLS TRAINING FOR CHRONIC SCHIZOPHRENIA

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Poor clinical insight (awareness of having a mental illness that requires treatment) is prevalent in schizophrenia and predicts treatment compliance and course of illness. This study examined insight as a predictor of intervention-specific skill acquisition, social functioning skill performance, everyday functioning, symptom severity, and cognitive insight (metacognitive processes of reevaluation and correction of distorted beliefs and misinterpretations on the Beck Cognitive Insight Scale) in a randomized, controlled trial of cognitive behavioral social skills training (CBSST) versus treatment as usual (TAU) for middle-aged and older outpatients with chronic schizophrenia (N=74). We previously reported that CBSST improved intervention-specific skills acquisition, everyday functioning, and cognitive insight to a significantly greater extent than TAU. Baseline clinical insight measured using the Birchwood Insight Scale and the group by insight interaction were regressed onto outcome variables measured 12 months following completion of the 6-month intervention, while controlling for baseline scores on outcome measures. Clinical insight moderated the relationship between treatment group and everyday functioning (on the Independent Living Skills Survey) such that participants in CBSST having greater clinical insight at baseline more frequently engaged in everyday functioning activities. Clinical insight also moderated the relationship between treatment group and negative symptoms and total symptoms (on the Positive and Negative Syndrome Scale) such that participants having greater baseline clinical insight showed greater decrease in negative symptoms and total symptoms if they received CBSST. Greater clinical insight at baseline predicted greater cognitive insight for both groups at 12-month follow-up but did not moderate the treatment effect. Positive symptoms, depressive symptoms, social functioning skills performance, and intervention-specific skill acquisition at 12-month follow-up were not significantly predicted by baseline clinical insight. Improvement in functional behaviors represents a meaningful change in the quality of life of individuals with schizophrenia, as well as a socially relevant treatment goal. Clinical insight is an important moderator of the treatment effect of CBSST on everyday functioning activities, negative symptoms, and total symptoms and should be examined in future studies of cognitive behavioral therapies for schizophrenia.

TRANSITIONING FROM INTRAMUSCULAR (IM) TO ORAL ARIPIPRAZOLE IN PATIENTS WITH SCHIZOPHRENIA

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Data are reported from the oral treatment phase of a clinical trial for IM aripiprazole and IM haloperidol in acutely agitated patients with schizophrenia. The objective of this trial phase was to evaluate the effectiveness and safety of transitioning patients to oral treatment following 24 hours of IM treatment for acute agitation. A total of 360 agitated patients diagnosed with schizophrenia or

schizoaffective disorder (18-69 years) were randomized to receive ≤3 injections of IM aripiprazole 10 mg or IM haloperidol 6.5 mg within 24 hours. Inclusion criteria were PANSS Excited Component (PEC) total scores between 15-32 and ≥4 on at least 2 PEC items. Patients (n = 304) were then transitioned to oral formulations (aripiprazole 10-15 mg/d or haloperidol 7-10 mg/d) for 4 days. Patients were assessed using PEC, Clinical Global Impression-Improvement (CGI-I), and Clinical Global Impression-Severity of Illness (CGI-S) Scale scores, as well as the Agitation Calmness Evaluation Scale (ACES), and the Corrigan Agitated Behavior Scale (CABS). Mean changes from baseline (last value obtained during IM treatment) to endpoint (Day 5, LOCF) were analyzed using an ANCOVA model controlling for treatment, country, and baseline value. Results showed that PEC scores were reduced 24 hours after IM injection with either aripiprazole or haloperidol (mean change of -8.3 and -8.1, respectively). Improvements in all other scales were also observed 24 hours following IM injection of aripiprazole or haloperidol. Treatment with oral aripiprazole or haloperidol for 4 days further reduced mean PEC scores (-1.4 for both aripiprazole and haloperidol). Reductions in all other scales were also maintained for 4 days following the transition to oral therapies. The incidence of AEs, and changes in laboratory values and vital signs were similar for both phases. The effectiveness of aripiprazole and haloperidol appears to be maintained in patients with schizophrenia following transition from IM to oral formulations.

THE USE OF SELECTIVE ESTROGEN RECEPTOR MODULATORS IN THE TREATMENT OF MENOPAUSAL WOMEN WITH SCHIZOPHRENIA

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Estrogen modulates rat brain dopamine and serotonin systems in a way that mimics atypical antipsychotics. Our work indicates that adjunctive estrogen is a useful treatment in women of child-bearing age with schizophrenia. We studied the use of a selective estrogen receptor modulator (SERM) in menopausal women with schizophrenia. To test and compare the effects of adjunctive use of a SERM (raloxifene) and standard hormone therapy (HT) on psychotic symptoms in menopausal women with schizophrenia. To examine the effect of a SERM and HT on cognition in menopausal women with schizophrenia. A double-blind, three month, placebo controlled, adjunctive study of raloxifene (60mg/day) versus HT (2mg estradiol plus 10mg dyhydroprogesterone) versus placebo. Participants received standardised doses of risperidone (or equivalent doses of similar antipsychotic medication). Psychopathology was measured fortnightly using the PANSS rating scale. Cognitive testing and sex hormone assays were conducted monthly. Data collected from 23 participants indicated that while SERM or HT adjuncts did not result in an improvement in psychotic symptoms when compared to risperidone alone, the use of adjunctive SERM resulted in improved cognitive performance on working and verbal memory tasks when compared to the HT or risperidone alone. In conclusion, the use of adjunctive SERM at 60mg/day may induce a mild increase in cognitive performance in menopausal women with schizophrenia. Yaffe et al 2005 shows that 120mg/day raloxifene was more effective in improving cognition in healthy postmenopausal women. We are undertaking a new study with this increased dose of raloxifene. This research was supported by The Stanley Medical Research Institute.

THE COMBINATION OF CDP-CHOLINE AND GALANTAMINE AS A CLINICAL ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR (NACHR) AGONIST INTERVENTION IN SCHIZOPHRENIA

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Converging evidence implicates α7 nAChR hypofunction in the etiopathogenesis of schizophrenia. For example, diminished hippocampal expression of the receptor may be responsible for impairment of auditory sensory gating that is an autosomal dominant among schizophrenia patients and unaffected biological relatives. Development of a selective α7 nAChR agonist intervention is challenging because nAChRs in general desensitize rapidly upon exposure to agonist, so that an agonist becomes a functional antagonist. This would be especially problematic in the context of diminished expression of the α7 nAChR. Galantamine (GAL) is a positive allosteric modulator of nAChRs that enhances the efficiency of coupling between binding of agonist and channel opening, and may preserve the receptor in a sensitive, as opposed to a refractory, state. GAL is also an inhibitor of acetylcholinesterase and thus leads to nonselective stimulation of muscarinic and nicotinic acetylcholine (ACh) receptors. Choline, the hydrolytic split product of ACh that is derived locally in the cholinergic synapses, is a selective α7 nAChR agonist, mimicking the agonist properties of ACh at this receptor. We hypothesize that combining GAL and CDP-choline, a dietary source of choline, would obviate the limitations associated with administration of either GAL (nonselective stimulation of ACh receptors) or CDP-choline (receptor desensitization) alone. We studied the tolerability, safety and preliminary efficacy of CDP-choline (2g/day) and GAL (24 mg/day) in six schizophrenia patients with residual symptoms in a 12-week, open-label trial. Patients were maintained on stable dose regimens of antipsychotic medications for four weeks prior to study entry and for the trial duration. All reached target doses of both agents and completed the trial. Transient side effects resolved without slowing of dose titration. GI adverse effects were most common. All patients showed reduction in CGI severity scores and three showed evidence of efficacy based on the Positive and Negative Syndrome Scale Total score. Three patients requested continuation of the adjunctive combination at the end of the trial, including one who had not shown objective evidence of efficacy. These results support further investigation of the combination of CDP-choline and GAL as an α7 nAChR agonist intervention with adjuvant therapeutic efficacy in schizophrenia. Supported in part by VISN5 Mental Illness Research, Education, and Clinical Center.

EFFECTS OF PALIPERIDONE ER IN PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY TREATED WITH OLANZAPINE

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Paliperidone extended-release (ER) tablets, an investigational pyschotropic, may be efficacious in patients with acute symptoms of schizophrenia previously treated with olanzapine. This is a post-hoc analysis of pooled data from the ITT population of three 6-week, double-blind, placebo-controlled trials. Patients were randomized to fixed doses of paliperidone ER 3-12 mg/day or placebo and had received

treatment with oral olanzapine within 2 weeks prior to randomization. Assessments included PANSS, PSP, and CGI scores, and adverse event reports. Between-treatment differences for continuous variables were analyzed using the analysis of covariance model. A total of 199 patients (paliperidone ER 3-12 mg/day, n=139; placebo, n=60) met inclusion criteria. In the active treatment group, patients had a mean±SD age of 38.7±10.3 years and a mean length of illness of 12.3±9.9 years; mean baseline total PANSS score was 93.0±11.5. Patient characteristics were similar in the placebo group. The median duration of prior olanzapine treatment was 131 days in the paliperidone ER group and 92 days in the placebo group; median olanzapine dose in both groups was 15.0 mg/day. The study completion rate was 56.1% for paliperidone ER vs 38.3% for placebo. At endpoint, significant improvement was observed with paliperidone ER (–16.9±21.3) vs placebo (–4.7±22.7) in mean±SD PANSS total score ($P<0.001$). There was a significantly greater improvement with paliperidone ER than placebo in all mean PANSS factor change scores at endpoint ($P\leq0.02$). Mean±SD PSP and CGI scores improved significantly at endpoint for paliperidone ER vs placebo (+8.4±14.9 vs –0.9±14.8 [$P<0.001$]); (–1.0±1.2 vs –0.2±1.1 [$P<0.001$]), respectively. No significant difference was observed in mean±SD SAS change scores at endpoint (paliperidone ER, 0.02±0.2 vs placebo, –0.01±0.2 [$P=0.380$]). Adverse events noted in >5% of patients in the active treatment group were (paliperidone ER vs placebo): insomnia (12.2% vs 8.3%), tachycardia (7.9% vs 5.0%), anxiety (7.2% vs 13.3%), nausea (6.5% vs 10.0%), dyspepsia (5.8% vs 5.0%), dizziness (5.8% vs 1.7%). In this analysis, paliperidone ER was significantly superior to placebo for improving acute symptoms and functioning in patients with acute symptoms of schizophrenia who received prior treatment with olanzapine. There were no unexpected tolerability findings. Supported by funding from Janssen, L.P.

A PILOT STUDY OF COGNITIVE REMEDIATION FOR POOR INSIGHT IN NON-AFFECTIVE PSYCHOSIS: A MINIMIZED, CONTROLLED TRIAL

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Introduction. Recent evidence in first episode schizophrenia sufferers indicates a particular correlation between poor insight and a neuropsychological deficit - in the ability to assess and improve task performance, "metacognition". Remediating neuropsychological deficits in schizophrenia using techniques of errorless learning, massed practice and scaffolding has had some recent success. We hypothesized that successful remediation of metacognition in this way was possible in non-affective psychosis; and that this would lead indirectly to improved insight. Methods. Participants, aged 18-60, recruited from in- and out-patient units in Manchester, had: DSM IV schizophreniform disorder, schizophrenia or schizoaffective disorders; poor insight (<20 on the Schedule for the Assessment of Insight – Extended; SAI-E); & no concurrent psychotherapy. They were allocated to remediation or control by minimization, which allows balancing of groups but contains a random element. Allocation was independent of therapists and raters. Raters stayed blind to allocation. Remediation aimed for 15 hours of neuropsychological task practice over 3-5 weeks, then 7-9 hours over 7 weeks of sessions designed to link neuropsychological skills to broader function. Control involved social contact matched for time. Participants were assessed before allocation and after 3 months. Primary outcome was SAI-E score; secondary, metacognition measured by Forced Choice Improvement (FCI) on the metacognitive Wisconsin Card Sort. Social functioning, PANSS symptoms, depression, self concept, IQ, trails A and medication attitudes were also measured. Results. 36 were allocated: age 22-59; 0.2-40 years illness. SAI-E total was not significantly better in the remediation group (mean 16.4, SD 7.6) than controls (mean 15.8, SD 6.2) even after covarying for baseline (mean 11.5, SD 5.4) and potential demographic or neuropsychological confounders; or adjusting for medication effects. FCI, depression, social function and various aspects of insight did not differ significantly. Post hoc, adjusted PANSS positive subtotal was less in the remediation group (95% CI -0.06, -6.55). Conclusions. FCI and insight did not improve significantly more in the intervention than control group. Many of the sample were chronically unwell and they benefited least. The finding of a specific effect on positive symptoms bears further investigation.

ACP104 SAFETY AND PHARMACOKINETICS IN PSYCHOSIS

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ACP104 is the des-methyl metabolite of clozapine with inverse 5HT2A and partial D2 dopamine agonism. The receptor affinity profile of ACP104 is similar to the profile of clozapine, except for one major difference: ACP104 is an M1 partial agonist and does not have any muscarinic antagonist activity. This suggests that ACP104 will demonstrate many of the antipsychotic characteristics of clozapine but, in addition, will possess cognitive enhancing activity due to the muscarinic stimulation. Recently, we conducted a clinical study to determine the safety, tolerability, and pharmacokinetic profile of ACP104 in psychosis in single dose administration and to gather preliminary information about it potential for clinical action. Twenty-three participants who were otherwise free from antipsychotic drugs completed the single dose study. The 23 patients formed five cohorts who each received two doses of drug and one of placebo in rising dose fashion from 25 mg to 250 mg. ACP104 was safe and well tolerated; no maximally tolerated dose was achieved during the study. Vital signs were stable across all dosing groups and ECG tracings were not abnormal at any dose. Routine laboratories were performed throughout the course of the study for each dosing group and no changes were found that were inconsistent with antipsychotic drug effects. PANSS scores before and after single doses of ACP104 showed a decrease after the two higher (225mg and 250mg) doses, but not at the lower dose levels. There were no unexpected or serious adverse events that occurred across the dose groups. Among all adverse events, sedation was most frequent. Pharmacokinetic data were collected and will be reported.

DRUG ATTITUDE DURING THE INITIAL TREATMENT PERIOD: A PROSPECTIVE FOLLOW-UP STUDY IN PATIENTS WITH SCHIZOPHRENIA

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A prospective study was conducted in patients with schizophrenia to examine the impact of sociodemographic factors, psychopathol-

ogy, and side effects on subjective response and attitudes toward antipsychotics. 42 patients starting treatment with a new-generation antipsychotic were investigated. Apart from the registration of demographic data various rating scales were done: the Positive and Negative Syndrome Scale (PANSS), the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale, and the Drug Attitude Inventory (DAI). Next to the duration of illness amelioration of psychopathological symptoms, particularly of cognitive symptoms, negative symptoms, and excitement, had a positive impact on subjective response to treatment. On the other hand, correlations between antipsychotic-induced side effects and drug attitude tended to be weak. Next to the need of pharmacotherapy, our results emphasize the necessity of providing both psychotherapeutic and psychosocial interventions focusing especially on cognitive symptoms, negative symptoms, and excitement during the initial treatment period in order to improve attitudes toward and compliance with treatment.

EFFICACY AND TOLERABILITY OF ORAL PALIPERIDONE EXTENDED-RELEASE TABLETS IN THE TREATMENT OF ACUTE SCHIZOPHRENIA: POOLED DATA FROM THREE 52-WEEK, OPEN-LABEL EXTENSION STUDIES

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Three recently completed 6-week, double-blind (DB) studies demonstrated consistent efficacy and favorable tolerability for paliperidone extended-release tablets (paliperidone ER) in the treatment of patients with acute schizophrenia. The objective of this analysis was to evaluate the efficacy and safety of paliperidone ER during the long-term open-label extension (OLE) phase of these 3 studies. The analysis included pooled data from 3 international, 52-week, multicenter, OLE studies in patients (n=1083, aged ≥18 years) who had been switched to flexibly dosed paliperidone ER (3, 6, 9, 12 or 15mg; starting dose=9mg) from their previous DB study treatment group. Efficacy analyses included change from baseline to end point in Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression—Severity (CGI-S) scores and the Personal and Social Performance (PSP) scale, a measure of personal and social functioning. Safety assessments included treatment-emergent adverse events (TEAEs), movement disorder scales, vital signs and bodyweight. The mean age of patients who entered these studies was 37.6y±10.9 and their mean baseline (open-label; OL) PANSS total score was 72.9±20.5. In the OL intent-to-treat analysis set, the mean modal dose of paliperidone ER was 10.1mg. Mean PANSS total score improved (–7.17±20.7) compared with OL baseline. CGI-S median scores and patient functioning were maintained from OL baseline to end point. In the safety analysis set, 15.7% of patients experienced serious AEs, and 7.3% of patients discontinued due to an AE (most frequent=psychosis, 5% and 1%, respectively). TEAEs occurred in a total of 76% of patients, the most common being insomnia (14%), headache (12%), akathisia (11%), anxiety (9%) and psychotic disorder (9%). Consistent with the incidence of TEAE—extrapyramidal symptom rates, the majority of patients had no change on SAS, AIMS and BARS at end point. Total mean change in bodyweight during the OLE was 1.1±5.5 kg, whereas 15% of patients experienced a weight increase of ≥7%. In this analysis, improvements in efficacy with paliperidone ER observed in previous DB, 6-week studies were maintained in the long-term. The safety profile was generally consistent with the short-term data. No unexpected AEs emerged that appeared to be related to long-term exposure to paliperidone ER. Supported from funding from Johnson & Johnson Pharmaceutical Services, LLC and Johnson & Johnson Pharmaceutical Research and Development.

NICOTINIC CHOLINERGIC THERAPEUTIC MECHANISMS IN SCHIZOPHRENIA

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Nicotinic receptor activation has been postulated as a potential therapeutic target for schizophrenia. The evidence for the efficacy of nicotinic receptor activation is not established, but there are several demonstrations of the possibilities: (1) the effects of nicotine from cigarette smoking on psychophysiological and neuropsychological deficits in schizophrenia; (2) evidence for indirect activation of a nicotinic cholinergic mechanism in the action of clozapine and to a lesser extent olanzapine; and (3) preliminary evidence for therapeutic effects of two drugs that directly activate nicotinic receptors, tropisetron and 3-(2,4 dimethoxybenzylidene)-anabaseine, and (4) case material supporting positive effects of the nicotinic receptor allosteric modulator, galantamine. The clinical evidence will be reviewed, along with basic evidence that suggests that most of these compounds are acting through low affinity alpha7-nicotinic acetycholine receptors. Therapeutic challenges for agonist therapies include limited duration of action, tachyphylaxis at high doses, and specificity. These issues may favor some agents—indirect agonists, partial agonists, and allosteric modulators—over others, such as full agonists. Alpha7-nicotinic agonists are not likely to be effective as sole therapeutic agents for schizophrenia, but they could be effective in specific roles, such as increasing the cognitive effect of dopamine-D2 antagonists and acting as substitutes for nicotine itself.

NUMBER NEEDED TO TREAT: A METHOD OF ASSESSING RELIABLE CHANGE IN COGNITION WITH NEAR COGNITIVE REMEDIATION

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Number needed to treat (NNT) is a useful measure of treatment efficacy that has become a popular method for clinical decision-making in recent years. NNT refers to the number of individuals that would need to be treated with a specific intervention in order to obtain one additional positive outcome that would not have occurred with an alternative intervention. The objective of the present study was to calculate NNT for NEAR cognitive remediation in psychiatric patients. Data was drawn from two randomized controlled trials on cognitive remediation comparing Neuropsychological Educational Approach to Remediation (NEAR) to treatment as usual (TAU). The first study examined the pre- and post-intervention scores of 54 inpatients with diagnoses of either schizophrenia or schizoaffective disorder (36 experimental; 18 controls) on the Problem Solving subscale of the Independent Living Scales (ILS-PS). The second study examined the pre- and post-intervention scores of 32 outpatients with diagnoses of schizo-

phrenia (18 subjects; 11 experimental, 7 controls) and affective disorder (14 subjects; 6 experimental, 8 controls) on the California Verbal Learning Test, 2nd Edition (CVLT-II) and Wisconsin Card Sorting Test (WCST). Subjects were determined to have made significant improvement if their reliable change index (RCI) scores exceeded 1.96 on a particular outcome measure. NNT was then calculated as the inverse of the difference between the percentage of patients determined to have made significant improvement in the experimental and control groups [1/(experimental % change - control % change)]. The results of these calculations indicate NNT values ranging from 2-5. That is, one out of every 2-5 individuals appeared to benefit from NEAR by exhibiting significant reliable change on neuropsychological and functional outcome measures post-intervention. These values compare favorably to the NNTs reported for widely used pharmacologic treatments, indicating that NEAR, a behavioral treatment for cognitive dysfunction, is a useful addition to psychiatric treatment programs.

CLUSTER ANALYSIS OF PANSS ITEMS: IDENTIFICATION OF SCHIZOPHRENIA PATIENT SUBTYPES WITH SIMILAR SYMPTOM PROFILES

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Cluster analysis applied to PANSS scores can identify distinct patient groups with schizophrenia who may differ in treatment response, psychopathological variables and course of illness. Agglomerative hierarchical cluster analysis was applied to baseline PANSS item scores for 6847 patients with schizophrenia and schizoaffective disorder from 14 studies. Five distinct patient clusters were identified, representing groups of patients with similar symptom profiles. The clusters were characterized as: highly symptomatic, negative/disorganized, minimally symptomatic, predominant positive, and depressive/positive/negative. Cluster analysis is a powerful approach to examine the complex heterogeneous disorder of schizophrenia. Future work will focus on treatment response and genetic polymorphisms associated with specific patient clusters. Support: Janssen, LP

Table. Clustering by baseline PANSS scores (LOW: < 2.20; MED: 2.20 – 3.20; HIGH: ≥ 3.20)

PANSS Score Mean (SD)		Negative/ Disorganized (n=1292)	Minimally Symptomatic (n=1430)	Mixed Symptoms (n=876)	Highly Symptomatic (n=1558)	Positive Symptoms (n=1691)
Positive Subscale	P1	MED	LOW	HIGH	HIGH	HIGH
	P2	HIGH	LOW	HIGH	HIGH	MED
	P3	MED	LOW	HIGH	HIGH	MED
	P4	LOW	LOW	HIGH	MED	MED
	P5	LOW	LOW	MED	MED	MED
	P6	MED	LOW	HIGH	HIGH	HIGH
	P7	LOW	LOW	HIGH	MED	LOW
Negative Subscale	N1	HIGH	MED	MED	HIGH	MED
	N2	HIGH	MED	MED	HIGH	MED
	N3	HIGH	MED	MED	HIGH	LOW
	N4	HIGH	MED	HIGH	HIGH	MED
	N5	HIGH	MED	HIGH	HIGH	MED
	N6	HIGH	MED	MED	HIGH	LOW
	N7	HIGH	LOW	HIGH	HIGH	MED
General Subscale	G1	MED	LOW	MED	MED	MED
	G10	MED	LOW	LOW	LOW	LOW
	G11	MED	LOW	MED	MED	LOW
	G12	HIGH	MED	HIGH	HIGH	HIGH
	G13	HIGH	LOW	MED	HIGH	MED
	G14	LOW	LOW	HIGH	MED	LOW
	G15	HIGH	LOW	HIGH	HIGH	MED
	G16	HIGH	MED	HIGH	HIGH	MED
	G2	MED	MED	HIGH	HIGH	MED
	G3	LOW	LOW	MED	MED	MED
	G4	MED	LOW	HIGH	HIGH	MED
	G5	MED	LOW	MED	MED	LOW
	G6	MED	LOW	MED	MED	MED
	G7	MED	LOW	LOW	MED	LOW
	G8	LOW	LOW	HIGH	MED	LOW
	G9	MED	LOW	HIGH	HIGH	HIGH

TAMOXIFEN- A POTENTIAL TREATMENT FOR WOMEN IN THE MANIC PHASE OF BIPOLAR AFFECTIVE DISORDER? TAMOXIFEN- A POTENTIAL TREATMENT FOR WOMEN IN THE MANIC PHASE OF BIPOLAR AFFECTIVE DISORDER?

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Bipolar Affective Disorder (BPAD) is an illness with high morbidity and mortality. Lithium and other anti-convulsant drugs are the main treatments for BPAD, despite little being known about their mechanisms of action. Recent attempts to elucidate the biochemical actions of these drugs have focussed on the Protein Kinase C (PKC) pathways. Another PKC inhibitor hypothesised to be effective in the treatment of mania is tamoxifen, a synthetic non-steroidal antiestrogen. The aim of the current study was to test and compare the effectiveness of two adjunctive antiestrogen agents (tamoxifen or progesterone) in the treatment of acute mania. A 28-day three-arm (40mg/day oral tamoxifen or 20mg/day oral progesterone or oral placebo) double-blind, placebo controlled adjunctive study of 34 women with mania was conducted. All patients also received a mood stabiliser as the baseline treatment. Manic symptoms and psychopathology were measured weekly using the CARS-M and PANSS rating scales together with estrogen, progesterone, and gonadotropin levels. Cognitive functioning (RBANS) was assessed in a sub-sample of participants at baseline and repeated on day 28. Results indicated a decline in the symptoms of mania and psy-

chopathology in the tamoxifen group, and to a lesser extent in the progesterone and control groups. The tamoxifen group also had significant changes in estrogen levels, as well as correlations between estrogen and mania ratings. The results suggest that tamoxifen may be a useful adjunct in the treatment of acute manic symptoms in women with BPAD. This research was supported by The Stanley Medical Research Institute and the National Health and Medical Research Council of Australia.

NEUROCOGNITIVE PREDICTORS OF OUTCOME IN COGNITIVE BEHAVIORAL SOCIAL SKILLS TRAINING FOR PEOPLE WITH CHRONIC SCHIZOPHRENIA

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Cognitive Behavioral Social Skills Training (CBSST) is a 24-session weekly group therapy intervention that combines cognitive behavior therapy with social skills and problem solving training to improve functioning in people with chronic schizophrenia. In a randomized controlled trial (Granholm et al. Amer J Psychiatry, 162, 520-529, 2005) that compared treatment as usual (TAU) with TAU plus group CBSST in 76 outpatients with chronic schizophrenia, blind raters obtained assessments of CBSST skill mastery, functioning, psychotic and depressive symptoms, and cognitive insight (metacognition and belief flexibility on the Beck Cognitive Insight Scale self-report measure). At the end of treatment, patients in CBSST groups showed significantly greater skill acquisition and self-reported functioning in the community than patients in TAU, and these gains were maintained at 12-month follow-up. Participants in CBSST also showed significantly greater cognitive insight at end of treatment relative to TAU, but this improvement was not maintained at follow-up. The treatment group effect was not significant for symptoms at any assessment point, but symptoms were not the primary treatment target in this stable outpatient sample. Neuropsychological evaluation of executive, attention, verbal learning/memory, and psychomotor speed functions were also completed at baseline, end of treatment, and 12-month follow-up. Greater global neurocognitive impairment at baseline had a similar negative impact on functional outcome at 12-month follow-up for both groups, so severity of neurocognitive impairment did not differentially impact outcome in CBSST. Finally, although participants learned new strategies to test beliefs/hypotheses and think about thinking (i.e., showed significantly improved metacognition) in CBSST, executive functions did not improve significantly more in CBSST relative to TAU. Executive functioning and metacognition measures also were not significantly correlated at baseline. Neurocognitive flexibility and metacognitive flexibility, therefore, appeared to be distinct constructs. Greater impairment in executive functioning at baseline, however, was associated poorer metacognition outcome in TAU, but not in CBSST, after treatment. CBSST, therefore, may have compensated for the negative impact of poor neurocognitive flexibility on metacognitive belief flexibility in people with chronic schizophrenia.

FIRST EPISODE PSYCHOSIS AND SUBSTANCE ABUSE: OLANZAPINE VS. HALOPERIDOL

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In a recently completed double-blind randomized study of olanzapine (OLAN) and haloperidol (HAL) in 263 patients with first episode psychosis (schizophrenia, schizoaffective or schizophreniform disorder), 37% had a lifetime diagnosis of substance use disorder (SUD). Patients with SUD were more likely to be men and to have more positive and fewer negative symptoms at baseline than those without SUD. Those with cannabis use disorder (CUD) had an earlier age of onset. Moreover, those with SUD had a poorer response over the first 12 weeks of treatment with either OLAN or HAL. Here, we describe a post-hoc analysis of the effects of co-occurring SUD on outcome over the course of the 2 year study. Responders were identified by: (1) no rating of >3 (mild) on items P1, P2, P3, P5 and P6 of the PANSS; and (2) CGI severity score <4 (moderately ill). SUD was assessed at baseline to determine whether there was a lifetime history or current evidence of alcohol or other SUD. Information was available for substance (including alcohol) use disorder, alcohol use disorder (AUD), and CUD. Patients with SUD (as compared to those without SUD) were less likely to respond to treatment (56.3% vs. 72.4%; Fisher Exact P<0.0094). If analyzed by treatment group, this difference was significant for the subgroup of patients treated with HAL, but not OLAN. If assessed by substance and treatment group, the difference in response was confined to those with a history of CUD who were treated with HAL. Improvement in PANSS total (and PANSS positive symptoms) was less in patients with a SUD diagnosis than in patients without SUD. Among patients with AUD, change in PANSS total (and PANSS negative symptoms) was less; among patients with CUD, improvement in PANSS total and PANSS positive were less in those without SUD. There was a trend for patients with SUD to stay in the study for a shorter time than those without SUD (significant for patients with CUD; p=.0216). The difference of time in study among those with SUD or CUD was confined to the HAL group, such that there was a trend to shorter time in study in those with SUD (p=.06) and a significantly shorter time in the study for the CUD group (p=.006). A post-hoc analysis of data from a 2-year trial of OLAN vs. HAL in patients in their first episode of psychosis suggests that the benefits provided by OLAN appear to occur largely in patients with a co-occurring SUD, particularly those with CUD. Grant from Eli Lilly.

OPEN-LABEL ASSESSMENT OF THE LONG-TERM TOLERABILITY, SAFETY, AND EFFICACY OF SERTINDOLE IN PATIENTS WITH SCHIZOPHRENIA

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An open-label, flexible-dose study of sertindole was conducted at 68 European centres. Patients had a primary diagnosis of schizophrenia (DSM-III-R), and had previously completed the double-blind treatment period of an 8-week sertindole/haloperidol comparative study. A dose-titration period was followed by a flexible-dose maintenance period of 6 to 18 months. The primary objective was to assess the long-term tolerability and safety of sertindole, assessed as the proportion of patients reporting an AE judged to be possibly or probably related to sertindole treatment and laboratory parameters, vital signs, and ECG. Long-term efficacy was evaluated using PANSS and CGI. 295 patients entered the open-label study (238 sertindole and 57 haloperidol in the previous double-blind study). Most patients (56%) received a modal dose of 16 mg sertindole. 151 patients completed at least 6 months of treatment and the mean exposure was 306 days. 85 patients were withdrawn prematurely; 23 due to lack of efficacy, 37 due to informed consent withdrawal and 6 due to AEs. A total of 243 patients reported AEs during the study, of

which 230 were treatment-emergent. 20% relapsed. The most frequent TEAEs were: asthenia (16%), decreased ejaculatory volume (14%) and metabolic disorder/weight gain (12%). No statistically significant changes in laboratory values or vital signs were observed. Sertindole treatment was associated with a reduction in prolactin and an increase in the QTc interval compared to baseline. Statistical analyses reveal that the QTc interval was increased in the 8-week study and then decreased over time during the extension study. There was a further treatment-related improvement from the acute study baseline in total PANSS and component subscale scores (PANSS total, $p<0.0001$; PANSS positive, $p=0.021$; PANSS negative, $p<0.0001$). There was also a significant improvement from baseline in general psychopathology scale ($p<0.0001$). Statistical analysis of the CGI-S score, using a linear model for repeated measurements, showed a significant improvement with time during sertindole treatment ($p<0.001$). The study indicated long-term efficacy of sertindole in treatment of schizophrenia. The effective dose for most patients was 16 mg/day. The safety profile of sertindole was similar to that seen in earlier studies. The low withdrawal rate due to AEs (2%), indicates that sertindole is continuously well tolerated beyond acute treatment.

REASONS FOR SWITCHING FROM PREVIOUS THERAPY AND PREFERENCE OF MEDICATION IN THE LARGE, RANDOMIZED, NATURALISTIC SCHIZOPHRENIA TRIAL OF ARIPIPRAZOLE (STAR)

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Purpose: This subanalysis of the open-label, randomized, naturalistic Schizophrenia Trial of Aripiprazole (STAR) explored medication preference and reasons for switching in 555 community-treated schizophrenia patients who were switched from olanzapine or risperidone (due to intolerance +/or suboptimal control of clinical symptoms) to the atypical antipsychotic aripiprazole (10-30 mg/day) or standard of care (SoC) agents. Methods: Investigators selected the SoC agent (olanzapine 5-20 mg/day, quetiapine 100-800 mg/day or risperidone 2-8 mg/day) according to treatment history; patients were not to receive the agent prescribed just prior to the study, or one not previously tolerated/effective. Clinicians were asked to provide the primary reason for changing agent. The Preference of Medication (POM) questionnaire was used to assess preference of current vs. prior agent at Weeks 8, 18 and the end of Week 26/time of early discontinuation. The 2-item POM, rated from 1 (much better; prefer this medication) to 5 (much worse; prefer the prior medication), directs one question each to the patient and caregiver. Between-group comparisons were assessed by a Cochran-Mantel-Haenszel General Association test. Results: The most common primary reasons for switching from olanzapine (n=123) to aripiprazole (n=61) or SoC (risperidone/quetiapine; n=62) were weight gain (24%) and suboptimal control of positive (24%) or negative (23%) symptoms. The most common primary reasons for switching from risperidone (n=103) to aripiprazole (n=49) or SoC (olanzapine/quetiapine; n=54) were suboptimal negative (39%) or positive (20%) symptom control. Proportions of patients and caregivers who rated current medication as 'much better' vs. the prior agent on the POM scale (Week 26; LOCF analysis) are shown in the table. Conclusion: Primary reasons for switching were weight gain and poor control of positive or negative symptoms with olanzapine, and persistence of positive or negative symptoms with risperidone. Greater proportions of patients and caregivers preferred aripiprazole to SoC agents after switching. Patients who experience problems with tolerability/symptom control with olanzapine/risperidone may benefit from switching to aripiprazole.

Treatment after randomization	Prior olanzapine treatment		Prior risperidone treatment	
	Patient's preference, n (%)	Caregiver's preference, n (%)	Patient's preference, n (%)	Caregiver's preference, n (%)
Aripiprazole	24/55 (43.6)	4/14 (28.6)	23/46 (50.0)	5/15 (33.3)
Standard of care agents	16/55 (29.1)	2/13 (15.4)	15/48 (31.3)	4/21 (19.0)
p value	0.072	1.000	0.144	0.780

LIPID PROFILE AMONG PATIENTS WITH SCHIZOPHRENIA RANDOMIZED TO BIFEPRUNOX, PLACEBO, OR RISPERIDONE: A COMPARISON OF RESULTS

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(a) To examine lipid changes in patients with an acute exacerbation of schizophrenia treated with bifeprunox. (b) In this 6-week randomized, double-blind, placebo-controlled, risperidone-referenced study of bifeprunox, 599 patients with acutely exacerbated schizophrenia (DSM-IV-TR) were randomly assigned to once-daily treatment with bifeprunox 30 mg (n=148), 40 mg (n=148), placebo (n=149) or risperidone 6 mg (n=154). Bifeprunox doses were titrated, beginning with a dose of 0.25 mg on day 1 and approximately doubled every day until 30 mg or 40 mg (day 8) were reached; risperidone was titrated over 3 days. All lipid measures included were non-fasting: total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL). (c) In this study, bifeprunox 20 and 30 mg trended towards an improved lipid profile compared to risperidone (Table 1). In addition, the bifeprunox groups had a lower incidence of normal to high shifts in TG, VLDL, and LDL than the placebo and risperidone groups (TG: 40 mg bifeprunox: 4%; 30 mg bifeprunox: 3%; placebo and risperidone: 6% each; VLDL: 40 mg bifeprunox: 3%: 30 mg bifeprunox: 4%; placebo: 6%; risperidone: 7%; LDL: 40 mg bifeprunox: 4%; 30 mg bifeprunox: 2%; placebo and risperidone: 8% each). (d) The results of this study suggest that bifeprunox may have favorable effects on lipids in patients with schizophrenia.

Table 1

	Treatment Group			
Lipid Parameter	Bifeprunox 30 mg (N=145)	Bifeprunox 40 mg (N=147)	Placebo (N=149)	Risperidone 6 mg (N=154)
Total Cholesterol, n	121	110	123	136
Baseline Mean	184.5	187.5	198.6	185.1
Mean Change from Baseline (SD)	-9.7 (32.0)	-15.7 (31.0)	-14.2 (32.0)	-2.2 (31.4)
Triglycerides, n	121	110	123	136
Baseline Mean	189.9	157.2	198.3	186.9
Mean Change from Baseline (SD)	-31.7 (138.5)	-31.6 (80.3)	-27.9 (104.4)	-6.7 (136.2)
VLDL, n	113	103	112	127
Baseline Mean	34.4	30.3	36.3	33.3
Mean Change from Baseline (SD)	-6.3 (16.8)	-6.5 (13.5)	-3.7 (16.9)	-1.4 (17.7)
LDL, n	105	103	102	119
Baseline Mean	104.4	108.1	112.7	103.7
Mean Change from Baseline (SD)	-5.5 (25.5)	-9.7 (26.3)	-7.5 (29.8)	-2.8 (28.8)
HDL, n	113	105	112	128
Baseline Mean	44.8	46.4	44.6	45.5
Mean Change from Baseline (SD)	0.9 (7.5)	1.0 (8.7)	-0.7 (6.8)	2.1 (10.3)

PROBING THE PATHOPHYSIOLOGY OF AUDITORY/VERBAL HALLUCINATIONS BY COMBINING FUNCTIONAL MAGNETIC RESONANCE IMAGING AND TRANSCRANIAL MAGNETIC STIMULATION

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In order to better understand the pathophysiology of auditory/verbal hallucinations (AVHs), repetitive transcranial magnetic stimulation (rTMS) was combined with functional magnetic resonance imaging. Sixteen patients with schizophrenia-spectrum disorder and continuous or near continuous AVHs were studied. For patients with intermittent hallucinations (N=8), blood-oxygenation-level-dependent (BOLD) activation maps comparing hallucination and non-hallucination periods were generated. For patients with continuous hallucinations (N=8), correlations of BOLD signal time series relative to Wernicke's area were mapped. Both mapping methods were then used to identify 3-6 cortical sites per patient that were then probed with suppressive 1-hertz rTMS and sham stimulation. rTMS to a left temporoparietal region incorporating Wernicke's area and the neighboring supramarginal gyrus was accompanied by statistically greater improvements in auditory/verbal hallucinations compared to sham stimulation and rTMS to anterior temporal sites. For intermittent hallucinators, left temporoparietal rTMS rate of response was robustly and negatively correlated with hallucination-related activation in Broca's region. For continuous hallucinators, left temporoparietal rTMS rate of response was robustly and negatively correlated with coupling between Wernicke's and a right homologue of Broca's area. These findings suggest that AVHs arise from a distributed network incorporating, at minimum, posterior receptive language and inferior frontal language production areas.

TREATMENT OF BEHAVIOURAL EMERGENCIES WITH OLANZAPINE IN PATIENTS WITH SCHIZOPHRENIA, SCHIZOAFFECTIVE OR BIPOLAR I DISORDER

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Objective Up to 20% of inpatients with schizophrenia spectrum disorders have to be treated because of behavioural emergencies (BE), i.e. severe aggression or impulsivity. Although these situations require quick and effective interventions, observational data on specific BE treatment is sparse. The current study was designed to give an overview on treatment regimes and short-term effectivity in German inpatients with schizophrenia, schizoaffective or bipolar I disorder. Sample and methods Data from 166 adult German inpatients receiving first-line monotherapy with olanzapine (OLA) for specific treatment of aggression or impulsivity were used for current analyses. The following parameters were rated prospectively at baseline (day 0) and days 1 to 5: PANSS-EC (excited component), CGI-aggression, CGI-suicidality, tranquillisation score. PANSS-EC course was analysed using a multifactorial model (MMRM). Results 67.5% of the subjects were diagnosed with non-affective psychosis, 25.9% were reported to have co-morbid substance abuse or dependency, mean PANSS-EC total score was 25.5 points (SD 5.3). Clinicians prescribed significantly higher mean daily doses of OLA in affective psychoses and in severely aggressive (CGI-A ≥ 4) patients. During the observation period, PANSS-EC and CGI-aggression improved significantly across all subgroups. MMRM analysis confirmed the independent contribution of a lower PANSS-EC at baseline, age below 30, and the presence of a severe behavioural emergency (PANSS-EC $\geq$ 25) at baseline to worse development of PANSS-EC. Subjects with a higher mean dose of OLA showed less PANSS-EC improvement (day 1 only). Additionally, patients receiving a higher mean daily dose of benzodiazepines (BZD) showed worse PANSS-EC course throughout the study. Discussion In German hospitals, pharmacological first-line OLA treatment of BE is adapted to patient diagnoses (higher dose in affective psychoses) and level of aggression (higher dose in severe aggression). Whereas PANSS-EC and CGI-A improved over the observation period in all patient subgroups, low age and severe BE were independently associated with worse PANSS-EC course. Improvement was also slower in subjects with low PANNS-EC at baseline, demonstrating better short-term treatment response in severe BE. Patients whom clinicians chose to treat with higher doses of OLA or BZD still showed less improvement with respect to PANSS-EC. This study was supported by Eli Lilly Company, Germany.

HOW USEFUL ARE LARGE OBSERVATIONAL STUDIES IN SCHIZOPHRENIA? RESULTS FROM THE SCOTTISH SCHIZOPHRENIA OUTCOMES STUDY

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Despite advances in various types of intervention for schizophrenia in the last decade, there is a general perception that outcome remains poor for many patients. The expectation that the introduction of community based care, second generation antipsychotics and

psychosocial interventions would improve outcomes, is open to challenge and has not been assessed adequately in 'real-world' settings. Although the aspiration for 'evidence based healthcare' is widely supported, there is a considerable paucity of good quality research data upon which to base treatment decisions. Randomised controlled trials (RCTs) of pharmacological interventions, undertaken for regulatory purposes, provide quality efficacy data, but far fewer effectiveness RCTs have been completed, with notable exceptions such as the recent CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study [1]. This paper investigates whether longitudinal observational studies can provide data that assists our understanding of diseases such as schizophrenia, and have utility to inform clinical decisions [2]. Results from a large observational study undertaken in a mainly community based Scottish cohort will be presented (Scottish Schizophrenia Outcomes Study, SSOS)[3]. Results from SSOS provide a useful description of pharmacological and psychosocial interventions and health outcomes over 3 years in a cohort of 1000 participants with multi-episode schizophrenia. This work raises questions about the effectiveness of current interventions for schizophrenia and how best to assess clinical outcomes in representative patient populations. The way in which large observational studies such as SSOS can complement data from efficacy RCTs will be discussed. REFERENCES: [1] Effectiveness of Antipsychotic Drugs in patients with Chronic Schizophrenia. Lieberman JA, Stroup TS, McEvoy JP etal (2005). New England Journal of Medicine 353, 1209-1223. [2] Black N(1996). Why we need oservational studies to evaluate the effectiveness of healthcare. British Medical Journal,312,1215-1218. [3] Hunter R and Cameron R (2006).The Scottish Schizophrenia Outcomes Study. Quality Improvement Scotland, Edinburgh. www.nhshealthquality.org

EFFICACY AND TOLERABILITY OF ATYPICAL ANTIPSYCHOTICS IN ADOLESCENTS WITH PSYCHOSIS

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The use of typical antipsychotics in adolescents with psychosis has previously been confounded by a high rate of EPS. The atypical antipsychotics may represent a promising treatment alternative in this population, but data from trials of their efficacy and tolerability are limited. This 12-week, open-label study examined the effects of risperidone, olanzapine and quetiapine in adolescents (aged 12–18 years) with psychosis. Twenty-one patients meeting DSM-IV criteria via Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) for schizophrenia, schizophreniform, schizoaffective disorder or psychosis Not Otherwise Specified (NOS) were enrolled to date. Washout was variable due to patient safety. Patients were randomly allocated to risperidone (0.5–6 mg/day), olanzapine (2.5–20 mg/day) or quetiapine (100–800 mg/day) groups. The primary efficacy variable was the change in Positive and Negative Symptom Rating Scale (PANSS) score from baseline. Assessments of tolerability were also collected. At endpoint, all treatments reduced PANSS scores from baseline. Mean daily doses were 4.8, 13.5 and 675 mg for risperidone, olanzapine and quetiapine, respectively. AIMS scores improved from baseline with risperidone and remained constant for patients in the quetiapine group, but there were no significant differences between the groups. Only quetiapine was associated with improvements in both SAS and Barnes scores at endpoint. Weight gain as an adverse event was reported less frequently with quetiapine. The results of this study suggest that all agents reduced symptoms of psychosis and were generally well tolerated. Supported by funding from an AstraZeneca Pharmaceuticals LP Investigator-Sponsored Study Grant (IRUSQUET0149).

VASOPRESSIN V2-RECEPTOR BLOCKADE WITH TOLVAPTAN IN SCHIZOPHRENIC PATIENTS WITH HYPONATREMIA: RESULTS FROM A DOUBLE-BLIND, RANDOMIZED TRIAL

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Tolvaptan (OPC-41061), a novel, oral, non-peptide vasopressin V2-receptor antagonist may improve hyponatremia by decreasing water reabsorption in the kidney. Schizophrenic patients constituted 5% of subjects in two prospective, multi-center, placebo-controlled trials patients with chronic hyponatremia. This report describes the effects of tolvaptan in this sub-population. The SALT trials enrolled 448 subjects with hyponatremia of all causes (e.g. congestive heart failure, cirrhosis, SIADH), of which 24 schizophrenic patients were identified. These were predominantly male (17/24) with a mean age of 50 years with 5 having co-morbidities of CHF or cirrhosis. All but 3 subjects with schizophrenia completed the 30 day trial. One subject was excluded after psychogenic polydipsia was diagnosed. The 24 patients were randomly assigned to placebo (n=13) or tolvaptan (n=11) [initially15 mg, titratable to 30 or 60 mg] once daily for 30 days, generally without fluid restriction. The average AUC change in sodium from baseline was compared to placebo at Day 4 and 30 as the co-primary endpoints. The increase in serum sodium concentration was significantly greater for tolvaptan for the overall study ($p<0.0001$, each period) and for the subpopulation of schizophrenic subjects ($p<0.01$ and <0.005, respectively). The sodium concentration rose from 129 ± 5 mEq/L (mean ± SD), to 135 ± 6 mEq/L by day 30 in the tolvaptan group (mean increase of 6 mEq/L), compared with a mean increase of 1 mEq/L for the placebo group ($p<0.001$). Seven days after discontinuation of study drug, (Day 37) the tolvaptan group's sodium fell to baseline levels. Approximately 45% of subjects in each group experienced adverse events (AE), the most common of which for tolvaptan were thirst, dehydration, hypotension and ataxia, each occurring in two subjects. One subject in each group died during the period of observation of causes deemed unrelated to study drug (pulmonary embolism and septic shock). In schizophrenic patients with hyponatremia, tolvaptan was well tolerated and normalized serum sodium. Side effects consistent with its mechanism of action may be expected, however while tolvaptan treatment appears safe, return to hyponatremia may be expected on discontinuation of therapy.

DRUG INTERACTIONS BETWEEN ARIPIPRAZOLE AND HALOPERIDOL: DOUBLE BLIND, PLACEBO CONTROLLED STUDY

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Purpose: Aripiprazole and haloperidol are metabolized primarily by hepatic enzyme systems such as cytochrome P450 (CYP) 3A4 and

2D6 enzyme systems, the addition of aripiprazole on haloperidol has the potential to alter plasma concentrations and metabolism of haloperidol and its metabolite. In this study, we investigated pharmacokinetic interactions between aripiprazole and haloperidol. Method: 26 patients with schizophrenia who has been treated with haloperidol were enrolled in this eight-week, double blind, placebo-controlled study. Haloperidol dose was fixed throughout the study and aripiprazole was dosed at 15mg/day for the first 4 weeks then 30mg for next 4 weeks. Serum haloperidol and aripiprazole levels were measured at the baseline, week 1, 2, 4 and 8. Plasma concentrations of haloperidol, reduced haloperidol, and aripiprazole were determined by high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS). The lower limits of quantification for haloperidol, reduced haloperidol, and aripiprazole were 0.1, 0.1 and 1.0 ng/mL. The interassay precision for all analytes were less than 14.3%. Genotyping for CYP2D6 and 3A4 was done for excluding poor metabolizer of haloperidol and aripiprazole. Two-tailed student's t-test, chi-square test, and Repeated measures ANOVA was used to analyze data. An alpha level of 0.05.was considered statistically significant and all tests were two tailed. Result: Demographic and clinical characteristics did not significantly differ between the aripiprazole and placebo groups. The mean dose of haloperidol was not significantly different between aripiprazole and placebo groups (20.7±12.6mg/day vs. 24.8±14.2mg/day). Baseline plasma level of haloperidol and reduced haloperidol were not significantly different between two groups. In a repeated measure ANOVA design, plasma level of haloperidol and reduced haloperidol did not demonstrate significant time effect and time-group interaction after adjunctive treatment of aripiprazole. Plasma levels of aripiprazole increased by a time dependent pattern, 102.0±60.8 nM/mg at week 4 and 183.2±79.2nM/mg at week. Conclusion: Adjunctive treatment with aripiprazole to haloperidol did not affect plasma level of haloperidol and reduced haloperidol.

EFFICACY AND TOLERABILITY OF ONCE DAILY QUETIAPINE SUSTAINED RELEASE FOR THE TREATMENT OF ACUTE SCHIZOPHRENIA: A RANDOMIZED, DOUBLE BLIND, 6 WEEK, PLACEBO-CONTROLLED TRIAL

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Introduction: This was a 6-week, double-blind, randomized study (D1444C00132) comparing efficacy and tolerability of quetiapine sustained release (SR) with placebo. Methods: 588 patients with acute DSM IV schizophrenia (PANSS total score ≥70; CGI-S ≥4) were randomized to fixed dose quetiapine SR 400, 600 or 800 mg/day (placebo in the morning, active dose in the evening), quetiapine immediate release (IR) 400 mg/day (200 mg twice-daily), or placebo (twice-daily). Quetiapine SR was initiated at 300 mg on Day 1; target doses were reached by Day 2 (SR 400 and 600 mg), Day 3 (SR 800 mg), and Day 5 (IR 400 mg). Primary endpoint: change from baseline to Day 42 in PANSS total score (LOCF), analyzed using ANCOVA. OC analysis also performed. Secondary endpoints (to Day 42) included: PANSS response rates (percent of patients with ≥30% reduction in total score from baseline); percent of patients with CGI-I rating ≤3; change in CGI-S, incidence of AEs. Results: 446 patients (76%) completed the study (72% placebo; 74-81% SR; 78% IR). PANSS total score decreased significantly in all groups compared with placebo (LOCF [table]). Furthermore, OC analysis also demonstrated efficacy versus placebo. Statistical separation from placebo was shown for PANSS response rates and percent of patients with CGI-I ≤3. Improvement in CGI-S was statistically significant for quetiapine SR 600 mg (p=0.001), 800 mg (p<0.001), and quetiapine IR (p=0.033) versus placebo. The tolerability profile of quetiapine SR was consistent with the known profile for quetiapine IR. Most AEs with quetiapine SR were mild to moderate in severity. The most common AEs with SR and IR were somnolence and dizziness. Incidences of somnolence were: 7.1% to 11.6% (quetiapine SR), 7.3% (IR) and 1.7% (placebo); and dizziness: 5.3% to 8.8%, 5.7% and 0.8%, respectively. Four patients discontinued due to AEs in the first week (two with SR [400 and 600 mg]; two with IR). Incidence of EPS-related AEs was similar to placebo. Conclusions: Once-daily quetiapine SR (400 to 800 mg) was effective in patients with acute schizophrenia compared with placebo. Rapid dose escalation of quetiapine SR (300 mg Day 1, 600 mg Day 2, 800 mg Day 3) was well tolerated, with a therapeutically effective dose reached by Day 2.

	LS mean change from baseline (95% CI) in PANSS total score at Day 42				
Treatment (n)	Placebo 115	SR 400 mg 111	SR 600 mg 111	SR 800 mg 117	IR 400 mg 119
LOCF	-18.8 (-23.6, -13.9)	-24.8 (-29.8, -19.9)	-30.9 (-35.8, -26.0)	-31.3 (-36.1, -26.4)	-26.6 (-31.4, -21.7)
p value vs placebo		0.030	<0.001	<0.001	0.004

THE ISCDD SCHIZOPHRENIA INITIATIVE: A COLLABORATIVE AND DATA DRIVEN INITIATIVE FOR NEW SCALE DEVELOPMENT

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The field of schizophrenia assessment is currently focusing on specific areas such as cognition, negative symptoms and social functioning. It is important to re-examine instruments currently used to measure psychopathology generally to insure that the most reliable and sensitive scales are used.. The development of a new data-driven, reliable, valid and easily administered instrument would be valuable in the assessment of schizophrenia and evaluation of new medications. The International Society for CNS Drug Development (ISCDD) is a forum for improvement of methodology in CNS research. Building on previous programs in scale development in depression, the ISCDD launched an initiative to address scale development in schizophrenia. A steering committee was formed including members form both academia and the pharmaceutical industry. The steering committee agreed that the process should be data-driven, collaborative with a resulting instrument freely available to researchers and clinicians.The overall goal of this initiative is to develop a scale for general psychopathology to reflect current diagnostic criteria and conceptualizations of schizophrenia,to be used in drug development and to complement more specific measures under development for cognition and negative symptoms. As a first step in this process a Workgroup will identify symptoms clusters and dimensions believed to be important to the measurement of schizophrenia. The workgroup is currently analyzing data sets from clinical trials

conducted by pharmaceutical companies and research centers by using Item Response Theory (IRT) to evaluate the psychometrics properties of current instruments (e.g. PANSS and BPRS). IRT has been demonstrated to be a powerful method to evaluate the performance of individual items of rating scales by assessing the relationship between item scores and the overall disease severity. In addition, domains, symptom clusters and dimensions believed to be important to the disease are identified based on input from a variety of sources such as clinical experts, patients and regulatory agencies. Subsequent steps in scale development involve creation of new items to assess specific symptoms within each cluster, if needed, drawing upon expertise of international schizophrenia researchers and assessing the reliability and validity of the new items in a clinical population of patients with schizophrenia. This collaborative effort welcomes input from schizophrenia researchers.

ASSESSMENT OF AKATHISIA IN ACUTE SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER PATIENTS: RESULTS FROM A POOLED ANALYSIS OF 5 SHORT-TERM, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDIES WITH ARIPIPRAZOLE

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Although akathisia is usually associated with first generation antipsychotics (FGAs), it remains a challenge in routine psychiatric practice, despite the widespread use of second generation antipsychotics (SGAs). Recently reported prevalence rates cites 11.5% of akathisia in a sample of psychiatric inpatients and 15% in outpatient schizophrenia patients. A post hoc analysis of the aripiprazole (Ari) safety dataset was performed to quantify and qualify clinical characteristics of akathisia in five 4- or 6-week, double-blind, randomized trials. In these trials, schizophrenia or schizoaffective disorder patients experiencing an acute relapse were randomized to receive Ari (2, 5, 10, 15, 20, 30mg/day) or placebo (Pbo). The following akathisia parameters were assessed: incidence, time to onset, duration and severity of symptoms, concomitant use of benzodiazepine (BZD), and scores on the Barnes Akathisia Rating Scale (BARS). This analysis showed that the incidence of akathisia was 9% in the Ari group and 6% in the Pbo group. More patients receiving Ari reported this adverse event (AE) within the first 2 weeks of the trials when compared to Pbo. In both groups, the mean and median duration of akathisia was generally low. Of interest, the severity of akathisia was similar among patients receiving Ari and Pbo, with the majority of patients reporting this AE as mild or moderate (Ari: 91%; Pbo: 93%). Mean changes from baseline to endpoint in the BARS scores were not statistically different between Ari versus Pbo groups. When the same analyses were performed excluding the two lower doses of aripiprazole (2 and 5 mg), no differences were found in the variables analyzed. Extrapyramidal symptoms, including akathisia, are more commonly associated with the use of FGAs. However, they may also be reported by patients using SGAs but in lower rates. In this analysis, in the aripiprazole and placebo groups, akathisia appeared to occur early in treatment, be time-limited, and associated with high rates of concomitant benzodiazepine usage. Additionally, most cases of akathisia were reported as mild to moderate and rarely associated with treatment discontinuation.

	Aripiprazole n=1170	Placebo n=465
% of patients reporting akathisia in first 2 weeks	83	69
Mean/Median duration of akathisia	12.5/5.0	4.2/1.5
Discontinuation rates due to akathisia	0.3	0
Benzodiazepine use among patients reporting akathisia (% of patients)	95	86
% of patients with BARS Global Assessment Item ≥ 2 at endpoint	16	14

ADJUNCTIVE GALANTAMINE'S EFFECT ON SCHIZOPHRENIC SYMPTOMATOLOGY: A CASE REPORT

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Galantamine enhances the availability of cholinergic neurotransmitters by acting as both an acetylcholinesterase inhibitor and an allosterically potentiating ligand that is postulated to modulate nicotinic receptors. We report the clinical findings from one individual enrolled in an open-label trial of adjunctive galantamine to improve functional impairments in outpatients with schizophrenia over nine months of treatment. The subject of this case report is a female patient, age 32, with paranoid schizophrenia. At baseline, she was stable on antipsychotic medication, but her treatment-refractory symptoms included infrequent auditory and visual hallucinations, paranoid ideation, mild depression, moderate anxiety, affective flattening, amotivation, and limited social interaction. Adjunctive galantamine was initiated at 4 mg b.i.d., raised to 8 mg b.i.d. after four weeks and raised to 12 mg b.i.d. after eight weeks. The subject reported an almost immediate response to treatment, including a decrease in mood symptoms, an increase in motivation, an increase in social activity, and improved interpersonal relations. She also reported improvements in attention and concentration. As per the subject, all of these improvements progressed over the first eight weeks of treatment. Her reports were confirmed by a 43% decrease in total score on the Scale for Assessment of Negative Symptoms (SANS) from baseline (total raw score = 45) to Study Week 12 (total raw score = 26). However, after approximately five weeks on the 12 mg b.i.d. dose, the subject experienced an acute exacerbation in symptoms, including increased auditory hallucinations, heightened anxiety, and insomnia. After 16 weeks of study participation, she self-discontinued galantamine in reaction to ongoing exacerbated symptoms. Two weeks after discontinuing galantamine, the subject's symptomatology and functioning had returned to baseline levels. Based upon these observations, in this female subject, galantamine, given at lower doses, may have decreased the negative symptoms and self-reported cognitive problems associated with schizophrenia, but at a higher dose may have exacerbated symptomatology.

EFFICACY AND SAFETY OF ARIPIPRAZOLE A 12 WEEKS, MULTI-CENTER, OPEN-LABEL SWITCHING TO ARIPIPRAZOLE STUDY IN STABLE OUTPATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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To evaluate the efficacy, safety and tolerance of a 12 weeks aripiprazole administration to patients with schizophrenia or schizoaffective disorder and to determine whether the patients can be successfully switched from existing antipsychotics to aripiprazole without serious concerns about symptom exacerbations. Subjects aged 18 – 65 years who required long-term antipsychotic therapy and who have been symptomatically stable on a stable dose of antipsychotics during the last month were enrolled in this study. CGI, PANSS,GAF, Investigator's Assessment questionnaire(IAQ) and Udvalg for Kliniske UndersÌgelser side effect rating scale (UKU) were measured for evaluation of efficacy and safety of aripiprazole and non-aripiprazole group at 1, 2, 4, 8, and 12 weeks. A total of 270 patients were enrolled and randomly assigned to receive aripiprazole (N=226) or non-aripiprazole (N=44) for switching from previous oral antipsychotics. Drop out rates were 32.7% (74/226) in aripiprazole group and 22.7% (10/44) in non-aripiprazole group at endpoint. CGI-I score at end point showed that aripiprazole was effective in maintaining stable state. Aripiprazole improved all symptom measures including PANSS total, positive, negative, general subscale, and CGI scores, compared with baseline. The proportion of symptom improvement at endpoint was 31.1% in aripiprazole group where symptom imrpovement was defined as ≥20% decrease in PANSS total score. At baseline, 43.9% (N=90) of patients met remission criteria. Of these remitted patients at baseline, 84.4% (LOCF, N=76) maintained remission state at study endpoint. Of non-remitted patients (N=115, 56.1%) at baseline, 35.7% (LOCF, N=41) achieved remission at endpoint. Both IAQ and UKU scores showed that switching to aripiprazole was associated with significantly fewer prolactin related adverse events than switching to non-aripiprazole(p=0.02). The proportion of symptom worsening at endpoint was low (12.4%) and similar to that in non-aripiprazole group(10.7%). There were no significant differences in time to failure to maintain remission, time to drop outs between aripiprazole and non-aripiprazole group. The study results confirmed that most of clinically stable out-patients with schizophrenia were successfully switched from existing antipsychotics to aripiprazole without serious concerns about symptom exacerbation or adverse events during the course of 12 weeks switch.

PREDICTING RESPONSE TO ATYPICAL ANTIPSYCHOTICS BASED ON EARLY RESPONSE IN THE TREATMENT OF SCHIZOPHRENIA

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Our objective was to test whether early onset of response to antipsychotic medications accurately predicts subsequent response in the treatment of patients with schizophrenia. We used data from 5 randomized, double-blind clinical trials comparing olanzapine with other atypical antipsychotic drugs in the treatment of patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder, who were at least moderately ill at baseline (N=1314). Conditional probabilities (sensitivity, specificity, positive and negative predictive values) were used to characterize the likelihood of "ultimate response to treatment" (defined as at least 20% improvement from baseline on the PANSS total score during treatment for up to 3 months [endpoint of this analysis]), based on achieving at least 20% improvement on the PANSS total score at 2 weeks. In addition, Receiver Operating Characteristic (ROC) curve was generated to predict ultimate response by the magnitude of improvement in PANSS total at 2 weeks. Using the conditional probabilities approach, 90% of non-responders at endpoint were correctly identified as non-responders at 2 weeks (high specificity). However, only 45% of responders at endpoint were correctly identified as responders at the 2-week time-point (moderate sensitivity). The area under the ROC curve (AUC) was 77%, indicating that the magnitude of early symptom improvement at 2 weeks can discern subsequent response at 3 months. Early non-response to antipsychotic medications appears to be a strong predictor of subsequent lack of response in the treatment of patients with schizophrenia. Further research is needed to determine if early non-responders will benefit from a switch to another antipsychotic agent in order to minimize exposure to potentially ineffective or sub-optimal treatment. Funded by Eli Lilly and Company

COMPARISON OF EFFICACY AND SAFETY OF CONTINUING OLANZAPINE TO SWITCHING TO QUETIAPINE IN OVERWEIGHT OR OBESE PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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Time to relapse (primary objective) was compared in patients maintained on olanzapine (OLZ) drug therapy to those switched to quetiapine (QUE). Secondary objectives included treatment effects on metabolic parameters, discontinuation rates, symptomatology, functioning and safety. Patients with schizophrenia or schizoaffective disorder who were psychiatrically stable on OLZ treatment and obese or overweight with metabolic disorders were randomized to continue OLZ treatment (n=68; 7.5-20 mg/day) or switch to QUE drug therapy (n=65; 300-800 mg/day) for 6 months. Relapse was defined as the occurrence of at least 1 out of 3 conditions: 1) hospitalization for psychiatric reasons, 2) 20% worsening on the Positive and Negative Syndrome Scale (PANSS) Total score and an increase in level of care for psychiatric reason, or 3) 20% worsening on the PANSS Total score and worsening of CGI-S by at least one level (CGI score ≥4). Additional psychometric scales and a standard panel of laboratory tests were performed. Due to poor enrollment, the study was terminated prior to breaking the blind when about 33% of the intended sample size was achieved. No significant difference in time to relapse was observed between OLZ and QUE treatment groups (log-rank test, p=.293). Significantly more patients remained on treatment in the group continued on OLZ treatment (70.6%) compared to the group who switched to QUE treatment (43.1%) (Fisher's exact test; p=.002). OLZ-treated patients had significantly lower rates of study discontinuation for lack of efficacy and occurrence of psychiatric adverse events (OLZ: 2.9%; QUE: 15.4%; p=.015) and for "all other reasons" capturing patient and clinician decisions, protocol violations and lost to follow-up (OLZ: 14.7%; QUE: 33.8%; p=.014), but not for non-psychiatric adverse events (OLZ: 11.8%; QUE: 7.7%; p=.562).

Switching from olanzapine drug therapy to quetiapine did not improve weight, body mass index (BMI), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, fasting glucose, or hemoglobin A1c. However, statistical comparisons were significantly underpowered due to limited patient enrollment. For patients with schizophrenia or schizoaffective disorder who are psychiatrically stable on OLZ drug therapy but overweight or obese and with metabolic disorders, switching to QUE led to earlier and more frequent discontinuations from the study. Funded by Eli Lilly and Company

DELAYING SYMPTOM RECURRENCE IN PATIENTS WITH SCHIZOPHRENIA WITH PALIPERIDONE EXTENDED-RELEASE TABLETS: AN INTERNATIONAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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The objectives of this study were to evaluate the efficacy of paliperidone extended-release tablets (paliperidone ER) in delaying recurrence of symptoms of schizophrenia, and to assess the safety and tolerability of this investigational psychotropic agent. Patients with acute schizophrenia (n=530; age 17—64 years; PANSS total score=70—132) entered 8-week run-in (RI) phase, receiving open-label (OL), flexible paliperidone ER doses (3mg—15mg once daily; starting dose 9mg). Patients achieving protocol-specified symptomatic control during the last 2 weeks of RI phase entered the 6-week OL stabilization (ST) phase (n=312). Patients who remained stable during the ST phase entered the double-blind (DB) phase (n=207). The primary efficacy variable was time to first recurrence event in DB phase. Secondary efficacy measures included change in PANSS total score. Safety assessments included treatment-emergent AEs (TEAEs). The study population=68% male, 53% white, mean age=37.9±10.5y. Baseline mean±SD PANSS total score=92.1±11.5. The study terminated at the preplanned interim analysis (time of 43rd recurrence event; recommendation of the Independent Data Monitoring Committee based on efficacy data). At study termination, final analysis showed mean±SD exposure to paliperidone ER=74.1±78.1 days vs 56.1±66.3 days with placebo in the DB phase. Mean modal dose during DB=10.8mg. In the ITT set (DB phase, n=205), 52% on placebo experienced recurrence events vs 22% on paliperidone ER ($p<0.001$, based on the log rank test). The time point at which 25% of patients experienced a recurrence event was 23 days with placebo vs 68 days with paliperidone ER ($p<0.001$). Patients in the placebo group (15.1±19.1) deteriorated significantly more (mean endpoint change in PANSS total score, DB phase) than those in the paliperidone ER group (6.0±13.6; $p<0.001$). TEAEs were reported in 73% patients receiving paliperidone ER in the RI/ST phases. In the DB phase TEAEs were reported in 40% and 35% of patients in the placebo and paliperidone ER groups, respectively. EPS-related AEs in the DB phase occurred in 7% of patients (paliperidone ER) vs 3% (placebo). In summary, paliperidone ER treatment was effective in delaying symptom recurrence in patients with schizophrenia and consistent with earlier short-term data, it was well tolerated in this longer-term study. Supported from funding from Johnson & Johnson Pharmaceutical Services, LLC and Johnson & Johnson Pharmaceutical Research and Development.

FACTORS ASSOCIATED WITH IMPROVED PSYCHOSOCIAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Factors can be identified that are associated with improved psychosocial functioning in stable patients with schizophrenia or schizoaffective disorder receiving risperidone long-acting injectable (RLAI). This post-hoc analysis evaluated data from an international, randomized, double-blind, 1-year study of RLAI 25 or 50 mg every 2 weeks. Regression models were used to identify factors associated with improved psychosocial functioning. Dependent variables were endpoint change scores on the Personal and Social Performance (PSP) and Levels of Functioning (LOF) scales. Independent variables were age, sex, continent, prior antipsychotic dose, RLAI dose, duration of illness, duration in study, Positive and Negative Syndrome Scale (PANSS) insight item (G12), and PANSS negative symptoms factor. Mean (±SD) PSP total score improved from 62.1(14.2) to 64.1(14.0) at endpoint ($P = 0.003$). Multiple linear regression models found significant factors associated with change in PSP as: days in study (estimate = 0.03; $P<0.001$), change in PANSS insight score (estimate = −1.73; $P<0.01$), and change in PANSS negative factor score (estimate = −0.72; $P<0.001$). Factors associated with change in LOF were: days in study (estimate = 0.005; $P<0.05$) and change in PANSS negative factor score (estimate = −0.23; $P<0.0001$). A multivariate regression model using both LOF and PSP change scores as dependent variables identified change in insight ($P<0.01$), duration in study ($P<0.001$), and change in PANSS negative factor score ($P<0.0001$) as significant factors. These data show that distinct factors may be associated with improved psychosocial functioning in stable patients with schizophrenia or schizoaffective disorder receiving RLAI. Source of Funding: Janssen, L.P.

THE ESTROGEN 100

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Estrogen has been shown in animal studies to have dopamine down-regulation effects and has also been shown to impact the serotonergic system. Additionally, there are clinical case reports of women whose schizophrenic symptomatology is exacerbated at low estrogen phases of the menstrual cycle. Similarly, there are clinical case reports of women with chronic schizophrenia improving during pregnancy when estrogen levels are extremely high. The aim of the current study was to compare the efficacy of adjunctive transdermal estradiol with adjunctive placebo in the treatment of acute psychotic symptoms in 100 women with schizophrenia. A double-blind 28-day placebo controlled adjunctive study was conducted comprising two groups of women of child-bearing age. While one group of women received 100mcg transdermal estradiol the other group received transdermal placebo. The differences in psychopathology between the two groups were subsequently compared. Hormone, psychopathology and cognitive assessments (measuring attention, verbal fluency, memory and executive function) were performed routinely throughout the four week trial period. PANSS rating scale scores indicated that women receiving 100mcg estradiol improved significantly more in terms of their

psychotic symptoms compared to women receiving placebo. Importantly women who received estradiol improved with regard to positive, negative and general symptoms on the PANSS, in contrast to women on the placebo arm. Results also indicated no significant changes in cognition following four weeks of adjunctive estrogen treatment. In conclusion, estradiol appears to be a useful treatment for women with schizophrenia. We are furthering this exciting area of research by conducting a multisite 'proof-of-concept' study to determine whether estradiol can be used as an adjunctive treatment of psychotic symptoms in women with schizophrenia. This research was supported by The Stanley Medical Research Institute, The National Alliance for Research into Schizophrenia and Depression, and The National Health and Medical Research Council of Australia.

METABOLIC EFFECTS OF ARIPIPRAZOLE VERSUS OLANZAPINE, QUETIAPINE, OR RISPERIDONE (THE STAR TRIAL)

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Certain atypical antipsychotics are associated with increased risk of diabetes and cardiovascular disease. The present subanalysis directly compares metabolic parameters of aripiprazole with the atypical antipsychotics used in the STAR trial (Kerwin 2006;APA). Patients were equally randomized to open-label treatment of aripiprazole (10-30 mg/day) or Standard-of-Care (SOC) (olanzapine 5 - 20 mg/day, quetiapine 100 - 800 mg/day or risperidone 2 - 8 mg/day, up to 16 mg/day). Investigators selected the SOC agent most appropriate for the patient. Changes from baseline in body weight and levels (mg/dL) of fasting total, high-density lipoprotein (HDL), low density lipoprotein (LDL) cholesterol, triglycerides (TGs), and glucose were computed at 26 weeks (LOCF). Each of the 3 SOC drugs was compared against aripiprazole using ANCOVA after correcting for covariates potentially related to selection and outcome (gender, age, baseline body mass index, schizophrenia type, duration of illness, primary reason for switch, completion or discontinuation reasons, country, and baseline value). A significant gain in body weight at week 26 relative to aripiprazole was observed for olanzapine (+4.6 kg, N=73, p<.001), quetiapine (+1.2 kg, N=108, p=.034) and risperidone (+2.11 kg, N=77, p=.001). For fasting lipid levels, olanzapine patients (N=37) showed significant increases in total cholesterol (+22.4, p<.001), LDL (+11.8, p=.026), and TGs (+66.9, p=.001); quetiapine patients (N=51) showed numerically increased lipid levels (+8.1 total cholesterol, +3.8 LDL, and +21.4 TGs), and risperidone patients (N=41) had slightly increased levels (+0.32 total cholesterol, -0.20 LDL, and +6.2 TGs) relative to aripiprazole. HDL levels were significantly decreased for olanzapine (-3.7, p=.012), and somewhat decreased for quetiapine (-1.3) and risperidone (-2.3) relative to aripiprazole. No significant differences in fasting glucose levels were observed. Olanzapine, quetiapine, and risperidone treatment produced significant weight gain relative to aripiprazole. Olanzapine patients also experienced significant worsening of lipid parameters; quetiapine patients showed a consistent trend toward worsening lipid parameters and risperidone patients showed some worsening relative to aripiprazole patients. The stable or possibly improved metabolic profile of patients treated with aripiprazole may correspond to clinically relevant reductions in subsequent diabetes and cardiovascular risk.

PREDICTING REMISSION AND RECOVERY IN 583 DRUG-NAïVE PATIENTS WITH SCHIZOPHRENIA

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Objective: With respect to the open discussion on remission and recovery in schizophrenia and the lack of empirical data, the aims of this post-hoc analysis of the European Schizophrenia Outpatient Health Outcomes study (SOHO) were to assess remission, recovery, and respective predictors in a cohort of patients with schizophrenia followed over 36 months. Method: Data were collected in an observational 3-year study of 538 drug-naïve subjects with schizophrenia. Both, remission (at least 6-month) and recovery (at least 24-month) required concurrent achievement of symptomatic and functional remission as well as adequate subjective wellbeing. The relationships between baseline and treatment characteristics and remission or recovery were analyzed using a stepwise logistic regression model. Results: At 3-year follow-up, 6-month remission rates for symptoms, functioning, and subjective wellbeing were 58%, 43%, and 53%; respective 24-month recovery rates were 39%, 35%, and 40%. At endpoint, 26% were in combined remission and 16% in recovery. The interrelation between outcome domains was low. In the logistic regression models, combined remission and composite recovery were best predicted by the functional status at baseline and by the early remission of single outcome domains, especially by the early change of subjectively assessed wellbeing. Conclusions: Despite advances in treatments of schizophrenia, the proportion of patients who met composite remission or recovery criteria is low. The finding that the 3-year outcome mainly depends on the early course of treatment, points toward a critical 'window of opportunity' and the need of treatment adaptations in case of early non-remission.

GROUP COGNITIVE BEHAVIORAL THERAPY FOR PARANOIA

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Background: Studies have shown that patients' reasoning styles as well as cognitive biases underlie the formation and maintenance of paranoid beliefs. We developed the Group Cognitive Behavioral Therapy (GCBT) intervention to address specific for paranoid delusions cognitive biases and to teach patients new, more adaptive ways of processing information, and performed an initial assessment of this method. Methods: GCBT of patients with paranoid delusions was conducted. Five patients with Schizophrenia and Schizoaffective disorder (as defined by DSM-IV) participated in the study. Outcome measures included PSYRATS and CDRS. 2-tailed t tests were used to compare pre, post, and one year follow up measurements. Patients were also assessed to identify specific reasoning biases. Group interventions (18 sessions) were focused on: (1) Increasing patients' cognitive flexibility and changing maladaptive methods of forming judgments by learning and utilizing meta-cognitive processes needed for making more accurate judgments; (2) Learning to identify and correct cognitive biases; and (3) Using learned methods of reasoning to analyze and replace patients' delusional beliefs with more adaptive ones. While the focus of therapeutic intervention was on helping patients learn and

apply cognitive operations, principles of cognitive therapy were applied to create supportive, collaborative and empowering relationships among group members. Results: After the GCBT treatment and in one year follow up there was a statistically significant reduction in delusional conviction, and an increase in ability to dismiss a delusional thought ($p<0.05$). The majority of patients became aware of their maladaptive cognitive processes and biases, and began to use cognitive procedures they did not use earlier. The one year follow up assessment showed that patients continued using cognitive procedures they learned in treatment, as well as they began using these cognitive procedures in a different context. Conclusions: These initial results suggest that paranoid patients can benefit from discussing their delusional beliefs, learning cognitive operations needed for making more accurate judgments, and applying these skills to modify their paranoid delusions in the context of GCBT therapy. Further controlled studies are planned.

A GLUTATHIONE PRECURSOR, N-ACETYL-CYSTEINE,MODULATES MISMATCH NEGATIVITY GENERATION IN SCHIZOPHRENIA PATIENTS

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Schizophrenia patients exhibit deficits in low-level processing, including pitch discrimination. This deficiency manifests in auditory evoked potentials (AEPs) as an impaired mismatch negativity (MMN), an electrophysiological response to infrequent target stimuli interspersed among frequent standard stimuli that typically peaks ~100ms post-stimulus onset. NMDA receptor antagonists have been shown to block MMN generation in both animals and humans, and NMDA dysfunction has been linked to the underlying pathophysiology of schizophrenia. A parallel line of evidence indicates that glutathione (GSH) regulation is perturbed in schizophrenia patients at the gene, protein and functional levels (Tosic et al., 2006). This GSH dysregulation leads to NMDA receptors' hypofunction through interaction with their redox site (Steullet et al., 2006). The present study aimed to modulate GSH levels in schizophrenia patients and assessed the effects of such a modulation on MMN generation mechanisms. N-acetyl-cysteine (NAC), a GSH precursor, was administered to schizophrenia patients, using a double-blind cross-over protocol. One group received NAC (2g/day) for 60 days and then placebo for another 60 days, and vice-versa for the second group. AEPs from patients were recorded at the onset of the protocol, at the point of cross-over, and at the end of the study. Participants were instructed to manually respond to target stimuli (2kHz pure tones occurring 20% of the time among 1kHz pure tones). Analyses of AEPs recorded at protocol onset indicated that patients (n=11) were significantly impaired in generating the MMN relative to age-matched controls (n=11). Specifically, the global field power (GFP), an index of AEP magnitude, was measured over the 70-155ms post-stimulus interval and submitted to an analysis of variance (ANOVA). There was a significant interaction between population and stimulus frequency, indicating impaired MMN generation in patients at protocol onset. Analyses of AEPs recorded during administration of NAC (n=7) versus placebo (n=7) revealed the efficacy of this GSH precursor in modulating MMN generation mechanisms. ANOVA of GFP over the 70-155ms post-stimulus interval, using stimulus frequency and treatment as within-participants variables, revealed a significant interaction and indicated that NAC can ameliorate MMN generation. We discuss these results in terms of potential therapeutic strategies for schizophrenia.

EFFECTIVENESS OF GROUP COGNITIVE-BEHAVIOUR THERAPY FOR FIRST EPISODE PSYCHOSIS – RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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Introduction: Contemporary studies suggest that treatments offered early to people presenting a first psychotic episode could improve prognosis. Of the different treatments, recent studies have demonstrated the efficacy of cognitive-behavioral therapy (CBT) in diminishing symptoms and in increasing indices of well-being in people with psychosis. This study aimed at verifying if a group CBT approach would be effective for first episodes in reducing their symptoms, and improving other indices of well-being following treatment and at 6 months post-treatment, compared to a wait-list control group. We also wished to determine if group CBT would be superior to skills training in symptom reduction, and in improving other indices of well-being. Methods: 129 first episodes were randomized to: 1) a group CBT treatment, 2) a group Skills Training focusing on symptom management, or 3) a wait-list control group. Both treatments were delivered twice a week for 24 sessions by mental health staff, following a brief training. Subjects answered measures at baseline, 3 months, and 9 months. Interviewers were blind to treatment allocation. Results: Differences between baseline and 3 months, as well as baseline and 9 months were entered in ANCOVAs, including cohort, medication changes and number of sessions as covariates. Effects were not due to cohort nor medication changes for most results, though number of sessions attended was influent in some cases. Both treatments significantly improved over time on the BPRS total score, though only the CBT was significantly different from the control group at follow-up ($F(2,59)=5.38$, $p<.01$). Other significant results were found for positive symptoms, self-esteem, drug abuse, as well as other indices of well-being. Of significance, the CBT group had a 23% drop-out rate whereas the Skills training group had 57% of drop-outs. Discussion: Group CBT for first episodes appears to offer specific advantages over treatment as usual, and over Skills training, mostly at follow-up. Other applications of the CBT group as well as future research questions will be discussed.

AN ACUTE EFFECT OF THETA-NESTED GAMMA FREQUENCY RTMS OVER THE PREFRONTAL CORTEX IN SCHIZOPHRENIA: AN FMRI STUDY OF LETTER FLUENCY

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Decreased prefrontal activity has been associated with a variety of cognitive deficits and negative symptoms in patients with

schizophrenia. We used repetitive transcranial magnetic stimulation (rTMS) at Gamma frequency (50 Hz) nested within theta frequency (5 Hz) (theta burst stimulation, TBS) in an attempt to facilitate prefrontal activity in patients with schizophrenia. Four patients with chronic DSM-IV schizophrenia and predominantly negative symptoms (2 males and 2 females; mean age 42.5 years, SD = 11.7) were scanned, immediately before and after TBS. We applied intermittent TBS (2s stimulation for every 10s) for 190s (600 pulses in total) over the left dorsolateral prefrontal cortex (F3 site according to the international 10-20 EEG system) at an intensity of 80% motor threshold. TBS was performed with a 70mm figure-of-eight coil and a Magstim Super Rapid magnetic stimulator (Magstim Company, Whitland, UK). A standard Letter fluency paradigm was applied during fMRI scanning. Functional imaging datasets were acquired at 3T (Intera 3.0T, Philips Medical Systems) using a single-shot, gradient recalled, SPARSE echo-planar technique (TA=2.2s; TR=6.0s). Resultant data were analyzed using statistical parametric mapping (SPM2, www.fil.ion.ucl.ac.uk). The Letter fluency task pre-TBS and post-TBS resulted in activation in anterior cingulate, medial prefrontal and dorsolateral prefrontal areas, and bilateral inferior frontal gyri. Post- versus pre-TBS Letter fluency scans indicated significantly increased activity in the left dorsolateral prefrontal cortex (BA 9) and bilateral caudate nuclei ($p < .05$, corrected). This preliminary data demonstrates enhanced activation of several cognitively relevant brain areas following the acute administration of theta-nested Gamma frequency rTMS in patients with schizophrenia.

A RANDOMIZED, PLACEBO-CONTROLLED PHASE IIA TRIAL OF SGS518 FOR TREATING COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

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BACKGROUND: Cognitive impairment associated with schizophrenia (CIAS) adversely affects functioning, prompting investigators to consider treatment with a 5HT6 receptor antagonist SGS518, shown safe and effective in pre-clinical animal models. PATIENTS AND METHODS: Twenty patients with stable schizophrenia, including 5 of Caucasian descent, 14 of African-American descent, and 1 of Hispanic descent, were recruited and, after giving informed consent, were in residence for 15 days. Patients were randomized to one of two cohorts of 10 subjects (8 active and 2 placebo per cohort). Group 1 received 60 mg for 7 days followed by 180 mg for 7 days. Group 2 received 120 mg for 7 days followed by 240 mg for 7 days. Endpoints were evaluation of safety, pharmacokinetics and cognition using the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline, day 6 (before escalation), and day 13 (end of treatment). BACS assesses 6 domains of memory, including executive function, a key deficit in schizophrenia. Composite Z scores were calculated as average (unweighted) standardized scores of all function tests. RESULTS: Patients ranged in age from 25 to 54 years, and each group's mean weight ranged from 181.5 to 191.9 pounds. All patients had stable schizophrenia with19 of 20 patients treated with monotherapy (Risperdal, Zyprexa, Abilify, Seroquel). Eighteen of twenty patients completed the 15 day study; one patient withdrew consent at day 7 and another patient at day 10. Ten of the 20 patients reported adverse events (2 in group 1, 4 in the group 2 and all 4 placebo patients). Clinical complaints were infrequent and included dizziness, headache, agitation and dyspepsia.. All adverse events resolved within 24 hours. There were no clinically relevant, vital sign, EEG or ECG findings. Pharmacokinetic analysis showed SGS518 has a t-max of 2-3 hrs. and a t -1/2 of 12-13 hrs. with steady state achieved within 3 days. Baseline BACS testing indicated no significant differences between groups (p=0.1592). A dose-response effect was observed in overall change from baseline: 0.31 (SD, 0.55) (p=0.15) for Group 1 and 0.83 (SD, 0.76) (p=0.03) for Group 2. BACS composite Z scores in the placebo group fell (-0.03 [SD=0.51]; p=0.91), but not significantly. CONCLUSION: SGS518 was very well tolerated and produced a statistically significant change from baseline in BACS scores in patients with stable schizophrenia receiving up to 240 mg/day, warranting further studies.

MODAFINIL AS AN ADJUNCTIVE TO SECOND GENERATION ANTIPSYCHOTIC TO IMPROVE COGNITIVE FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA: A PILOT STUDY

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Schizophrenia is associated with significant cognitive difficulties. Although second generation antipsychotics have a more favorable impact that older agents on cognition, patients still experience deficits on functions spanning attention, memory, verbal fluency or executive functions that interfere with daily functioning and threaten remission. Modafinil is wake-promoting agent approved to treat daytime sleepiness associated to narcolepsy, chronic shift work sleep disorder and is an adjuvant to the standard treatment of sleep apnea/hypopnea syndrome. It possesses promising properties in treatment of attention deficit hyperactivity disorder and depression. In schizophrenia, interesting preliminary data support a possible cognitive enhancer effect. We conducted an open pilot study (N=5) to assess modafinil adjunctive effect to a second generation antipsychotic in patients with schizophrenia. Neurocognitive assessment performed before and during treatment with modafinil included Continuous Performance Test-II, Color Trail Test, Stroop Test, Mesulam & Weintraub Cancellation Test, digit span and verbal fluency tests. Other tolerability and safety evaluations included Positive and Negative Syndrome Scale, Extrapyramidal Syndrome Rating Scale, Clinical Global Impression, Global Assessment Functioning, Schedule for Deficit Syndrome and UKU side effect rating scale. Five men aged between 19 to 26 years old and treated with a second generation antipsychotic were prescribed modafinil (100mg, up to 200mg) (3 patients on clozapine, 1 on quetiapine and 1 on olanzapine). Overall, 4 out of 5 patients experienced positive impact of modafinil while one was deteriorated as objectively measured by neuropsychological battery. Among those four, 3 patients had an improved Global Assessment Functioning Score. Globally, no patient experienced worsening of psychosis or anxiety. All participants were subjectively improved on fatigue impression. Modafinil may be an interesting adjunctive to antipsychotic in patients with schizophrenia experiencing residual impaired cognition. This pilot study led to the development of a placebo-controlled, cross-over prospective study currently going on at our clinical setting and raised great clinical interest since cognition impairment still remains an important target to reach full and complete remission.

ANTIPSYCHOTIC EFFICACY OF POLYPHARMACY VS. MONOTHERAPY IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: A PROSPECTIVE STUDY

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BACKGROUND: Despite extensive research and recommendations regarding the optimal prescription of antipsychotic drugs, polypharmacy and excessive dosing still prevail. The aim of this study is to identify the efficacy between polypharmacy and monotherapy on patients with schizophrenia or schizoaffective disorders. METHOD: This is a 12-week parallel group, controlled, clinical trial of patients who were on two antipsychotics and either remained on two antipsychotics or were switched to one new antipsychotic treatment. Thirty three patients, age 18 - 65 years, diagnosed with DSM-IV criteria of schizophrenia or schizoaffective disorder and currently on two pre-study antipsychotics were enrolled in the study. RESULTS: Eighteen patients were in the monotherapy group and fifteen patients were in the polypharmacy group. No significant differences between groups were observed in change in psychpathology as measured by the PANSS. Change in Simpson Angus Scale from baseline to endpoint indicate that values of the group effect show that there was a 1.09 point difference in score for the polypharmacy group, and the difference between polypharmacy and monotherapy groups was statistically significant ($F(1,29) = 12.646$, $p = .001$). CONCLUSIONS: The results of this study support previous reports of the lack of efficacy of use of combination antipsychotic therapy for psychopathology in clinical practice. Prospective controlled trials are needed to substantiate perceptions that combination antipsychotic therapy is clinically beneficial and to provide guidelines on when and for whom antipsychotic polypharmacy should be considered.

A FIVE YEAR RANDOMIZED CONTROLLED TRIAL OF SPECIALISED CARE AND PARENT GROUPS VS STANDARD CARE FOR FIRST EPISODE PATIENTS

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First episode intervention studies, including family intervention studies in schizophrenia-like disorders have shown initial beneficial effects, followed by a return to a relapsing or chronic course in the early phase of schizophrenia,in which the severity of the disorders is established. - Objective: to evaluate the effectiveness of 5 year specialized interventions, including parent groups for early psychosis in a randomized controlled trial. - Participants: consecutively admitted referred young adult patients (n=188) aged 16-30 years with a first psychotic episode of schizophrenia-like disorders. - Interventions: youth oriented specialized care group (SCG), specialized care plus parent group (SCPG) and standard care (CG). - Primary outcome measure: time to first relapse after remission. - Analysis: in the early phase of the interventions 33 patients changed from the assigned condition mostly for reasons that were not related to treatment. The effect of the three interventions was compared using Cox regression analyzing both intention to treat (ITT) and actual realized treatment grouping (ART). - Results: The relapse rate after 5 years was relatively low (0.48, 95% confidence interval 0.40-0.56). No significant differences between the 3 conditions were found in the ITT analysis. However, compared with the standard care (0.55, 95% CI 0.44-0.67) the ART analysis showed a significant beneficial effect for parental SCPG (0.30, 95% CI 0.18-0.45) but not for SCG intervention (0.53, 95% CI 0.38-0.67), - Discussion: interventions in the early phase of schizophrenia-like disorders were associated with a relatively low relapse rate, suggesting an important role for continuity of care over an extended period. Specialised care with parent groups had a beneficial effect on time to relapse over a 5 year period, underlining the importance of staying connected with the family.

PREDICTORS OF LONG-TERM OUTCOME IN SCHIZOPHRENIA: A DOUBLE-BLIND, 196-WEEK STUDY OF ZIPRASIDONE AND HALOPERIDOL

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Objective: Recently published consensus-based operational criteria for remission in schizophrenia1 provide clinicians with a new, well-defined treatment goal. In a long-term (nearly 4-year) double-blind study comparing ziprasidone and haloperidol, results suggest symptom remission is strongly associated with quality of life using longitudinal analyses.2 The current analysis was conducted to identify predictors of remission in that study. Methods: One hundred and eighty six subjects completed an initial 40-week randomized, double-blind trial and enrolled in a 3-year, double-blind continuation study. We reported predictors evaluated at pre-treatment baseline of the 40-week phase. Primary outcome variable was the likelihood of attaining full remission in the final 6 months of participation in the continuation study. Logistic regression was used to control simultaneously for multiple variables predicting remission, with adjustment for treatment duration. Results: Treatment was a significant predictor of remission (p=0.015). The predictive model found that ziprasidone-treated subjects (N=139) had a 3-fold (adjusted odds ratio [OR] 95% CI 1.1-7.9) increase in the likelihood of remission than the haloperidol-treated subjects (N=47). After controlling for treatment effect, the following factors were significantly associated with sustained remission: better baseline QLS total score ($p<0.001$), Caucasian race (OR 4.5; p=0.006), lower baseline symptom severity (p=0.02), schizoaffective diagnosis (p=0.02), younger age (p=0.038), no prior psychiatric hospitalization (OR 3.3; p=0.046), and no family history of psychiatric illness (OR 2.3; p=0.07). Single (never married) subjects were less likely to attain remission (p=0.035). The predictive validity of these findings was confirmed using the area under the receiver operating characteristic curve (ROC) (AUC 0.85, SE=0.03, 95% CI 0.8-0.9). Conclusions: Consistent with prior reports, these findings suggest that patients with relatively good prognosis may be less chronically ill and have a schizoaffective diagnosis, history of close interpersonal relationship and a favorable global QLS score. Treatment with ziprasidone was a significant predictor for sustained remission. These results suggest the potential for enhanced symptom remission and long-term outcomes among patients treated with a second-generation antipsychotic.

SLEEP ASSESSMENTS IN PATIENTS WITH SCHIZOPHRENIA FOLLOWING TREATMENT WITH PALIPERIDONE EXTENDED-RELEASE TABLETS

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The objective of this analysis was to evaluate the impact of an investigational psychotropic agent, paliperidone extended-release tablet (paliperidone ER), on sleep in patients with schizophrenia in two independent studies. Dataset 1 evaluated sleep architecture changes in patients with schizophrenia-related insomnia. Dataset 2 assessed patient-rated changes in quality of sleep and daytime drowsiness in patients with schizophrenia. Data were collected for Dataset 1 in a multicenter, double-blind, randomized, placebo-controlled study in patients with stable schizophrenia receiving paliperidone ER 9mg or placebo daily for 2 weeks. Polysomnography (PSG) variables were assessed at baseline and end point. Dataset 2 contained pooled data from three 6-week double-blind, controlled studies in patients with acute schizophrenia receiving paliperidone ER 3mg, 6mg, 9mg, 12mg, 15mg, or placebo daily. Subjects completed visual analogue scale (VAS) assessments of sleep quality and daytime drowsiness. Patients in Dataset 1 (n=36) had mean±SD: age=32.2±7.3y and baseline PANSS total score=62.9±11.2. Following treatment with paliperidone ER, statistically significant (10% level) and clinically relevant improvements in sleep parameters were observed at end point (Table). Dataset 2 (ITT: n=1306 [placebo=351, paliperidone ER=955], age (mean±SD)=38.3±10.9y, baseline mean±SD PANSS total score=93.5±11.8) further supported the clinical relevance of these findings. All 5 doses of paliperidone ER had significantly greater improvements in quality of sleep compared with placebo, as rated by VAS assessment ($p<0.05$). No increases in daytime drowsiness versus placebo were observed ($p>0.3$). Paliperidone ER treatment was well tolerated in both Dataset populations. Paliperidone ER treatment had favorable effects on sleep architecture, sleep continuity and patient-rated sleep quality in patients with schizophrenia without producing or worsening daytime drowsiness. Supported from funding from Johnson & Johnson Pharmaceutical Services, LLC and Johnson & Johnson Pharmaceutical Research and Development.

	Placebo (n=19)		Paliperidone ER 9mg (n=17)	
Sleep parameter	Baseline	Change from baseline	Baseline	Change from baseline
Total sleep time (min)	380.9 (45.3)	-24.4 (17.9)	341.9 (77.5)	+28.5 (15.6)
Latency to sleep onset (min)	42.3 (33.6)	+12.8 (8.5)	58.3 (47.8)	-22.5 (12.7)
Latency to persistent sleep (min)	50.3 (34.0)	+14.9 (10.8)	68.0 (55.8)	-26.1 (15.6)
Sleep efficiency index (%)	79.3 (9.4)	-5.0 (3.7)	71.5 (16.2)	+6.0 (3.3)
Stage 2 sleep duration (min)	228.4 (42.1)	-15.3 (11.1)	183.9 (60.2)	+35.4 (14.0)
REM duration (min)	87.0 (24.6)	-10.9 (6.4)	72.7 (31.1)	+7.4 (6.8)

PHARMACOKINETICS OF BIFEPRUNOX

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(a) Assess the human pharmacokinetics (PK) of bifeprunox. (b) The PK of bifeprunox in healthy subjects were investigated based on a pooled analysis of PK parameters from 21 clinical pharmacology studies. Pooled analysis included PK profiles after single and multiple doses to 132 and 399 subjects, respectively, and explored the potential effects of age, gender, body weight and race. In addition, PK in patients (PTS) with schizophrenia were investigated using a population PK approach based on samples from 376 PTS in phase II studies and 434 PTS in phase III studies (c) Bifeprunox was rapidly absorbed after oral administration (tmax from 1.5 to 2 hours at all dose levels). Bifeprunox multiple-dose PK were dose-proportional in the 20–40 mg/day range. Steady-state mean apparent clearance and apparent volume of distribution were 62.2L/h and 1300L, respectively. Bifeprunox was eliminated with a mean plasma steady-state half-life of 14.4 hours. Administration of a 40 mg dose with a standard high-fat meal was associated with slight delay in tmax and small increase in Cmax (10%) and AUC (29%). Bifeprunox is approximately 99% bound to serum proteins. Bifeprunox is metabolized by CYP2C9, CYP3A4 and to a lesser extent, CYP2D6. Bifeprunox exposure was increased by co-administration with fluconazole (CYP2C9 inhibitor) and to a minor extent ketoconazole (CYP3A4 inhibitor), but not by coadministration with paroxetine (CYP2D6 inhibitor). Co-administration with famotidine (an H2-antagonist increasing gastric pH) did not affect the absorption of bifeprunox. Bifeprunox exposure was reduced by co-administration of carbamazepine (CYP3A4 inducer). Co-administration of narrow therapeutic index compounds warfarin and lithium with bifeprunox did not affect the PK of these compounds to any relevant extent. In CYP2C9 slow/intermediate metabolizers, higher plasma levels of bifeprunox were observed than in subjects with normal enzyme activity. After a single oral dose of [14C]-labeled bifeprunox, 13% and 74% of the radioactivity was excreted in the urine and feces, respectively. No clinically significant age-, gender-, body weight- or race-related effects on bifeprunox PK were noted. PK in PTS with schizophrenia were similar to that seen in healthy subjects. (d) Bifeprunox is rapidly absorbed after oral administration; the mean elimination half-life is about 14 hours. Multiple-dose PK were dose-proportional in the 20–40 mg range. Bifeprunox has a low drug interaction potential.

AS REQUIRED MEDICATION VERSUS BEHAVIORAL INTERVENTION IN THE TREATMENT OF AGITATION CAUSED BY SEVERE MENTAL ILLNESS: DATA FROM THE SOUTH LONDON AND MAUDSLEY INTENSIVE CARE UNITS TRIAL EVALUATION (SLAMICUTE) STUDY

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Data to inform the emergency treatment of agitated psychotic patients who cannot give consent is sparse. Here we report preliminary data from an ongoing naturalistic observational study of the management of acute incidents in the setting of 4 UK Psychiatric Intensive Care Units, (PICUs). Our aim is to inform best practice and guide future controlled studies. Over 12 months data were collected on every incident requiring an intervention that

occurred on 4 PICUs based within the South London and Maudsley NHS Trust. This included information on incident and intervention type as well as the outcome rated using the PANSS-EC. Interventions include oral or intramuscular as required medications, (PRN), and behavioral interventions, (BEH), including Time out, De-escalation, and Special observation/Seclusion. These were carried out as per Trust procedures and clinical need. The study received local ethical approval. Here we describe the types of incidents and interventions. 308 patients (80% males, 20% females, mean age 33±12) were admitted consecutively. 23.7% of patients were not involved in an incident. The remaining 235 patients were responsible for 638 individual incidents. 39.15% of these patients were responsible for 1 incident; 21.7% had 2 and 15.74% had 3 incidents. The most frequent incident was Threat of Violence, (28.66%); Act of violence alone accounted for 11.44% of incidents; Threat of Violence and Act of Violence, were 23.35%; and Increased agitation/anxiety/tension, alone for 18.55%. The most common interventions were PRN +BEH (294 interventions, (46%), BEH only, (189, 30%) and PRN only, (102, 16%). (Please see table) Although this preliminary report does not allow a full statistical analysis, despite what might be predicted, numerically in the Act of Violence and Threat of Violence groups the rates of PRN+ BEH intervention and BEH intervention are similar. An Act of Violence plus a Threat of Violence, however, appears to increase the likelihood of receiving PRN + BEH. This finding may reflect current practice and as such has implications for clinical trial design and the treatment of agitated patients.

Frequency of interventions by incident type

Incident	PRN	PRN+BEH	BEH
Threat of Violence Only	24 (13%)	70 (38%)	73 (40%)
Threat of Violence + Act of Violence	14 (9%)	95 (64%)	28 (19%)
Act of Violence Only	9 (12%)	30 (41%)	32 (44%)
Increased agitation/anxiety/tension	37 (31%)	31 (26%)	41 (34%)

A LARGE, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY OF THE EFFECTS OF ARIPIPRAZOLE IN OVERWEIGHT PATIENTS WITH SCHIZOPHRENIA/SCHIZOAFFECTIVE DISORDER SWITCHED FROM OLANZAPINE

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Purpose: Due to close associations between obesity, diabetes and dyslipidemia and cardiovascular disease (CVD), there is heightened interest in the relationship between atypical antipsychotics and development of such CVD risk factors. This ongoing, 16-week, multicenter, randomized, double-blind study aims to compare the metabolic effects of aripiprazole and olanzapine in overweight patients with schizophrenia/schizoaffective disorder. Methods: To be eligible, male and female patients aged 18-65 years must have received olanzapine monotherapy 10-20 mg/day for 1-24 months immediately prior to screening, have a body mass index ≥27 kg/m^2 and Clinical Global Impressions (CGI) - Severity of Illness scores ≤4. Weight gain during prior olanzapine therapy will be verified in the patient history. Patients will continue to receive their prior olanzapine therapy for 2 weeks, then be reassessed for eligibility, weight and psychiatric stability (baseline). Eligible patients will be randomized to continue olanzapine or switch to aripiprazole. Aripiprazole will be dosed as follows: titrated to 15 mg/day over 2 weeks (with down-titration of olanzapine); fixed at 15 mg/day for 4 weeks; flexibly-dosed 10-30 mg/day to Week 16. Olanzapine will be continued at the prior dose for 4 weeks after a mock titration, then flexibly-dosed 10-20 mg/day to Week 16. Up/down-titration of medication will be allowed at 5 mg every 7 days. Patients will be assessed every 2 weeks. Results: In total, 83 patients/group are planned to be randomized, anticipating that ~7% will not be evaluable for the primary objective—weight change from baseline to Week 16 assessed by longitudinal repeated measures analysis (LRMA). The secondary outcome measure is the relative baseline to Week 16 change in fasting triglycerides via LRMA. Other measures include: change in fasting plasma glucose, insulin, c-peptide; oral glucose tolerance test; and relative change from baseline in fasting lipids. Efficacy will be assessed via CGI scales. Safety assessments will include: adverse events, vital signs, electrocardiograms, laboratory tests, physical examinations, extrapyramidal syndrome-related side effects, change in safety rating scale scores, use of anticholinergic medication and waist circumference. Conclusion: This study will provide data from a large, randomized, prospective comparison of aripiprazole vs. olanzapine in overweight olanzapine pre-treated patients with schizophrenia/schizoaffective disorder.

TWO YEAR OUTCOMES ON RISPERIDONE AND OLANZAPINE IN STABLE PATIENTS WITH SCHIZOPHRENIA

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Background: The goals of long-term treatment for schizophrenia include preventing psychotic relapse and improving physical health and functional outcomes. We characterized these outcomes in patients who were randomly assigned to double-blind risperidone or olanzapine. Methods: : One hundred seven stable outpatients with schizophrenia or schizoaffective disorder were randomly assigned to receive double-blind olanzapine vs risperidone, and supported employment with and without a skills training module. (This report will focus on the drug conditions.) Using a double dummy design, clinicians were instructed to target doses of 4 mg of risperidone and 15 mg of olanzapine. (At one year the mean risperidone dose was 6.3 (sd,3.1) mg/day and mean olanzapine dose was 17.1 (sd, 5.8) mg/day.) Patients were followed prospectively for 24 months or until they discontinued their medication for lack of efficacy or adverse effects. Regular evaluations included measures of psychopathology, quality of life, and metabolic factors (body mass index, lipids, glucose, and glycosolated hemoglobin. In contrast to other studies, early evidence of weight gain, glucose or lipid elevations was considered an event leading to drug discontinuation. Results: Product limit survival estimates for all cause discontinuation was 54% vs. 47% at 12 months, and 37% vs. 33% at 24 months for olanzapine vs. risperidone respectively (p=ns). There were no significant differences in psychopathology ratings between the two drugs. We found a time by drug interaction indicating less weight gain on risperidone (p=0.04). However, weight gain on olanzapine in patients who remained in their drug condition was only about 1 kg for 24 months. We did not find significant medication effects on lipids or glycemic control. Entering the study on a first-generation antipsychotic or risperidone, or randomization to change medication to olanzapine, was associat-

ed with a significant increase in BMI. Discussion: The findings indicate that olanzapine and risperidone demonstrated similar effectiveness in stabilized outpatients with schizophrenia. Our finding of relatively less weight gain and metabolic derangement than that reported in CATIE may reflect the impact of intervening before patients demonstrated serious metabolic disturbances.

COGNITIVE-BEHAVIORAL THERAPY FOR PSYCHOSIS: A NATURALISTIC CLINICAL TRIAL IN A FRENCH-QUEBEC POPULATION

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Previous studies have indicated that 25% to 50% of patients with psychotic disorders experience persistent positive psychotic symptoms, despite recent advances in pharmaceutical treatments. Reviews of CBT for psychosis have demonstrated efficacy in reducing positve symptoms and that these gains are maintained over time. This poster will review a pilot study which applied a manualised CBT model for first episode psychosis (FEP) developed at ORYGEN Youth Health (Australia) in a French-Quebec population (Canada). The sample consisted of 20 FEP patients between the ages of 14 to 35. This study was unique in that it was the first to utilise individual CBT for FEP in Quebec and the first study of CBT for FEP to introduce CBT in a stabilised phase of illness, as well as to include patients below the age of 16. This poster will examine the acceptance and compliance of treatment, as well as the patterns of psychotic symptoms and other psychpathology at the end of treatment and 6 months follow up. Predictors of evolution of the participants will also be exposed.

SEXUAL DYSFUNCTION DURING LONG-TERM ANTIPSYCHOTIC TREATMENT OF PATIENTS WITH SCHIZOPHRENIA: 3 YEAR RESULTS FROM THE INTERCONTINENTAL SCHIZOPHRENIA OUTPATIENT HEALTH OUTCOMES (IC-SOHO) STUDY

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Sexual dysfunction in patients with schizophrenia can reduce quality of life and treatment compliance. The presence and emergence of sexual dysfunction are reported for a large, international population of outpatients with schizophrenia who received long-term, antipsychotic monotherapy. Outpatients ≥18 years with schizophrenia (DSM-IV or ICD-10), who initiated or changed antipsychotic treatment entered this 3-year, prospective, observational study (F1D-SN-HGJR). Patients who remained on a monotherapy of olanzapine (n=2641), risperidone (n=863), quetiapine (n=142), or haloperidol (n=189) for at least 3 months were included in the analyses for as long as they maintained their initial treatment. Clinicians determined the presence and severity of symptoms. For patients without sexual dysfunction at baseline, symptoms at any subsequent visit were considered treatment emergent. Differences were evident between treatment groups in the presence and emergence of symptoms related to sexual function (Table 1). When compared to patients treated with quetiapine or olanzapine, a higher proportion of haloperidol and risperidone recipients had symptoms of sexual dysfunction at 3 years, and the emergence of symptoms over the treatment period was more frequent. This large, prospective, naturalistic study provides insight into the presence and emergence of sexual dysfunction in patients who received antipsychotic monotherapy over 3 years. Divergence in the sexual adverse event profiles were highlighted for selected atypical and typical antipsychotic agents. These data will be further evaluated through longitudinal statistical analyses. This study was funded by Eli Lilly and Company.

Table 1: Presence and emergence of sexual dysfunction symptoms.

Adverse event	Present at 36 months % [a]	Emergent during 36 months % [a]
Loss of libido[b] Olanzapine Risperidone Quetiapine Haloperidol	20.8 29.8 19.6 36.8	41.5 64.5 59.3 65.8
Impotence/Sexual dysfunction [b] Olanzapine Risperidone Quetiapine Haloperidol	14.5 20.8 13.6 22.6	27.8 52.9 47.8 58.8
Amenorrhea/Menstrual disturbances [b,c] Olanzapine Risperidone Quetiapine Haloperidol	10.7 25.5 7.4 38.5	30.6 55.3 31.6 66.7

[a] Percentages based on patients with available treatment and sexual dysfunction data.

[b] Includes only patients without symptoms at enrollment, and with available treatment and sexual dysfunction data (Loss of libido, n=958; Impotence/Sexual dysfunction, n=893; Amenorrhea/Menstrual disturbances, n=484).

[c] Recorded only for female patients aged ≤ 55.

MOTOR FUNCTION IMPAIRMENT DURING LONG-TERM ANTIPSYCHOTIC TREATMENT OF PATIENTS WITH SCHIZOPHRENIA: 3 YEAR RESULTS FROM THE INTERCONTINENTAL SCHIZOPHRENIA OUTPATIENT HEALTH OUTCOMES (IC-SOHO) STUDY

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When compared to conventional antipsychotics, lower rates of treatment-emergent tardive dyskinesia (TD) and extrapyramidal symptoms (EPS) have been reported in patients treated with atypical agents.[1] Presence and emergence of TD and EPS are presented for a large, international population of outpatients with schizophrenia who received long-term, antipsychotic monotherapy. Outpatients ≥18 years with schizophrenia (DSM-IV or ICD-10) who initiated or changed antipsychotic treatment entered this 3-year, prospective, observational study (F1D-SN-HGJR). Patients who remained on a monotherapy of olanzapine (n=2641), risperidone (n=863), quetiapine (n=142), or haloperidol (n=189) for at least 3 months were included in the statistical analyses for as long as they maintained their initial treatment. At each visit, clinicians recorded the severity of EPS and TD. For patients without EPS or TD at enrollment, symptoms at any subsequent visit were considered treatment emergent. No significant differences ($p>0.05$) were initially detected between treatment groups (Table 1), but after 3 years, the presence and emergence of EPS and TD were greater in haloperidol and risperidone recipients compared to olanzapine and quetiapine patients - despite

greater use of anticholinergics during this time. This large, prospective, naturalistic study provides insight into the presence and emergence of motor dysfunction in patients who received antipsychotic monotherapy over a period of 3 years. Differences in motor tolerability between antipsychotic agents were highlighted. These data will be further evaluated through longitudinal statistical analyses. This study was funded by Eli Lilly and Company. 1 Kane JM. Extrapyramidal side effects are unacceptable. Eur Neuropsychopharmacol 2001; 11 (Suppl 4):S397-S403.

Table 1: Presence and emergence of motor dysfunction, as evaluated by the treating clinician

	Extrapyramidal Symptoms (Dystonia/Akathisia/Parkinsonism) % [a]	Tardive Dyskinesia % [a]
Present at Enrollment Olanzapine Risperidone Quetiapine Haloperidol	38.7 39.5 34.8 31.5	7.8 8.1 7.9 6.0
Present at 3 years Olanzapine Risperidone Quetiapine Haloperidol	3.6 15.2 0.0 36.8	1.3 5.0 2.0 10.5
Emergence during 3-year period [b] Olanzapine Risperidone Quetiapine Haloperidol	19.7 59.0 9.1 84.9	3.6 11.4 6.3 39.2

[a] Percentages based on patients with available treatment and motor dysfunction data.

[b] Includes only patients without symptoms at enrollment, and with available treatment and motor dysfunction data (EPS n=1079, TD n=1433).

A DOUBLE BLIND, PLACEBO-CONTROLLED RANDOMIZED TRIAL OF LOW-DOSE RISPERIDONE, COGNITIVE-BEHAVIOUR THERAPY, AND BEFRIENDING IN YOUNG PEOPLE WITH SUBTHRESHOLD SYMPTOMS AT INCIPIENT RISK OF PSYCHOTIC DISORDER: SIX MONTH OUTCOME DATA

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Intervention during the prodromal phase of psychotic disorder has become the frontline focus in early intervention research and is aimed at delaying or preventing the onset of psychosis in already symptomatic high risk patients, as well as alleviating current symptoms, distress and disability. The PACE Clinic at ORYGEN Youth Health has conducted a second randomized controlled trial (RCT) under double blind conditions comparing the effectiveness of low-dose risperidone (0.5-2.0 mg/day) and intensive CBT-based psychological treatment versus placebo and intensive CBT-based psychological treatment versus placebo and a control psychological treatment (befriending). The trial consists of a 12-month treatment phase, followed by a 12-month follow up phase, due to be completed in March 2007. The primary outcome is the proportion of patients meeting onset of psychosis criteria during the treatment and follow up phases. The validity of potential predictors of transition from the subthreshold or ultra-high risk (UHR) mental state to acute psychosis will also be assessed. Secondary outcomes involve improvement on dimensional measures of symtpoms, distress, functioning and quality of life. This presentation will report six month outcome data. 119 participants (mean age = 18.36 years, male = 41.2%) meeting ultra high risk (UHR) criteria for psychotic disorder were randomized to the three treatment groups. A range of psychopathological, neuropsychological, and physical assessments were conducted at baseline and at regular follow up points. At the six month follow up point, 94 (79%) participants remained in the trial, 68 (72%) of whom remained adherent to trial medication. Eight participants had made the transition to first episode psychosis (FEP). At the time of writing, the blind has just been broken, hence specific results are not yet available by group. However, the transition rate and dimensional outcomes by treatment group is being examined and the results of specific and detailed analysis, which is currently underway, will be presented at the session.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EFFICACY AND SAFETY STUDY OF BIFEPRUNOX AS TREATMENT FOR PATIENTS WITH ACUTELY EXACERBATED SCHIZOPHRENIA

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(a) Investigate the efficacy, safety and tolerability of bifeprunox in patients with an acute exacerbation of schizophrenia. (b) In this 6-week randomized, double-blinded, placebo-controlled, risperidone-referenced study, patients with acutely exacerbated schizophrenia were randomly assigned to once-daily treatment with bifeprunox 30 mg (n=148), 40 mg (n=148), placebo (n=149) or risperidone 6 mg (n=154). Bifeprunox doses were titrated, beginning with a dose of 0.25 mg on day 1 and approximately doubled every day until 30 mg or 40 mg (day 8) were reached; risperidone was titrated over 3 days. Primary efficacy measure was change in PANSS total score. Secondary efficacy measures included: CGI-Severity of Illness, PANSS negative, positive, the general psychopathology (GPP) subscale of the PANSS, PANSS-derived BPRS score, BPRS psychosis cluster and CGI-Improvement scores. Patients were monitored for EPS, weight gain, non-fasting lipids, serum prolactin and adverse events (AEs). (c) Bifeprunox 30 mg was statistically superior to placebo (P=0.020) on PANSS total score. Bifeprunox-treated patients showed improvement in PANSS positive and GPP subscales, BPRS total and psychosis cluster scores and CGI-I responder rate versus placebo. Bifeprunox 40 mg significantly separated from placebo on PANSS positive symptom subscale (P=0.020) and BPRS psychosis cluster score (P=0.031), but not PANSS total score. Risperidone was statistically different from placebo for the primary endpoint and thus provided proof of assay sensitivity. Discontinuation due to AEs was similar across all active treatment groups. Most common AEs observed with bifeprunox (incidence >5% and twice placebo) included: nausea, vomiting, constipation, dyspepsia, diarrhea, dizziness and decreased appetite. Bifeprunox 30 mg was associated with decreased prolactin levels versus placebo, while risperidone increased levels. Use of anticholinergic medication and measures of EPS were similar between bifeprunox and placebo groups. Bifeprunox produced statistically significant (P<0.005) weight decreases in comparison to placebo, and bifeprunox-treated patients had decreases in non-fasting glucose at week 3 and endpoint, and reduced triglycerides. (d) In this study, bifeprunox 30 mg was effective and safe. Weight decreases and improvement in the lipid profile were noted. Bifeprunox may be a safe and effective treatment option for patients with schizophrenia.

EFFICACY AND TOLERABILITY OF ORAL PALIPERIDONE EXTENDED-RELEASE TABLETS IN THE TREATMENT OF ACUTE SCHIZOPHRENIA: POOLED DATA FROM THREE 6-WEEK PLACEBO-CONTROLLED STUDIES

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The objective of this pooled analysis was to evaluate the efficacy and safety of paliperidone extended-release tablets (paliperidone ER), an investigational oral psychotropic agent delivered using OROS technology, in patients with an acute episode of schizophrenia. Pooled data from 3 international, 6-week, multicenter, double-blind, randomized, placebo-controlled, dose-response studies in patients (n=1326, age ≥18 years) treated with fixed-doses of paliperidone ER (3, 6, 9, 12 or 15mg) or placebo daily were analyzed. Efficacy analyses included baseline to end point changes in PANSS total and factor scores, score on the Personal and Social Performance (PSP) scale and patient response (end point improvement in PANSS total score by ≥30%). Safety assessments included treatment-emergent AEs (TEAEs) and bodyweight. The ITT population=1306, mean age=38.3±10.9y and baseline PANSS total score=93.5±11.8. Mean PANSS total score at end point significantly improved for all paliperidone ER doses vs placebo (3mg=−15.0±19.6, 6mg=−16.9±20.7, 9mg=−16.8±21.0, 12mg=−20.6±20.2, 15mg=−19.9±18.4, placebo=−4.8±22.0; p<0.001). All PANSS factor scores significantly improved at end point for paliperidone ER doses vs placebo (p≤0.001). Patient response was significantly higher with paliperidone ER vs placebo (3mg=39.8%, 6mg=53.2%, 9mg=48.2%, 12mg=56.7%, 15mg=52.7%, placebo=27.4%, p<0.001). PSP scores improved at end point for paliperidone ER vs placebo (3mg=8.3±17.1, 6mg=9.0±14.8, 9mg=7.8±14.3, 12mg=9.5±15.0, 15mg=12.2±15.7, placebo=0.5±15.0, p<0.001). TEAEs occurred in 66% of patients with placebo and in 66—77% with paliperidone ER. TEAEs occurring >3% more for paliperidone ER than placebo were extrapyramidal disorder, akathisia, headache, somnolence and tachycardia. TEAE—extrapyramidal symptom rates were comparable for paliperidone ER 3mg and 6mg and placebo, and increased with paliperidone ER 9mg, 12mg and 15mg. Serious AEs with paliperidone ER were comparable with placebo (6% each group). At end point, mean changes in bodyweight (kg) for placebo and paliperidone ER groups were –0.4±3.5 and 1.0±3.1, respectively. All doses of paliperidone ER showed significant efficacy, with the suggestion of a dose response between the lowest and highest doses. All doses were well tolerated and associated with improvements in personal and social functioning. Supported from funding from Johnson & Johnson Pharmaceutical Services, LLC and Johnson & Johnson Pharmaceutical Research and Development.

EFFECTS OF ARIPIPRAZOLE AND OLANZAPINE ON SERUM TRIGLYCERIDE:HIGH DENSITY LIPOPROTEIN RATIOS IN PATIENTS WITH SCHIZOPHRENIA

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Physiological abnormalities which define the metabolic syndrome significantly increase the risk of cardiovascular disease. Insulin resistance is a core feature of the metabolic syndrome, and is associated with future risk for type 2 diabetes, but insulin sensitivity is not easily measured without sophisticated endocrine testing. The ratio of serum triglyceride-to-high density lipoprotein cholesterol (TG:HDL-C) recently has emerged as a simple tool for early detection of insulin resistance in most patient groups. In nondiabetics, TG:HDL-C ratios > 3.0 detect highly insulin resistant individuals with greater sensitivity than criteria proposed by the Adult Treatment Panel III for metabolic syndrome. The objective of this post-hoc analysis was to compare TG:HDL-C ratios in patients treated with olanzapine or aripiprazole for up to 26 weeks. This was an exploratory post-hoc analysis of pooled data from 2 randomized, 26 week, double-blind controlled clinical trials of olanzapine versus aripiprazole. Blood samples from fasting subjects were used to calculate TG:HDL-C ratios, and within and between-group statistical comparisons were made over 3 time points using an observed case approach. At baseline, TG:HDL-C ratios for subjects randomized to aripiprazole (3.97, N=197) and to olanzapine (4.04, N=192) were similarly high, and not significantly different. In the aripiprazole group, significant improvements were seen compared with the baseline TG:HDL-C ratio at week 6 (3.26, P<.001), week 12 (3.11, P<.02), and week 26 (2.92, P<.001). In the olanzapine group, no differences from the baseline TG:HDL-C ratio were observed: week 6 (4.44, P>0.2), week 12 (4.02, P>0.3), and week 26 (4.21, P>0.4). The TG:HDL-C ratios were significantly lower in the aripiprazole group than in the olanzapine group at weeks 6, 12, and 26 (P<.02 for all). From these results, one can see that this marker of insulin sensitivity was significantly lower in the aripiprazole group compared with the olanzapine group as early as 6 weeks after treatment, and that patients in the aripiprazole group showed improvement in their TG:HDL-C ratios at each time point through week 26. Moreoever, the finding that mean TG:HDL-C ratios for aripiprazole-treated patients were < 3.0 at week 26 suggests long-term aripiprazole treatment may reverse the adverse metabolic effects of other antipsychotic medications, and thereby improve metabolic parameters in patients at high risk for insulin resistance.

TREATMENT OF CLOZAPINE PARTIAL OR NON-RESPONDERS

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There is a scarcity of evidence on how to treat patients with schizophrenia who fail to respond to clozapine as well as those who have a partial response. Until recently, most of the information available was from case reports or case series. Although randomized controlled trials have been completed recently of risperidone and lamotrigine augmentation in patients with a history of partial or poor response to clozapine monotherapy, none of the other medications commonly used for augmentation have been investigated. In the 3 randomized, double-blind, placebo-controlled trials of risperidone augmentation of clozapine, all patients improved significantly over time. Two out of three trials found no advantage of risperidone augmentation of clozapine. In the only published randomized, double-blind, placebo-controlled, crossover trial of lamotrigine augmentation of clozapine, lamotrigine was found to be superior to placebo for positive and general symptoms in patients with schizophrenia who were resistant to clozapine monotherapy. There have been 2 additional studies performed by GlaxoSmithKline investigating the use of lamotrigine augmentation of antipsychotics in patients with schizophrenia who had persistent residual symptoms (15% of the patients were on clozapine).

No statistically significant improvements in positive, negative or general subscales were observed for lamotrigine compared to placebo in either sample or in the subgroup receiving clozapine. The TMAP expert consensus panel chose not to change Stage 4 of the Antipsychotic Algorithm as it was felt that the data for risperidone and lamotrigine augmentation were not conclusive, and that their addition or exclusion would not be prudent as these are the only agents with randomized, placebo-controlled data. In addition, the panel supported the addition of a statement encouraging a "treatment refractory evaluation" before moving on to clozapine augmentation.

COGNITIVE REMEDIATION AND MEDICATION FOR COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA

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Persons with schizophrenia, despite receiving optimal doses of antipsychotic medications that reduce or entirely eliminate psychotic symptoms still fail to fully recover function. It is the cognitive dysfunction and negative symptoms that largely account for persistent psychosocial dysfunction. The field has recently focused on developing new treatments for cognitive dysfunction in schizophrenia initiated by the NIMH-sponsored MATRICS and TURNS projects (www.MATRICS.ucla.edu). These groups have (1) defined the nature of the cognitive dysfunction, (2) provided a battery of recommended neuropsychological tests to assess these cognitive features, and (3) suggested likely molecular targets for cognitive enhancement (Psychopharmacology, June, 2004). Based on considerable basic literature, we have been impressed that it may not only be a drug treatment (e.g., atomoxetine, in this study) but also psychological approaches (e.g., cognitive remediation) that need to synergize to optimally improve cognition in schizophrenia. Therefore, we have hypothesized that the use of cognitive remediation in the context of a cognitive enhancing medication will be necessary for optimal cognitive improvement in schizophrenia. To test this, we are administering atomoxetine (to putatively target the D1 dopamine receptor in prefrontal cortex through the NE/DA reuptake blockade) along with a cognitive remediation routine (designed by Alan Bellack) for the treatment of cognitive dysfunction in schizophrenia. The study design is a standard four cell design, comparing combinations of atomoxetine/placebo and cognitive-remediation/control. It lasts 12 weeks, with an additional 12 week blinded extension of drug. The MATRICS battery is completed at BL and at 12 and 24 weeks, as well as an evaluation of psychosocial outcome. Preliminary data show a three way interaction with both atomoxetine and cognitive remediation showing a sizable effect size, despite a small subject number. Additional data will be reported. (This project is funded in part by the Stanley Foundation for Research in Mental Health.)

Initial 12 week differences (preliminary)

Group	BL Mean	EP Mean	Diff Mean	Effect Size
Atomox/Control	30.7	42.7	12.0	3.6
Placebo/CogRem	36.0	42.7	6.7	2.0
Atomox/CogRem	47.7	49.7	2.0	0.6
Placebo/Control	44.7	43.7	-1.0	0.3

INFLUENCE OF THE COURSE OF ILLNESS ON PSYCHOTHERAPY OUTCOME IN SCHIZOPHRENIA: A LONGITUDINAL STUDY

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Up to now, psychotherapy evaluation studies only evaluate state of illness and rehabilitation status of schizophrenia patients at therapy intake. But the influence of dynamic course parameters (e.g. relapses, life events) before psychotherapy normally is not examined. A representative sample of 106 schizophrenia patients (DSM IV) participated in Integrated Psychological Therapy (IPT) for groups during six months. In this longitudinal study, assessments were applied before and after therapy and at one-year follow-up. Additionally, for the period of two years before and after starting therapy time and number of relapses as well as the time interval and the number of days of inpatient hospitalization and day-care treatment were documented. The present study examined a) whether the course of illness and rehabilitation could be empirically classified, and b) whether the course of illness before study intake influenced therapy outcome. By means of a cluster analysis covering six-months intervals of the two-year period before baseline, four process types of the course of illness could be identified: 1) outpatients with increasing day-care before study intake (process type 1, C1, n=32); 2) patient with repeated, short hospitalizations and increased day-care (C2, n=36); 3) outpatients with temporary inpatient admission within a half year before study intake (C3, n=22); 4) inpatients, whose placement has been changed into day-care setting before study intake (C4, n=16). Furthermore results indicate that a change to a higher structured care unit was associated with a relapse. Negative symptoms, neuro-cognitive and social functioning differed in the four process types: C1 and C2 patients showed more improvements in neuro-cognitive and social functioning compared to C3 and C4 patients. Negative symptoms and discontent with the own social situation were significantly more pronounced in C4 patients than in the other process types (C1-3). Nevertheless, significant improvements were evident in all treatment outcome variables after treatment and at follow-up independently of process type. Additionally, relapse rates were significantly reduced after two years. Consequently, process patterns could decisively contribute to explaining the variance of change in functional areas of schizophrenia during psychotherapy. The study was supported by a grant of the Swiss National Science Foundation (SNF).

2-3 YEAR OUTCOMES OF A RANDOMIZED CONTROLLED TRIAL OF COGNITIVE TRAINING AND SUPPORTED EMPLOYMENT FOR PEOPLE WITH SEVERE MENTAL ILLNESS

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Supported employment is an evidence-based practice that improves competitive work outcomes in people with schizophrenia. However, not all participants benefit from supported employment; 20-40% of patients fail to find jobs, and many who do have brief job tenures that end unsuccessfully. These findings have stimulated efforts to address illness-related factors, such as cognitive impairment, that limit the effectiveness of supported employment for schizophrenia. To improve the outcomes of supported employment, a cognitive training program was developed, the Thinking Skills for Work program, that was integrated into

supported employment services. The program includes four components: 1) Cognitive assessment and job loss analysis; 2) 24 sessions of computer-based cognitive training delivered over 12 weeks using COGPACK, a commercially available cognitive training program; 3) Review of gains made following cognitive training, and collaborative planning about preferred jobs and coping strategies for persistent cognitive impairments; and 4) Ongoing consultation with the employment specialist and the patient to develop additional compensatory strategies as needed. To evaluate the effects of this program, a controlled trial was conducted of 44 patients with severe mental illness with prior histories of job failures who were enrolled in supported employment programs at 2 sites in New York City. Patients were randomized to one of two programs: cognitive training + supported employment (CT + SE) or supported employment only (SE Only). 3-month outcomes indicated that patients in the CT + SE program demonstrated significantly greater improvements in performance on a neuropsychological battery, and on depression and autistic preoccupation on the PANSS. 2-3 year outcomes indicated that patients in the CT + SE program were more likely to work ($\chi 2 = 18.0$, $p < 0.001$), held more jobs ($Z = -4.4$, $p < 0.001$), worked more weeks ($Z = -3.9$, $p < 0.001$), worked more hours ($Z = -4.1$, $p < 0.001$), and earned more wages ($Z = -4.1$, $p < 0.001$) over the follow-up period than patients in the SE Only program. The findings support the feasibility of integrating cognitive rehabilitation into supported employment programs, and suggest that more research is warranted to evaluate the effects of the Thinking Skills for Work program.

ONCE-DAILY QUETIAPINE SUSTAINED RELEASE (SR) IS EFFECTIVE AND WELL TOLERATED IN PATIENTS WITH SCHIZOPHRENIA SWITCHED FROM THE SAME TOTAL DAILY DOSE OF QUETIAPINE IMMEDIATE RELEASE (IR)

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Introduction: This study evaluated the efficacy and tolerability of quetiapine SR in patients with schizophrenia switched from quetiapine IR. Methods: This was a randomized, double-blind, double-dummy study (D1444C00146) of patients with clinically stable schizophrenia on stable doses of quetiapine IR for ≥4 weeks. During a 4-week run-in period, patients received twice-daily quetiapine IR 400, 600 or 800 mg/day. After run-in, those who remained clinically stable on stable doses were randomized (1:2) to continue taking quetiapine IR (same dose twice-daily) or to switch to quetiapine SR (same total dose, active dose taken once-daily in the evening) for 6 weeks. Primary endpoint was percentage of patients who discontinued due to lack of efficacy or had an increase in PANSS total score ≥20% (randomization to any visit). A non-inferiority margin of 6% (for the upper 95% CI of the treatment difference) was used; modified ITT and PP populations were analyzed. Secondary endpoints included discontinuation rate due to AEs or lack of efficacy, change in PANSS total score and CGI-I score (LOCF analysis). Results: 630 patients enrolled; 497 were randomized to quetiapine SR (n=331) or IR (n=166); completion rates were 91.5% and 94.0%, respectively. For the primary endpoint, non-inferiority was narrowly missed for the MITT population, but was shown for the PP population (table). Rate of discontinuation due to AEs or lack of efficacy was 3.3% in the SR group and 1.8% in the IR group. The LSM (SE) changes in PANSS total score were -3.7 (0.8) and -4.2 (0.9), respectively. In both groups, 93% had no change or an improvement in their clinical condition (CGI-I score). The type, distribution and intensity of AEs were similar in the two groups. The incidence of drug-related AEs was 17.2% for SR and 15.7% for IR. The most common AEs were headache, dry mouth, somnolence, fatigue, dizziness and insomnia, but all were reported by <5% of patients and most were mild-to-moderate. Conclusion: Patients clinically stable on quetiapine IR can be switched to an equivalent dose of once-daily quetiapine SR without clinical deterioration and no compromise in safety or tolerability.

	% of patients discontinued due to lack of efficacy or with PANSS total ≥20%		Treatment difference	95% CI	P value†
	Quetiapine SR	Quetiapine IR			
Modified ITT	9.1	7.2	1.86%	-3.78, 6.57	0.0431
PP	5.3	6.2	-0.83%	-6.75, 3.71	0.0017

One-sided, for non-inferiority p<0.025

PREDICTION OF REMISSION BY EARLY (SUBJECTIVE) IMPROVEMENT IN 2960 PATIENTS WITH SCHIZOPHRENIA

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Objective: Comparability of results on remission in schizophrenia is limited by the lack of consistent definitions. Recently, the Remission in Schizophrenia Working Group published remission criteria. This study does assess remission according to these new criteria and investigates their applicability in a large cohort of patients with schizophrenia. Method: Data were collected in an observational 24-month follow-up study on 2960 patients with schizophrenia. Complete remission required that patients achieved symptomatic, functional, and remission of subjective well-being (SW) over at least 6 months. Results: At endpoint, 50.2% of the patients achieved symptomatic, 28.1% functional, and 42.2% subjective well-being remission. 14.1% were in complete remission at endpoint. Each single remission component as well as complete remission was mainly predicted by early remission within the first 3 months. First-line treatment with atypical antipsychotics increased the likelihood of complete remission compared to conventional antipsychotics. Discussion: The current study was able to identify 3-month remission of subjective well-being as one important factor predicting complete remission after 24 months. The relevance of early subjective improvement is further supported by a 12 week amisulpride trial (Lambert et al., Acta Psychiatr Scand. 2006). Of 727 patients with low SW at baseline, 220 did not improve within two weeks. In contrast to SW-responders (n=567) who showed further marked improvement of CGI, PANSS and SWN within the next 8 weeks, 91% of SW-nonresponders did not experience any relevant change. Conclusion: These data indicate the importance of early response to antipsychotic treatment for long-term outcome of schizophrenia and in

particular the necessity to achieve rapid improvement in subjective well-being.

A DOUBLE BLIND, PLACEBO-CONTROLLED RANDOMIZED TRIAL OF LOW-DOSE RISPERIDONE, INTENSIVE PSYCHOLOGICAL TREATMENT AND SUPPORTIVE THERAPY IN YOUNG PEOPLE WITH SUBTHRESHOLD SYMPTOMS AT INCIPIENT RISK OF PSYCHOTIC DISORDER: BASELINE CHARACTERISTICS OF THE SAMPLE

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Intervention during the prodromal phase of psychotic disorder has become the frontline focus in early intervention research and is aimed at delaying or preventing the onset of psychosis in already symptomatic high risk patients, as well as alleviating current symptoms, distress and disability. The PACE Clinic at ORYGEN Youth Health has conducted a second randomized controlled trial (RCT) under double blind conditions comparing the effectiveness of low-dose risperidone (0.5-2.0 mg/day) and intensive CBT-based psychological treatment versus placebo and intensive CBT-based psychological treatment versus placebo and a control psychological treatment (supportive therapy). The trial consists of a 12-month treatment phase, followed by a 12-month follow up phase, due to be completed in March 2007. The primary outcome of interest is the proportion of patients meeting onset of psychosis criteria during the treatment and follow up phases. The validity of potential predictors of transition from the subthreshold or ultra-high risk (UHR) mental state to psychotic disorder will also be assessed. Secondary outcomes involve improvement on dimensional measures of symptoms, distress, functioning and quality of life. This presentation will report baseline characteristics of the sample. 119 participants (mean age = 18.36 years, male = 41.2%) meeting UHR criteria for psychotic disorder were randomized to the three treatment groups. A range of psychopathological, neuropsychological, and physical assessments were conducted at baseline and at regular follow up points. Baseline characteristics will be compared between: i) the three treatment groups and ii) the treatment groups and a monitoring group (N = 83, mean age = 18.45 years, male = 41%), who received "treatment as usual".

FEASIBILITY OF TARGETED AND MAINTENANCE TREATMENT IN REMITTED FIRST EPISODE PSYCHOSIS

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Introduction: The main aim of the guidelines for the treatment with antipsychotics of patients with a first episode psychosis is to reduce the risk of a relapse. Unfortunately the guidelines vary widely between countries, due to the lack of robust scientific underpinnings. Two approaches in the treatment with antipsychotics can be distinguished: targeted and maintenance treatment. The comparison between targeted and maintenance treatment was subject of only a few studies. None of them described in detail how these strategies were carried out in practice. Methods: The Medication Strategies In First Onset Schizophrenia study (MESIFOS) is an RCT comparing targeted treatment and maintenance treatment primarily with regard to quality of life and social functioning. The target population are patients with a first onset non-affective psychosis, whose positive symptoms remitted within 6 months after commencing antipsychotic treatment. After a stable remission phase of 6 months, patients were randomly assigned to either maintenance treatment or targeted treatment with antipsychotics. These strategies had to be carried out during 18 months following the remission phase, according to an intention to treat. In the trial 131 patients were included. Among the data that were gathered of these patients were: medication prescription and use, side effects, symptom levels, social functioning and quality of life. Prescription and use (compliance) of antipsychotics and 18-months outcome are our parameters for determining feasibility. Results: Both treatments are feasible in real life practice. In the initial phase the treatments differ significantly, but they coincide after 18 months. Cumulative doses differed significantly as did the percentage of drugfree patients per months. Despite different relapse rates both groups have similar outcomes as regards quality of life. Conclusions: Both strategies should be considered in remitted first episode psychotic patients. The benefits and risks should be explained to eligible patients. This will foster autonomy and enhance compliance and satisfaction.

LOWERING HOMOCYSTEINE WITH ADJUVANT FOLIC ACID, B12 & B6 IN PATIENTS WITH FIRST EPISODE PSYCHOSIS TO PROTECT/ENHANCE COGNITION AND SYMPTOMATOLOGY. THE VITAMINS IN PSYCHOSIS (VIP) RANDOMIZED CONTROLLED TRIAL

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Background. In healthy and other disease populations mild hyperhomocysteinemia is associated with cognitive impairment and decline over time. Mild hyperhomocysteinemia is a feature of first episode psychosis (FEP) and correlates with poorer performance on neuropsychological tests at VIP trial baseline. Whether elevated homocysteine mediates or is merely an indicator of the underlying pathophysiology is unclear. If indeed homocysteine promotes cognitive dysfunction then lowering homocysteine levels by means of B vitamin supplementation may protect cognitive function by arresting the disease process and enabling recovery of function in FEP. Negative and positive symptom domains may also be beneficially affected as reported by two previous folic acid RCT's; Godfry (1990) & Levine (2006). Aims. The purpose of this study is to determine whether the homocysteine lowering properties of Folic Acid, B6 & B12 are effective as an adjunct to antipsychotics in FEP. Primary outcome measures will be psychopathology and cognition including the MATRICS 'candidate ' tests, Trail Making

Test (TMT; Trails A and B), the California Verbal Learning Test II (CVLT II), the Brief Assessment of Cognition in Schizophrenia–Digit Sequencing (BACS), the Brief Visuospatial Memory Test–Revised (BVMT-R) and the Neuropsychology Assessment Battery–Mazes (NAB). Secondary outcome measures will be tolerability and safety measures (drop-out rates, general side effect scale (UKU). Methods. We conducted a double blind parallel randomized placebo- controlled single center study in 120 young people, aged 15-25 years. Subjects were recruited from ORYGEN Youth health. Minimisation, a dynamic randomisation procedure, was used to ensure a balanced distribution of participants .Confounding variables assessed at baseline and at 3 months included homocysteine levels, B12, B6 and Folate. We assessed diet using a food frequency questionnaire and genotyped polymorphisms of the MTHFR enzyme in the participants. Participants received Folic Acid 5mg, Vitamin B12 0.4mg and B6 50mg as an oral supplement or placebo following randomization for 12 weeks. Results. The trial commenced recruitment in September 2004 and recruitment is now complete with 120 patients randomised. The results of the trial will be presented at the conference. ClinicalTrials.gov ID: NCT00202280. Generously funded by the Stanley Medical Research Institute.

PREDICTORS OF RESPONSE TO ANTIPSYCHOTIC MEDICATION IN ADOLESCENTS WITH PSYCHOSIS

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Introduction: There is scant data regarding efficacy of antipsychotic agents in adolescents suffering from psychosis. Additionally, little is known about the characteristics that are predictive of response to antipsychotic medication amongst teenagers. The purpose of this analysis was to examine the results of a recently completed study comparing the efficacy and tolerability of antipsychotics used in adolescents with psychosis and to determine what if any characteristics at baseline predicted response to medication. Methods: A sample of 23 adolescents treated with one of three second-generation antipsychotic agents was dichotomized into two groups, those that responded to medication and those that did not. Response was defined as a decrease of 40% or more in Positive and Negative Syndrome Scale (PANSS) total score. Responders were compared to non-responders on a variety of baseline characteristics, including gender, diagnosis, PANSS total, positive, and negative scores, Clinical Global Impression-Severity (CGI-S), depressive symptoms, and Global Assessment of Function (GAF) score. Results: Sixteen of 23 adolescents responded to medication and enjoyed a 40% or greater reduction on the PANSS total score. Patients with higher PANSS total, positive, and negative symptom scores tended to be more likely to respond to medication, though none of these differences were statistically signfiicant (p=0.092, p=0.075, and p=.134 respectively). Total Calgary Depression score, CGI-S, and GAF at baseline were not predictive of response to medication, nor was gender. Subjects diagnosed with Psychotic Disorder NOS were more likely to respond to medication than subjects suffering from other psychotic illnesses. Discussion: This study shows that 70% (16/23) of the adolescents treated with antipsychotic medication responded with a 40% or greater reduction in PANSS score. While there was a tendency for higher total, positive, and negative PANSS scores to predict response to antipsychotic medication, this tendency was not statistically significant in the sample studied. Supported by funding from an AstraZeneca Pharmaceuticals LP Investigator-Sponsored Study Grant (IRUSQUET0149).

NON-INFERIORITY OF INTRAMUSCULAR ARIPIPRAZOLE VERSUS INTRAMUSCULAR HALOPERIDOL FOR THE TREATMENT OF AGITATION ASSOCIATED WITH SCHIZOPHRENIA/SCHIZOAFFECTIVE DISORDER

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Purpose: To explore the non-inferiority of intramuscular (IM) aripiprazole to IM haloperidol for the treatment of patients with agitation associated with schizophrenia/schizoaffective disorder. Methods: In this multicenter, double-blind study, 448 patients with acute agitation (Positive and Negative Syndrome Scale [PANSS] Excited Component [PEC] score ≥15 and ≤32, with a score of ≥4 (moderate) on ≥2 of the five PEC items [poor impulse control, tension, hostility, excitement, and lack of cooperation]) were randomized to IM aripiprazole 9.75 mg/injection (n=175), IM haloperidol 6.5 mg/injection (n=185) or IM placebo (n=88). If deemed clinically necessary, second and third injections were given ≥2 and ≥4 hours, respectively, after the first. For IM placebo-treated patients, the third injection was IM aripiprazole 9.75 mg. The primary outcome measure was the change from baseline in PEC score at 2 hours. These analyses explore the non-inferiority of IM aripiprazole to IM haloperidol. The study aimed to enroll ≥420 patients to obtain 400 evaluable patients with a baseline and ≥1 post-injection PEC assessment. This sample size would yield 90% power to show non-inferiority of IM aripiprazole to IM haloperidol, when the non-inferiority bound for the difference in the mean PEC changes was 2.5 and assuming an expected difference in mean changes from baseline of 0.5 (in favor of haloperidol), a standard deviation of 5.5 and a 2-sided test at the 0.05 significance level. Results: IM aripiprazole was non-inferior to IM haloperidol with respect to the mean change from baseline in PEC Total score at 2 hours (-7.27 vs. -7.75; p=0.365). In addition, changes from baseline at 2 hours were significantly greater with IM treatment versus IM placebo for each of the individual PEC items (table). Improvements in PEC item scores with IM aripiprazole and IM haloperidol were comparable, with no significant differences between the active IM treatments. Conclusion: IM aripiprazole is non-inferior to IM haloperidol for the treatment of acute agitation associated with schizophrenia/schizoaffective disorder.

Change in score (p-value vs. placebo)	PEC Total	PEC item				
		Poor impulse contro	Tension	Hostility	Excitement	Lack of cooperation
IM placebo	-4.78	-0.99	-1.08	-0.95	-0.94	-0.63
IM aripiprazole	-7.27 (p<0.001)	-1.45 (p=0.003)	-1.55 (p=0.006)	-1.41 (p<0.001)	-1.56 (p<0.001)	-1.12 (p<0.001)
IM haloperidol	-7.75 (p<0.001)	-1.58 (p<0.001)	-1.64 (p<0.001)	-1.48 (p<0.001)	-1.65 (p<0.001)	-1.21 (p<0.001)

SUBJECTIVE ASSESSMENT OF ILLNESS AND TREATMENT AND SUBSEQUENT REHOSPITALISATION IN PATIENTS WITH SCHIZOPHRENIA – FIRST RESULTS OF THE FAME II STUDY

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Background: A continuing antipsychotic medication is a major factor for relapse prevention in schizophrenia. Patients' knowledge about the illness, their attitudes towards treatment and the therapeutic alliance are of major importance for adherence to medication. Methods: A one year follow-up of a prospective longitudinal survey that had included 300 patients with schizophrenia before discharge from hospital was conducted. Patients were contacted by mail. Again, the Insight Scale (IS), the Drug Attitude Inventory (DAI) and the Questionnaire on Therapeutic Alliance assessed by the patient (QTA-P) and the physician (QTA-MD) were applied. Data on rehospitalisation were collected. Results: 113 patients (38%) responded (male: 52%, female 48%; mean age: 42.1±11.2 years; mean age on onset of disease: 28.9±9.7). 37% had been rehospitalised for relapse of schizophrenia. Baseline and follow-up IS, DAI and QTA-P scores correlated positively. A significant improvement was only observed in the QTA-P (13.7±4.2 vs. 15.7±2.8; p<0.001), but not in the IS (11.5±3.1 vs. 11.3±3.2; p=0.62) nor in the DAI (3.7±4.7 vs. 4.5±4.4; p=0.14). Baseline IS, DAI and QTA-P scores as well as demographic variables were unable to predict rehospitalisation. Rehospitalisation only depended on a higher severity of illness at baseline, a lower awareness of illness at baseline and a lower alliance rated by the physicians (QTA-MD) at baseline (p<0.05 each). Conclusions: Patients who responded were well educated on their illness and showed a high level of acceptance of medication and alliance with their physician. Nevertheless one third had a relapse within a one year period in a naturalistic setting. Patients with a lower severity of psychopathology at discharge and with a higher awareness of illness after the index episode as well as those for who the physicians rated a better alliance were at lower risk for relapse.

BIFEPRUNOX, PLACEBO, AND OLANZAPINE-INDUCED WEIGHT CHANGES AMONG PATIENTS WITH SCHIZOPHRENIA

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(a) To evaluate body weight changes in patients with acutely exacerbated schizophrenia treated with bifeprunox.(b) A 6-week randomized, double-blind, placebo-controlled, olanzapine-referenced, safety and efficacy study of bifeprunox enrolled 604 patients with an acute exacerbation of schizophrenia (DSM-IV-TR). Patients were randomly assigned to once-daily treatment with bifeprunox 20 mg (n=154), 30 mg (n=150), placebo (n=150), or olanzapine 15 mg (n=150). Bifeprunox doses were titrated, beginning with a dose of 0.25 mg on day 1 and approximately doubled every day until 20 mg (day 7) or 30 mg (day 8) was reached; treatment with olanzapine began at 10 mg for the first 7 days, and was maintained at 15 mg for the remainder of the study. Weight and body mass index (BMI) were assessed at baseline and endpoint. (c) No statistically significant differences between active treatment groups and placebo existed for baseline body weights. At week 6, bifeprunox 20 mg showed statistically significant weight loss from baseline to endpoint (-2.3 kg, P<0.0002), bifeprunox 30 mg demonstrated nonsignificant weight loss (-0.5 kg) and olanzapine showed significant weight gain from baseline to endpoint (+2.4 kg, P< 0.0001). The incidence of markedly abnormal increases (≥7%) in body weight was comparable in the bifeprunox and placebo groups (1% to 3%) and much higher in the olanzapine (19%) group. In addition, small changes in BMI were observed across all treatment groups (-0.6 kg/m2, bifeprunox 20 mg; -0.1 kg/m2, bifeprunox 30 mg; -0.1 kg/m2, placebo; +0.7 kg/m2, olanzapine) at endpoint. (d) In this short-term study, bifeprunox 20 mg was associated with a reduction in body weight, while olanzapine 15 mg showed a significant increase in this parameter. Minor reductions in BMI were observed in the bifeprunox groups. These findings are consistent with other bifeprunox studies and are noteworthy given that weight gain is a problematic issue for some atypical antipsychotics.

ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN ANTIPSYCHOTIC-NAïVE ADOLESCENTS

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The purpose of the study was to compare weight gain after 6 months of treatment with risperidone (n=22), olanzapine (n=20), and quetiapine (n=25) in antipsychotic-naïve adolescent patients. A total of 67 antipsychotic-naïve adolescent patients (46 male (68.7%), and 21 female (31.3%), mean age (SD): 15.7 (1.8), range 9-18 years) who took the same second generation antipsychotic (SGA) formed the sample. Weight, height and body mass index (BMI) were obtained both at baseline and after 6 months of treatment. For the sample as a whole (5.5 kg, 1.7 kg/m2, P<0.01) significant BMI gain was observed. Olanzapine (10.1 kg, 3.3 kg/m2, P<0.01) and risperidone (5.4 kg, 1.6, P<0.01) groups, but not quetiapine group (2.1 kg, 0.7, P=0.25), showed significant BMI increase. BMI increase was significant greater in olanzapine group than in risperidone or in quetiapine group (P<0.01). The findings of the study showed that some SGA are strongly associated with weight gain in this population. The election of any particular SGA as treatment for a psychiatric disorder should translate this important issue to the clinical practice.

VOLUNTARY OUT-PATIENTS AND COERCION: DEPOT VERSUS ORAL ANTIPSYCHOTICS

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Background: Some clinicians consider depot antipsychotics to be stigmatizing and coercive but there is little empirical data on this issue. Former coercion studies predominantly considered the patient's experience of hospital admission rather than medication specifically. This cross-sectional study investigated patients' perspectives of coercion for both depot and oral antipsychotic treatment. Methods: The 72 participants with schizophrenia or schizoaffective disorder on voluntary maintenance medication were a random sub-sample from a community based attitudinal survey of attitudes to medication. The MacArthur Admission Experience (short form) was adapted to explore coercion regarding medication rather than admission experience. Subscale and total scores were compared for formulation groups (depot versus oral).

Results: Only 9 (12.5%) participants gave a score of zero, indicating no concerns about coercion. Mean total coercion scores were significantly higher for depot than oral (4.39 vs 2.80, p=0.027), as were perceived coercion (2.52 vs 1.73, p=0.041) and negative pressures subscales (1.17 vs 0.33, p=0.009). No significant differences were found for the "voice" subscale and affective reactions. Specifically, (i) more participants on depot felt that people try to force them to take medication (30% vs 2%, p<0.001); (ii) similarly, more participants on oral felt that no-one tried to force them to take medication than those on depot did (90% vs 65%, p=0.011); (iii) more participants on oral felt that they had more influence than anyone else on whether they take the medication (57% vs 24%, p=0.014). Conclusions: To our knowledge, this is study is unique in that it reports specifically on coercion regarding both depot and oral antipsychotic medication, using systematic quantitative methodology. Participants felt that treatment with depots was more coercive than with oral antipsychotics and was associated with a relative lack of true autonomy. One reason for this might be that depots are "given" rather than "taken"; thus the "power of others" may be seen as more potent. Greater perceived coercion may explain why some consider depots to be a more stigmatizing form of treatment.

DOES CANNABIS ABUSE DETERMINE OUTCOME AMONG PATIENTS WITH FIRST EPISODE PSYCHOSIS. RESULTS FROM THE OPUS-TRIAL

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Background: It is documented that use of cannabis can cause psychotic symptoms that cannot be distinguished from schizophrenia. Comorbid substance abuse and psychosis are related to bad outcome with regard to non-compliance, hospitalization, re-admission, psychopathodology and social function. Method: In a randomised clinical trial the effect on substance abuse of integrated treatment which consists of assertive community treatment, family involvement with multifamily groups and social skills training was compared to standard treatment Results: One-fourth of the first episode psychotic patients referred to the OPUS trial in Copenhagen and Århus had a second diagnosis of substance abuse, and the vast majority of these had abuse of cannabis. Integrated treatment significantly reduced substance abuse. Substance abuse at baseline predicted higher rates of hospitalisation, homelessness and being unable to work or study. Conclusion: Patients with schizophrenia and concomitant cannabis abuse have a poorer prognosis, and the treatment system should therefore develop treatment methods that are effective at alleviating cannabis abuse. Integrated treatment seem to be effective

A RANDOMIZED, PLACEBO-CONTROLLED, RELAPSE-PREVENTION STUDY WITH ONCE-DAILY QUETIAPINE SUSTAINED RELEASE IN PATIENTS WITH SCHIZOPHRENIA

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Introduction: This randomized, double-blind, placebo controlled study (D1444C00004) was designed to show superior efficacy of quetiapine sustained release (SR) compared with placebo for relapse prevention in patients with schizophrenia. Methods: 327 patients with schizophrenia and insufficient tolerability/residual symptoms were switched from their current antipsychotic, using cross titration, to open-label quetiapine SR [300 mg on Day 1, 600 mg on Day 2, then flexibly dosed (400, 600 or 800 mg/day in the evening)] for a 16 week stabilization period. Following this, patients on a stable dose of quetiapine SR who were clinically stable were randomized to either blinded flexible doses of quetiapine SR (400, 600 or 800 mg) or placebo. Primary endpoint, time from randomization to psychiatric relapse up to 1 year (hospitalization due to worsening schizophrenia, increase in PANSS score ≥30%, CGI I score ≥6, or need for additional antipsychotics), was analyzed using Cox proportional hazards model. Secondary endpoints included relapse rate at 6 months. Interim analyses by the Data and Safety Monitoring Board were planned after 45 and 60 relapses (to allow study termination if significant treatment difference for primary endpoint using sequential group testing) and final analysis after 90 relapses. Results: The study was terminated early after the first scheduled interim analysis showed that quetiapine SR was significantly superior to placebo for time to relapse (table).The estimated rate of relapse was significantly reduced with quetiapine SR (14.3%) compared with placebo (68.2%)(difference 54% [95% CI 42.5, 65.4]; p<0.001; total ITT). During the randomized period: mean daily dose of quetiapine SR was 669 mg/day; maximum treatment duration was 9 months; incidence of treatment-related AEs was 18% (quetiapine SR) and 21% (placebo); incidence of EPS AEs was 1.1% and 1%, respectively; only 1% of patients in each group withdrew due to AEs. Conclusion: Once-daily quetiapine SR (400 to 800 mg/day), compared with placebo, was effective in preventing relapse in patients with clinically stable schizophrenia. Quetiapine SR was well tolerated during long-term use.

		Interim ITT			Total ITT*	
	Placebo (n=87)		Seroquel SR (n=84)	Placebo (n=103)		Seroquel SR (n=94)
Hazard ratio (95% CI)		0.16(0.08, 0.34)			0.13 (0.07, 0.25)	
P Value		<0.001			<0.001	
Number (%) of relapses	36 (41.4)		9 (10.7)	50 (48.5)		11 (11.7)
*includes data occurring after interim analysis, before study termination						

PRE-EXISTING ILLNESS SEVERITY OF SCHIZOPHRENIA PATIENTS TREATED WITH OLANZAPINE IN STANDARD OR HIGH DOSES

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To assess whether schizophrenia patients who are treated in usual care settings with high doses of olanzapine have a more severe pre-existing illness profile compared to patients treated with olanzapine in standard doses. We used data from a large multi-site non-randomized 3-year prospective observational study of patients treated for schizophrenia and related disorders in the United States, conducted between 7/1997 and 9/2003 (US-SCAP). Study participation was not contingent upon being treated with a specific antipsychotic or with any drug, and decisions about medication changes, if any, reflected those made by the physicians and their patients. For this analysis illness severity parameters were compared between those treated with high doses of olanzapine (>20mg/day) and those treated only with standard doses of olanzapine (≤20 mg/day), within 1-year of enrollment. Medical record information was used for comparing the two groups during the 6 months prior to olanzapine initiation on rates of psychiatric hospitalization using Chi-square and days of hospitalization using Wilcoxon test. The groups were also compared on symptom severity levels at enrollment using the

clinician-rated (PANSS) and patient-reported outcomes using t-test. A small proportion of study participants (3%, 65/2263) were treated with olanzapine in high doses during the year following enrollment. During the 6 months prior to initiation on olanzapine, the high dose and the standard dose groups did not significantly differ on rates of inpatient psychiatric hospitalization, but the high dose group was hospitalized for a significantly longer total duration (p<.001). Furthermore, the groups did not significantly differ on the PANSS total score, the positive, negative or general psychopathology subscale scores, but the high dose group reported significantly more severe pre-existing symptomatology, especially more severe psychotic and depressive symptoms (all p<.01). In this large prospective observational study of schizophrenia patients treated in usual care settings, high dose of olanzapine was found to be reserved for a small subgroup of patients, who manifest a significantly more severe pre-existing illness profile, characterized by lengthier hospitalized duration and greater severity of reported psychotic and depressive symptoms. Funded by Eli Lilly and Company.

ASENAPINE COGNITIVE FUNCTION EFFECTS IN ACUTE SCHIZOPHRENIA: A PLACEBO- AND RISPERIDONE-CONTROLLED TRIAL

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From a previously reported 6-week, randomized, double-blind study in patients with acute exacerbation of schizophrenia (in which asenapine was well tolerated, superior to placebo on PANSS total score, PANSS positive and negative subscale scores, and CGI score, and superior to risperidone on PANSS negative subscale score), we now report the results of cognitive assessments performed. Patients were randomized to receive asenapine 5 mg twice daily (n=59), risperidone 3 mg twice daily (n=59), or placebo (n=62); a double-dummy placebo design was employed to maintain blinding. A comprehensive neurocognitive test battery was administered after the morning dose at baseline, week 3, and week 6 or last visit; last observations were carried forward for patients who did not complete the trial. The following domains were tested: speed of processing (Category Fluency, Verbal Fluency, Trails A and B, Digit Symbol Substitution Test [DSST]), working memory (Letter-Number Span), verbal learning and memory (Rey Auditory Verbal Learning Test, which includes Immediate and Delayed Recall and Delayed Recognition); visual learning and memory (Benton Visual Retention Test), and reasoning and problem solving (Wisconsin Card Sorting Test [WCST]). Placebo-corrected effect sizes (Dunlap's D) were calculated for individual neurocognitive tests to evaluate the impact of asenapine on neurocognitive functioning in schizophrenia. Asenapine-treated patients demonstrated improvements on tests of verbal learning and memory (Dunlap's D 0.45, 0.38, and 0.25 for Immediate and Delayed Recall and Delayed Recognition, respectively) and speed of processing (0.43, 0.34, and 0.31 for Trails A time, DSST, and Verbal Fluency, respectively). Risperidone-treated patients demonstrated improvements in speed of processing (Dunlap's D 0.31 and 0.24 for Trails A time and DSST, respectively), but their performance worsened in reasoning and problem solving (–0.35 and –0.31 for WCST percentage of perseverative errors and total number correct, respectively). Asenapine is a novel psychopharmacologic agent under development for the treatment of schizophrenia and bipolar disorder. In this study, patients treated with asenapine showed improvements in domains of cognitive function that are particularly relevant to functional outcome in schizophrenia: the speed of processing and verbal learning and memory domains. Further studies are needed to confirm and generalize these observations.

HIGH FREQUENCY RTMS IN THE TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: DOUBLE BLIND RANDOMISED TRIAL

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a)Repetitive transcranial magnetic stimulation (rTMS) presents a new opportunity for influencing negative symptoms of schizophrenia. A theoretical justification can be seen in the fact that high-frequency rTMS has an activating effect on cortex neurons. Another important fact is that dopamine can be released in the mezolimbic and mezostriatal brain systems by high-frequency stimulation of the frontal cortex. The aim of the present double blind randomised trial was to assess the ability of rTMS to alleviate negative symptoms of schizophrenia. b) Schizophrenic patients on stable antipsychotic medication with prominent negative symptoms were divided into two groups. The first one was treated with rTMS while the second one with sham rTMS. The inefficacy of sham rTMS was achieved through stimulation coil position. Stimulation was applied to the left dorsolateral prefrontal cortex. Stimulation frequency was 10Hz. Stimulation intensity was 110% of the motor threshold intensity. Each patient received 15 rTMS sessions on 15 consecutive working days. Psychopathology was rated by PANSS and SANS before and after stimulation, rater was blinded to the kind of rTMS application. c)In real rTMS subgroup (N=11) the mean score of total PANSS was 59,6 (SD=7,9), negative PANSS 21,8 (SD=3,2) and SANS 68,6 (SD=11,8) before treatment. After real rTMS the mean scores of all applied scales dropped statistically significantly: total PANSS 44,8 (SD=5,6;p=0,02 paired t-test), negative PANSS 14,6 (SD=3,2;p=0,01) and SANS 29,4 (SD=11,2;p=0,01). In sham rTMS subgroup (N=11) the mean score of total PANSS was 64,0 (SD=13,1), negative PANSS 21,8 (SD=5,8) and SANS 59,6 (SD=19,1) before treatment. After sham rTMS the mean scores of all applied scales did not change statistically significantly: total PANSS 57,0 (SD=10,3), negative PANSS 20,2 (SD=5,8) and SANS 52,2 (SD=21,2). d)rTMS proved the ability to influence the negative schizophrenic symptoms. The augmentation of rTMS meant for patients decrease of the significance of the negative symptoms. The explanation of this state can be seen in the posibility of the rTMS to influence patophysiologic basis of negative symptoms in different way then it was by antipsychotics. e)In conclusion, our result supports the therapeutic potential of rTMS at higher frequency for negative symptoms of schizophrenia. Supported by the Ministry of Education (Project MSM 0021622404) and Ministry of Health of Czech Republic (grant No. NR 7986-3).

AN INCREASE IN SERUM LIPIDS AND NOT WEIGHT IMPROVES THE SYMPTOMS OF SCHIZOPHRENIA IN SUBJECTS TREATED WITH CLOZAPINE

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Objective: The primary objective of this study was to determine if an increase in serum lipids is associated with improvement in the

symptoms of schizophrenia during steady state treatment with clozapine. Method: The data for this study represents a subset of data from a multi-site international randomized, double-blind trial that evaluated subjects with schizophrenia who demonstrated a poor treatment response to clozapine.(1) While continuing their clozapine therapy, subjects were randomly assigned to receive either risperidone 3 mg daily or placebo for eight weeks. This course of treatment was followed by an optional (open-label) 18 weeks of augmentation with risperidone. In the present study, all subjects who had fasting lipid analyses and Positive and Negative Syndrome Scale (PANSS) scores from days 7 and 63 were included in the analyses (N = 55). For the primary analyses, hierarchical multiple regression was used to test the hypothesis that changes in serum lipid concentrations would predict changes in PANSS total, positive and negative scores after controlling for change in weight. Results: The primary analyses showed that the change in serum lipid concentration predicted antipsychotic response over that of change in weight. Specifically, an increase in serum triglyceride concentration accounted for approximately 8% of the variance of the decrease in the total PANSS score (p = 0.037). In addition, an increase in either serum total cholesterol concentration (p = 0.007), serum triglyceride concentration (p = 0.017) or their combined effects (p = 0.010) were associated with decreases in PANSS negative subscale scores. In this case, these lipid changes accounted for between 11 and 16% of the variance of the change in negative symptoms. Conclusion: Elevation of serum lipids is associated with an improvement in the symptoms of schizophrenia in subjects treated with clozapine. While the mechanism is unclear, serum lipids may play an important role in influencing clozapine's therapeutic activity. 1) Honer WG, Thornton AE, Chen EYH, M.B., Chan RCK, Ph.D., Bergmann A, Falkai P, Pomarol-Clotet E, McKenna PJ, Stip E, Williams R, MacEwan GW, Wasan K, Procyshyn R. A Randomized Controlled Trial of Antipsychotic Polypharmacy: Risperidone Versus Placebo Augmentation of Clozapine in Refractory Schizophrenia. N Engl J Med 2006;354:24-34.

ZIPRASIDONE IN HOSPITALIZED PATIENTS WITH SCHIZOPHRENIA: EVIDENCE FOR RAPID DOSE TITRATION

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Optimal dosing of psychotherapeutic agents has implications not only for symptom control but also for patient compliance. Trials of ziprasidone in bipolar mania and schizophrenia[1,2] suggest a target dose range of 120-160 mg/d and that rapid titration to this level provides maximum symptom improvement. In this report, we analyzed 2 similarly-designed placebo-controlled trials of ziprasidone in the treatment of acute schizophrenia to explore the efficacy and tolerability of rapid titration to 120-160 mg/d. Data from 2 fixed-dose placebo-controlled clinical studies of ziprasidone (rapidly titrated to the target dose of 40, 80, 120, or 160 mg/d) in patients with acute schizophrenia were pooled. These studies used similar populations, dosing protocols, and outcomes measures. A total of 369 patients received ziprasidone and 171 patients were assigned to placebo. Efficacy was assessed using the Positive and Negative Symptom Scale (PANSS) at 1 week and week 6 (LOCF endpoint) of treatment. Tolerability was assessed by discontinuations (all cause and due to AEs) at the relevant visits. There was a significant linear dose-response relationship between ziprasidone dose and PANSS total score ($F=12.32$, $P\leq.001$). All ziprasidone doses produced statistically significant improvement in PANSS total score; the largest effect size was observed for the 160 mg/d group (0.52). At Week 6 (LOCF), least-squares mean PANSS total score decreases from baseline were 9.98, 9.54, 11.71, and 14.87 in 40, 80, 120, and 160 mg/d groups, respectively. The corresponding placebo decrease was 2.79. Tolerability of ziprasidone 160 mg/d was comparable to that of lower doses. Efficacy and tolerability of rapid titration of ziprasidone to 40, 80, 120, and 160 mg/d, within 1 week of treatment, will be presented. Rapid titration of ziprasidone to 160 mg/d was associated with greater efficacy compared to lower doses, and was well-tolerated in these studies. References 1. Keck PE Jr, Versiani M, Potkin S, et al. Ziprasidone in Mania Study Group. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry.* 2003;160:741–748. 2. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:491-505.

IDENTIFYING VARIABLES ASSOCIATED WITH ACHIEVING REMISSION IN PATIENTS WITH SCHIZOPHRENIA

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Remission in patients with schizophrenia has been the focus of numerous recent studies. We hypothesize that certain demographic characteristics and clinical domains may be associated with achieving remission in patients receiving risperidone long-acting injectable (RLAI). In a prior report, we identified several variables associated with achieving remission in a 1-year study of RLAI in stable patients. This analysis was undertaken to investigate these variables in a different 1-year study of RLAI. A post-hoc analysis of data from the intent-to-treat population (N=667) of an international, 1-year, open-label study of stable patients with schizophrenia or schizoaffective disorder assigned to RLAI at 25, 50, or 75 mg every two weeks. Patients were identified as remitted if they met predefined symptom severity criteria (Andreasen et al. AJP. 2005;162:441) for any 6-month period, regardless of baseline status. Assessments included PANSS and the patient-rated quality of life Short Form 36 Health Survey (SF-36). A stepwise multiple logistic regression model explored variables associated with remission. Independent variables included: age, sex, prior antipsychotic treatment, diagnosis (schizophrenia vs schizoaffective disorder), baseline scores on PANSS insight item (range 1-7), PANSS depression/anxiety cluster (range 4-28), and the SF-36 total and subscales (range 0-100). Regression analysis identified the following as variables significantly associated with remission: PANSS insight score (OR=0.65, $P<0.001$), suggesting a 35% lower chance to meet remission with each unit increase (worsening) in insight score; SF-36 mental health index (OR=1.02, $P=0.020$), suggesting a 2% greater chance to meet remission with each unit increase (improvement) in index score; SF-36 vitality dimension (OR = 0.99, $P=0.021$), indicating a 1% lower chance to meet remission with each unit increase (improvement) in vitality score; and diagnosis (OR=1.63, $P=0.052$) suggesting a 63% greater chance of meeting remission for patients with schizoaffective disorder vs schizophrenia. Results identified several variables significantly associated with achieving remission with RLAI. Taken together with findings from a similar analysis of another RLAI database, we found that certain patient characteristics may be associated with subsequent remission in stable patients receiving RLAI. Supported by funding from Janssen, L.P.

PREDICTORS OF OUTCOME AFTER 4 MONTHS OF TREATMENT FOR A FIRST EPISODE OF SCHIZOPHRENIA

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Background: We examined predictors of outcome after 4 months of treatment for a first episode of schizophrenia. Method: 112 subjects (70% male; mean age 23.3 years) with first-episode schizophrenia, schizophreniform disorder or schizoaffective disorder were randomly assigned to olanzapine (2.5 to 20 mg daily) or risperidone (1 to 6 mg daily). Response criteria required ratings on 2 consecutive visits of mild or better on the SADS-C+PD psychosis items plus a rating of much or very much improved on the CGI. Potential predictors examined were: sex; age; education; social class; premorbid social functioning; duration of psychiatric symptoms; duration of untreated psychosis (DUP); baseline positive, negative and depressive symptoms; alcohol, marijuana or other substance use before study entry and during treatment; motor side effects (Parkinsonism, EPS, akathisia) during treatment.Results: 49.1% (95% CI: 38.7%, 59.6%) of patients met response criteria and among those 29.9% (95% CI: 13.5%, 46.2%) failed to maintain their response. In univariate analyses, poor premorbid social functioning, longer DUP, alcohol use before study entry and EPS during treatment were significantly ($p<0.05$) associated with less likelihood of response. In a multivariate model including sex and medication assignment as factors, alcohol use ($p<0.01$) and EPS ($p<0.02$) remained significant predictors of response but DUP ($p<0.06$) and premorbid functioning ($p<0.29$) did not. In univariate analyses, alcohol use and marijuana use during treatment were significantly associated with failure to maintain response; poor premorbid social functioning was associated with response instability but the difference was not significant ($p<0.07$). Alcohol and marijuana use during treatment were highly correlated, thus we used a composite measure for our multivariate model. In this model that included sex and medication assignment, both the composite substance use measure ($p<0.04$) and poor premorbid social functioning ($p<0.03$) were significant predictors of response instability. Discussion: Our finding that substance use occurring before or during the trial affected outcome emphasizes the negative impact of substance use on the outcome of first episode schizophrenia. Our finding that poor premorbid social adjustment is associated with short-term response instability complements data from a previous study that poor premorbid social adjustment is associated with higher relapse risk over the first 5 years of illness.

TREATMENT OF FIRST-EPISODE SCHIZOPHRENIA

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Previous versions of the TMAP schizophrenia medication algorithm did not include a separate algorithm for first-episode patients. In developing the current revision of the algorithm, the panel examined the issue of whether a separate first-episode algorithm was warranted. The evidence available regarding antipsychotic treatment specific to first-episode schizophrenia – in contrast to that for multi-episode patients - is extremely limited. There are almost no data available regarding the newer second generation agents. Data do support the following: Medication doses studied in first-episode trials are lower than those used in typical trials with multi-episode patients. Despite these lower doses, studies have often reported high rates of adverse events. No antipsychotic, including clozapine, has been found to have superior efficacy to another with first-episode patients during an acute psychotic episode. Long term studies suggest that relapse risk following discontinuation of medication is as high as in multi-episode patients. Overall, the panel concluded that the current evidence did not warrant a separate algorithm for first-episode patients. Instead, the panel recommended a statement of principles for clinicians to consider when treating first-episode patients including using low doses of antipsychotics and the need to monitor side effects closely.

QUETIAPINE AND OLANZAPINE COGNITIVE EFFICACY IN A ADOLESCENTS WITH EARLY ONSET PSYCHOSIS

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This study compares changes in cognitive performance after 6 month treatment with quetiapine or olanzapine in a sample of adolescents with a first episode of psychosis. We conducted an open, comparative, randomized, pilot study with 50 adolescents aged 12 to 18, who were consecutively admitted to the Adolescent Psychiatric Unit of the Hospital G.U. Gregorio Marañón (Madrid, Spain), with a DSM-IV diagnosis of psychosis. Diagnostic information was collected at baseline by using the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL). Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Adolescents were randomized in one of two treatment groups quetiapine (n=24) or olanzapine (n=26), stratified by age and gender. The dose administered was determined by the clinician (mean doses at 6 months were 532mg/day for quetiapine and 9.7mg/day for olanzapine). A thorough neuropsychological battery measuring general cognition, attention, learning and memory, and executive functioning, was administered at baseline and after six months of treatment to examine cognitive changes. There was a significant improvement in psychopathology (positive and total subscales of the PANSS) after treatment with quetiapine and olanzapine, but no cognitive improvement was observed for any of the groups. There was no time of assessment by treatment interaction. Our results suggest that quetiapine and olanzapine are not effective for the treatment of cognitive deficits in this sample of adolescents with first episode, early onset psychosis. Lack of cognitive improvement can not be attributed to lack of psychopathological efficacy of quetiapine and olanzapine. Acknowledgments: This study was supported, in part, by Astra-Zeneca.

COGNITIVE GROUP THERAPY PROGRAMS FOR SCHIZOPHRENIA: EMPIRICAL RESULTS AND PRACTICAL CONSEQUENCES

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During the past 20 years our research group in Bern has developed group therapy programs for schizophrenia. Integrated Psychologi-

cal Therapy (IPT) is one of these approaches combining neuro-cognitive and social cognitive interventions with social skills. In the meantime 32 published studies including 1420 patients from 10 countries evaluated IPT. 7 studies are high quality ones (363 patients). A meta-analysis showed positive mean effect sizes favoring IPT over control groups in these therapy domains across different settings (inpatient/outpatient; academic/non-academic) and states of illness (post-acute/chronic). Against the background of these results we developed Integrated Neuro-cognitve Therapy (INT). This group therapy program restitutes and compensates neuro- and social cognitive functions in a more updated and specific way than IPT. INT is partly computer-based and the manual contains exercises to improve the following (MATRICS) areas: Speed of processing, attention, vigilance, working memory, verbal and visual learning and memory, reasoning and problem solving, emotion perception, ToM, social attribution and social schema. The program is embedded in the daily living context of the patients and starts from their resources with a special focus on facilitating intrinsic motivation and group processes. First INT-results (pre/post assessments) with 28 schizophrenia outpatients (DSM-IV) of a randomized multi-center study in Switzerland and Germany are available up to now. They indicate better outcome from 15 INT patients in neuro-cognitive variables, emotion perception, motivation, self-efficacy and self-perceived quality of life in comparison with a TAU control group (13 patients). Patients received 30 therapy sessions (90 minutes each) for 15 weeks. We found only a weak influence on social functioning and none on psychopathology. Further results with all 90 planned participants and data from the 1-year follow-up have to confirm the significance of INT and clarify the impact within other rehabilitation approaches. We conclude from our data and the practical implementation of our programs that (1) an optimal frequency of therapy is twice a week (2) patients with an illness duration lower than 6 years obtain highest effects (3) longer lasting therapies are necessary (at least 3 to 6 months) and (4) no change of therapists over longer time periods is advisable. The work was/is supported by various grants of the Swiss National Science Foundation (SNF).

COMPARING TREATMENT AND CLINICAL RESPONSE IN PATIENTS WITH SCHIZOPHRENIA IN COSTA RICA, MéXICO Y USA

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Introduction: In the US, atypical neuroleptics (AN) are considered first choice treatment for schizophrenia, due to their beneficial effect on negative symptoms and cognition; AN also show lesser severity and frequency of adverse effects when compared with typical neuroleptics (TN). We collected a multinational sample for the study of genetics of squizophrenia in Latino populations, including sites in the US, Mexico and Costa Rica. Therefore, we predicted that patients with schizophrenia in richer countries such as the US, would show lower ratings on scales measuring positive and negative symptoms, higher assessments of functioning and lower ratings on extrapyramidal symptoms scales, compared with poorer countries such as Mexico and Costa Rica. These findings would have implications at the time of defining phenotype subclasses in genetic studies. Subjects and Methods: 257 subjects with Schizophrenia or Schizoaffective Disorder enrolled in the "Genetics of Schizophrenia in Latino Populations" study (Escamilla M et al); 78 from Costa Rica (CR), 99 from Mexico (MX) and 80 from the US. Instruments: DIGS, FIGS, clinical records, SANS, SAPS, and AIMS. List of current medications was obtained from the DIGS. AN included clozapine, olanzapine, aripiprazole, quetiapine, and risperidone; TN included haloperidol, chloropromazine, and other classical neuroleptics; Anticholinergics (ACh): biperiden, benztropin; antihistaminics (AH): diphehydramine, hydroxycine. We did across-country comparisons of frequencies of use of AN, TP, ACh, and AH; SANS and SAPS global scores; and GAF scores, using Chi square or ANOVA. Results: CR sample was older than the MX sample. The US and MX sample had shorter duration of illness than the CR sample. The US had the highest frequency of AN use, followed by MX; CR had the lowest. The MX sample showed higher ratings in both SANS and SAPS and the lowest GAF scores. Patients under treatment with AN showed lower ratings in both SANS and SAPS, independently of country of recruitment. Conclusions: AN use is associated with milder symptomatology (SANS, SAPS, AIMS) independently of country of recruitment. The higher functioning level and relatively milder symptomatology seen in the CR sample, despite higher frequency of TN use, merits further study of gene and environment interactions.

SWITCHING THERAPY FROM CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS TO ZIPRASIDONE IN OUTPATIENTS WITH SCHIZOPHRENIA: AN 8-WEEK, OPEN-LABEL STUDY

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Many patients with schizophrenia may benefit from a change in antipsychotic medication if they are experiencing a suboptimal response or troublesome side effects. This study evaluated the efficacy and tolerability of ziprasidone after switching from conventional and atypical antipsychotics in outpatients with schizophrenia who required a change in medication due to unsatisfactory clinical response or intolerable side effects. A total of 312 outpatients with schizophrenia who had received another oral antipsychotic for > 2 months but required alternative medication were switched to 8 weeks of open-label treatment with ziprasidone (80 mg/d for the first 2 days, adjusted to 40-160 mg/d thereafter). Of these patients, 72.1% switched to ziprasidone due to inadequate efficacy and 26.3% due to poor tolerability (mostly weight gain, hyperprolactinemia, sedation, and sexual dysfunction). Most (228; 73.1%) patients completed the study. Change in Positive and Negative Syndrome Scale (PANSS) total score versus baseline (intent to treat, last observation carried forward) was statistically significant at Week 1 and at the end point (n = 307; baseline 86.7 ± 20.0; mean change: −12.8 ± 18.9; $P < .0001$). Significant improvements were also observed for all 3 PANSS subscale scores. Baseline-to-end–point change in Subjective Well-being under Neuroleptics scale total score was statistically significant (baseline 97.7 ± 25.3; mean change after 8 weeks +9.3 ± 20.3; $P < .0001$). Body weight decreased significantly from baseline to end point (−1.4 ± 2.6 kg; mean baseline 80.2 ± 16 kg; $P < .0001$), as did body mass index (−0.5 ± 0.9; baseline 27.7 ± 5.2; $P < .0001$). There were significant ($P < .05$) baseline-to-end–point improvements in all lipidic parameters: total cholesterol (−13.5 mg/dL), LDL cholesterol (−10.5 mg/dL), HDL cholesterol (+1.4 mg/dL), and triglycerides (−12.6 mg/dL). Glucose serum

level showed a statistically nonsignificant decrease after switching to ziprasidone (−1.8 mg/dL). Mean QTc interval increased by 4 ms. Ziprasidone was generally well tolerated, with 10.9% of patients discontinuing due to adverse events. In summary, switching from conventional and atypical antipsychotics to ziprasidone was associated with significant improvements in efficacy and tolerability, including several important cardiovascular risk factors. These data support the use of ziprasidone for outpatients with schizophrenia who require a change in their current antipsychotic medication.

LONG-TERM EFFICACY OF ZIPRASIDONE IN TREATMENT-RESISTANT SCHIZOPHRENIA: RESULTS FROM THE ONE-YEAR, OPEN-LABEL MOZART EXTENSION STUDY

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We set out to evaluate the efficacy and safety of ziprasidone over a one-year, follow-up period, in a sample of treatment-resistant and/or intolerant schizophrenic patients. Subjects who completed the randomized, double-blind, 18-week, trial (the "MOZART" study, designed to compare clozapine and ziprasidone in terms of efficacy and safety in refractory and/or intolerant schizophrenic patients) and responded to treatment with ziprasidone (≥20% reduction in the Positive and Negative Syndrome Scale [PANSS] total score) were enrolled in a one-year, open-label, multicenter, noncomparative, flexible-dose study. Subjects received the same daily dose of ziprasidone (80, 100, 120, 140, or 160 mg) upon which they completed the double-blind study. An increase in dose was permitted when Clinical Global Impression-Improvement (CGI-I) was ≥5 at any study visit and a dose reduction was permitted in response to adverse events. Study visits occurred at monthly intervals. The primary efficacy assessment was change in PANSS total score from core baseline to study endpoint. A secondary analysis assessed the proportion of patients maintaining ≥20% PANSS improvement at study endpoint. Safety was evaluated on the basis of adverse events, laboratory test results, body weight, vital signs, and electrocardiogram tracings (including the QTc interval). Of 45 patients who completed the double-blind phase of the "MOZART" trial, 44 (97.8%) met the entry criteria for this open study. Of those, 42 patients were enrolled in the study and 40 were included in the intent-to-treat analysis. The mean change from core study baseline in PANSS total score upon entry into the extension study was –37.0 (95% CI, –41.8 to –2.2; P<0.001) upon entry to the extension study. Following one year of treatment with oral ziprasidone, the mean change in PANSS total score from core study baseline was –32.2 (95% CI, –39.1 to –25.3; P<0.001) representing a mean change from extension study baseline of 5.1±16.7 (P=0.061). In the secondary analysis, 28 of the 40 patients (70%) included in the study, maintained ≥20% reduction in PANSS total score (vs core study baseline) at the extension study endpoint. The safety evaluation showed no detrimental effects. These findings show that the efficacy and safety of ziprasidone observed in the first 18-week, double-blind phase, in a sample of treatment-resistant and/or intolerant schizophrenic patients, is maintained also in a long-time follow-up period.

ADJUNCT EXTENDED-RELEASE DIVALPROEX IN LATE LIFE SCHIZOPHRENIA

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This prospective, 12-week open label study investigates the effects of using adjunct anti-convulsant medication(extended-release divalproex) in combination with antipsychotic compounds in older adults with schizophrenia. All diagnoses were confirmed by the Mini International Neuropsychiatric Inventory (MINI) among individuals receiving treatment with either typical or atypical antipsychotic medications. Those with active substance use disorders or active significant medical comorbidity were excluded. Divalproex sodium (valproate) was dosed to a target of 750-1500 mg/day. Primary outcome measures included the Positive and Negative Symptom Scale (PANSS), Geriatric Depression Scale (GDS) and Global Assessment Scale (GAS). In this preliminary analysis, twenty older adults (mean age 61.4 years, range 49.8-79.2 years) had significant reductions in psychosis scores (mean baseline PANSS = 75.3, SD ± 15.2, mean endpoint PANSS (LOCF) = 57.2, SD ± 16.2, p< .001), as well as in global functioning (GAS change from baseline to endpoint mean, p <.001). There was also significant improvement in depression scores. Mean dose of extended-release divalproex was 687.5 mg/day SD ± 263.8. Extended –release divalproex was well tolerated in this older adult population. The primary adverse effect was sedation, which appeared to be relatively dose and titration-speed dependent. Weight change was not significant. While extended release divalproex appears efficacious and well tolerated in older adults with schizophrenia, data from larger, controlled trials is needed. References: Citrome L, Levine J, Allingham B. Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994-1998. Psychiatric Services 2000: 51(5): 634-8 Casey DE, Daniel DG, Wassef AA, Tracey KA, Wozniak P, Sommerville KW. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 2003; 28(1): 182-92 This study was supported by a research grant from Abbott Laboratories.

THE NEUROSTEROID, PREGNENOLONE, REDUCES NEGATIVE SYMTPOMS IN PATIENTS WITH SCHIZOPHRENIA: RESULTS OF A PRELIMINARY DOUBLE-BLIND STUDY

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The neurosteroid, pregnenolone, is enriched in certain regions of the brain and is an indirect agonist of the NMDA receptor. The authors have recently completed a double-blind study of the addition of pregnenolone to patients with schizophrenia on stable medications. As pregnenolone has not been studied in patients with schizophrenia, the primary outcome was tolerability and side effects. Secondary aims included changes in symptoms and cognition. Method: Under double-blind conditions, patients were randomly assigned to one of four groups: placebo, low dose (100 mg/d), slow titration to high dose (500 mg/d), and rapid escalation to high dose. Patients were on study medication for 8 weeks after a 2-week, single blind lead in. Symptoms and side effects were measured every two weeks. Cognitive symptoms were assessed at the beginning and end of the study.

Steroid levels and blood tests were collected at the beginning, middle, and end of the study. Results: 24 out of 32 subjects completed the 10-week trial. Side effects were no higher in any of the pregnenolone treated groups than in the placebo group. There were no changes in weight, vital signs, abnormal movements, or routine blood tests. The analyses of the results utilized a mixed model ANOVAs with treatment group as the between-subjects factor and time as the within-subjects factor. There was a significant reduction in the total PANSS score in the rapid titration 500 mg group. There was a significant reduction in negative symptoms in both 500 mg groups as measured by the PANSS and the SANS with a 30% reduction in negative symptoms as assessed by the SANS. There was significant improvement in measures of verbal memory (as assessed by the Wechsler logical memory scale) and attention (as assessed by a visual sustained attention task). There was no improvement seen in working memory or visual perception. Qualitatively, subjects on 500 mg/d of pregnenolone felt better and requested to remain on the medication despite needing to take 10 extra pills a day. Conclusions: Pregnenolone is a well-tolerated medication in patients with schizophrenia. In this preliminary study, high dose pregnenolone led to a significant reduction in negative symptoms and improvement in some aspects of cognition. These results are being confirmed and extended to measure quality of life in a larger multi-center study. The study was supported by the Stanley Medical Research Foundation and the GCRC of Weill Medical College.

A "VIRTUAL" COMPARISON OF PALIPERIDONE ER AND RISPERIDONE IR IN PATIENTS WITH SCHIZOPHRENIA

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Paliperidone extended release (Pali ER) is an investigational agent using OROS technology to deliver 9-OH risperidone at a therapeutic dose with less plasma level fluctuations than immediate-release (IR) oral formulations. Placebo (PBO) controlled studies in schizophrenia showed efficacy of Pali ER at 3-15 mg/d (6 mg/d=anticipated recommended dose for most patients). The aim was to compare efficacy and tolerability data of Pali ER with risperidone (Ris) IR. All randomized PBO-controlled studies in adults with schizophrenia were identified from the manufacturer's database (3 per agent). Matched populations were selected based on: age 18-65 years, conventional antipsychotic exposure within 90 days, and treatment with Pali ER, Ris, or PBO (n=1103). Pali ER 6-12 mg/d (doses anticipated to be commonly used in schizophrenia) was compared to Ris 4-6 mg/d. Doses hypothesized by pharmacokinetic data to provide similar medication exposure were also compared (6-12 mg/d Pali ER vs 2-4 mg/d Ris). PBO group comparisons examined populations and responses across programs. Measures included PANSS total change at week-6 LOCF, weight, and AE reports. PBO^{PALI} (n=145) and PBO^{RIS} (n=215) groups had comparable PANSS scores and responses ($P>0.05$), with some cross-program differences in specific AE reports. Pali ER 6-12 mg/d (n=275) vs Ris 4-6 mg/d (n=174) had similar completion rates (67.6% and 65.5% respectively), and PANSS endpoint changes (–19.0 and –19.7 respectively; $P=0.83$). AE rates (adjusted for cross-program differences in PBO groups) showed Pali ER was associated with lower percentages of akathisia, restlessness, anxiety, insomnia, somnolence, dizziness, and GI reports. Mean weight change was 1.3±3.7 with Ris and 0.67±2.7 with Pali ER ($P=0.024$). Pali ER 6-12 mg/d vs Ris 2-4 mg/d (n=173) had completion rates of 67.6% and 53.8%, respectively. There was a greater reduction in PANSS total score with Pali ER (–19.0 and –11.4, respectively; $P=0.003$), with lower percentages of akathisia, restlessness, insomnia, somnolence, dizziness, and GI reports, but a higher percentage of tachycardia reports. Findings support the feasibility and value of such virtual comparisons. Results suggest that Pali ER 6-12 mg/d may be similarly efficacious to Ris IR at 4-6 mg/d, with some tolerability benefits; and more efficacious than Ris IR at 2-4 mg/d, with some tolerability differentials. In the absence of direct comparisons, such analyses can guide future research. Supported by Janssen, L.P.

METABOLIC EFFECTS OF BIFEPRUNOX IN PATIENTS WITH SCHIZOPHRENIA

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(a) To examine the metabolic effects of bifeprunox in patients with acute and stable schizophrenia. (b) Metabolic data was compiled from one 6-month and four 6-week studies of bifeprunox in patients with stable and acute schizophrenia, respectively. In the 6-month study, patients received bifeprunox (n=331) or placebo (PBO) (n=166). In the 6-week studies, the pooled treatment groups were: bifeprunox (n=1050), PBO (n=469), haloperidol (n=52), risperidone (n=274) and olanzapine (n=150). All studies were randomized, double-blinded and PBO-controlled; an active reference was included in all 6-week studies. Metabolic evaluations included body weight, body mass index (BMI), plasma glucose and lipid profiles. Fasting glucose and lipid values were assessed in one 6-week study and in the 6-month study. Triglyceride:HDL ratio (TG:HDL) was calculated as a marker of insulin resistance. (c) In the 6-month study, mean weight decreases occurred with bifeprunox (-1.1 kg) and PBO (-0.5 kg) treatment. Similar reductions were noted in 6-week studies (bifeprunox, -0.8 kg; PBO, -0.1 kg). Olanzapine (+2.4 kg) and risperidone (+1.7 kg) groups experienced weight increases. Mean weight loss occurred in patients receiving bifeprunox in all but the lowest BMI group (<18.5 kg/m2), with the greatest weight loss experienced by obese patients (>30kg/m2) in 6-week studies. A minor reduction in mean fasting glucose versus PBO was noted in one 6-week study; minimal glucose changes from baseline in PBO and bifeprunox groups were observed in 6 week and 6 month tests. Total cholesterol (TC) was decreased in the 6-month (bifeprunox, 6%; -0.31 mmol/L vs. PBO, 2%; -0.08 mmol/L) and 6-week studies (bifeprunox, 8%; -0.40 mmol/L vs. PBO, 6%; -0.32 mmol/L). Over 6-months, TG values decreased in the bifeprunox (19%; -0.32 mmol/L) and PBO groups (3%; -0.05 mmol/L). Additionally, a 23% decrease in TG:HDL was noted in patients receiving bifeprunox in the 6-month study, compared to a 4% decrease in the PBO group. Similar decreases in TG (24%, -0.44 mmol/L) and TG:HDL were observed in 6 week studies; the PBO group had comparable reductions in TG (20%; -0.38 mmol/L) and TG:HDL (17%). (d) Decreases in body weight and improvement in lipid profiles were observed in bifeprunox-treated patients. Reductions in weight, TG, TC and TG:HDL were sustained over 6 months. The metabolic profile of bifeprunox suggests that it may be a safe agent for use in the treatment of schizophrenia.

RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED ADJUVANT TRIMETHOPRIM CLINICAL TRIAL FOR THE SYMPTOMS OF SCHIZOPHRENIA

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In recent years evidence has accumulated indicating that some cases of schizophrenia may be associated with Central Nervous System (CNS) infection. One of the infectious agents proposed as a potential cause of schizophrenia is Toxoplasma gondii, a coccidial protozoan of the phylum apicomplexa, which is capable of infecting the human brain. To examine this hypothesis further we conducted a randomized double-blind placebo-controlled clinical trial in Butajira, Ethiopia in which trimethoprim, an anti-toxoplasma medication, was added to the antipsychotic medications the patients were already taking. Ninety-one male patients with a DSM-IV diagnosis of schizophrenia were randomly allocated to treatment and placebo groups using a double blind procedure. The treatment group received 200mg of trimethoprim per day for six months while the other group received placebo for the same period of time. A monthly clinical assessment was conducted. Positive and Negative Symptoms rating Scale (PANSS) score was used as a measure of clinical outcome. At the end of the six month period the preliminary analysis showed a general decline in PANSS mean score in both treatment and control groups over the study period but no significant difference between the two arms. The change in the total and cluster PANSS scores could be due to adherence to the ongoing follow-up and associated improved compliance to antipsychotic medication in both arms. Future trials should consider a wash-out period of 6-8 weeks with antipsychotic medications before the initiation of anti-toxoplasma Gondii medications or restrict the sample to first-onset cases. We will present our preliminary results.

ADJUNCTIVE TREATMENT WITH ARIPIPRAZOLE FOR HALOPERIDOLINDUCED HYPERPROLACTINEMIA: DUOBLE BLIND, PLACEBO CONTROLLED STUDY

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Purpose: We evaluated if adjunctive treatment of dopamine partial agonist, aripiprazole, improves hyperprolactinemia induced by haloperidol and is effective for the treatment of schizophrenia symptoms. Method: Fifty-six patients with schizophrenia who had hyperprolactinemia after taking haloperidol were enrolled in this eight-week, double blind, placebo-controlled study. Haloperidol dose was fixed throughout the study and aripiprazole was dosed at 15mg/day for the first 4 weeks then 30mg for next 4 weeks. Serum prolactin levels were measured by using electrochemiluminescent immunoassays, with commercial kits. The psychopathology and adverse event were rated by clinical rating scale such as BPRS, SANS, CGI-S, SARSBARSDAI at baseline and at weeks 1 2, 4, 6 and 8. Serum haloperidol and aripiprazole levels were measured at the baseline, week 1, 2, 4 and 8. Two-tailed student's t-tes, repeated measures ANOVA, Pearson correlation coefficient was used to analyze the data. Result: Baseline prolactin levels were not significantly different between two groups. During the eight week study, prolactin levels in aripiprazole group, as compared to placebo group, were significantly lowered demonstrating a significant time effect ($p<0.0001$) and time by group interaction ($p<0.001$) on repeated measure ANOVA.. No time effect was present in the placebo group over time. The percent decrease in prolactin levels for aripiprazole group was 29.9±19.0% (range;8.3% to 67.1%, Median; 19.4%) and 22.4±19.1% (range;4.3% to59.2%, median; 12.4%) from baseline levels at weeks 4 and 8, respectively. Among the 11 female patients with menstrual disturbances in the aripiprazole group, 7 patients regained menstruation during study, while no patients in placebo group. No significant effect over time and time by group interaction in total and subscale scores were noted for the BPRS or SANS, however, the number of responders, (defined by SANS total scores), was significantly higher in aripiprazole (8/26 ; 30.8%) as compared to the placebo group (4/28; 14.3%). Conclusion: Adjunctive aripiprazole treatment reversed hyperprolactinemia in both sexes, resulting in regaining menstruation in female patients, with overall no significant effect on psychopathology and extrapyramidal symptoms.

ATTENTION SHAPING PROCEDURES AS A MOTIVATION-BASED INTERVENTION TO IMPROVE ATTENTIVENESS AND SKILL ACQUISITION IN CHRONIC SCHIZOPHRENIA PATIENTS

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Impairments in attention are common in schizophrenia, and these interfere with the ability of patients to attend to, and learn information presented to them in skills training interventions. Moreover, attentional deficits are often not significantly improved by pharmacotherapy as they can represent a combination of cognitive and motivational deficits. Several published reports have indicated the effectiveness of the behavioral technique of shaping for improving attentiveness and treatment engagement among treatment-refractory schizophrenia patients. This presentation reports data from the first randomized, controlled, multi-site trial of a manualized version of attention shaping procedures (ASP). ASP involves the use of individualized, within-group, attentiveness goal-setting; specific behaviorally-oriented feedback procedures and interpersonal prompting techniques; and the systematic use, and eventual fading, of extrinsic reinforcers. Chronic schizophrenia patients were randomized to receive either ASP (n=47) within the context of social skills training (the UCLA Basic Conversation Skills Training module), or to receive social skills training in the standard format (control group; n=35). Outcome variables included pre-post changes in skill acquisition and overall attentiveness, slope of changes in within-group attentiveness over time, and symptomatology. Results indicated signficantly greater changes in attentiveness (1100%+), and significantly greater rates of skill acquisition (66% greater) in the ASP condition compared to controls. Among patients in the ASP condition, changes in attentiveness were not related to changes in medication dose or to symptoms. These data suggest that ASP is an effective method for promoting attentiveness and skill acquisition among chronic schizophrenia patients who are generally considered poor candidates for such interventions due to attention or motivation deficits.

EFFECTS OF OLANZAPINE AND RISPERIDONE ON C-REACTIVE PROTEIN AND INTERLEUKIN-6 IN PATIENTS WITH SCHIZOPHRENIA

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Second generation antipsychotics have been associated with weight gain and diabetic metabolic type changes which may also be associated with increased cardiovascular risk. C-reactive protein(CRP) and interleukin-6 (IL-6), inflammatory markers, have been associated with increased risk for cardiovascular disease and, in some reports, with increases in diabetes or insulin resistance. We have studied CRP and Il-6 response during 5 months of treatment with Olanzapine or Risperidone in chronically hospitalized patients with schizophrenia or schizoaffective disorder, most of whom had been treated with first and second generation antipsychotics during their prior course of treatment. We report results in a preliminary sample of 42 patients. Patient were randomly assigned to treatment with either Olanzapine or Risperidone for 5 months. CRP was evaluated in fasting samples at baseline and months 1 to 5 of study drug treatment and IL-6 was evaluated at baseline and month 2 of study treatment. Neither mean CRP or IL-6 levels were grossly elevated at baseline or during drug treatment and only a few patients had CRP levels above 1.0 at any time point. There were no differences in the effects of treatment with Olanzapine or Risperidone on CRP or IL-6 levels. Repeated measures ANOVA showed no significant time or drug x time effects and independent samples t-tests showed no significant differences between drug groups at any time point. In this sample there were no statistically significant correlations of CRP or IL-6 with measures of fasting glucose, cholesterol, triglycerides, or other lipid measures, and no significant correlations with insulin resistance as measured by HOMOIR. In conclusion our preliminary results do not suggest abnormalities in these inflammatory markers during treatment with the second generation drugs Olanzapine or Risperidone and no differential drug effects of these 2 antipsychotics on these inflammatory markers.

FMRI-GUIDED TMS TREATMENT FOR MEDICATION RESISTANT HALLUCINATIONS

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ABSTRACT BODY: Several studies have shown rTMS to be an effective treatment for medication-resistant hallucinations in schizophrenia. rTMS is generally directed at the left temporo-parietal area. However, the cerebral localisation of hallucination-related activity may vary considerably between patients. Therefore, prior determination of the location of main hallucination-related brain activity in individual patients may provide a more precise location for rTMS treatment. In this study we aimed to assess whether improves efficacy of rTMS treatment for medication-resistant hallucinations. 13 schizophrenia patients were selected who experienced frequent auditory-verbal hallucinations (at least once per hour), resistant to two or more trials of antipsychotic medication. All patients were scanned during one hour at a 3T MRI scanner, in which they indicated the experience of hallucinations by air-mediated button press. Successful activation-maps were acquired in 7 of 13 patients. These patients were treated with rTMS directed at the largest area of hallucination-related activation, which was the right temporo-parietal area in 5 patients and the left temporo-parietal area in 2 patients. The remaining 6 patients were treated at the standard left temporo-parietal area. Both groups were equal in severity of psychosis and hallucinations at baseline. Both patient groups were treated with rTMS at 1Hz on 15 days during 20 minutes. In both groups the frequency of hallucinations decreased significantly, with largest improvement after the first week of treatment ($F(1,11)=3.2$, $p=0.008$). There was a trend towards more improvement in the fMRI-guided group ($F(1,11)=1.7$, $p=0.1$). In conclusion, fMRI-guided rTMS treatment is feasible in approximately 50% of selected patients. In these patients, most hallucination-related activity was in the right temporo-parietal area. fMRI-guided rTMS may be more effective than non-guided rTMS, but replication in a larger sample is needed.

Focus of rTMS treatmtn in fMRI-guided and non-guided treatment

Treatment Group	Hemisphere	Area stimulated
fMRI-guided 1	R	supramarginal gyrus
fMRI-guided 2	L	superior temporal gyrus
fMRI-guided 3	R	supramarginal gyrus
fMRI-guided 4	R	superior temporal gyrus
fMRI-guided 5	R	angular gyrus
fMRI-guided 6	R	angular gyrus
fMRI-guided 7	L	supramarginal gyrus
all non-guided (n=6)	L	EEG-location T3-P3

A NURSING TOOL TO ENHANCE ADHERENCE AND RECOVERY IN PSYCHOSIS

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Adherence to medications is a problem in medicine generally, and can be even more compromised because of poor insight in patients with psychotic illnesses. Poor insight makes successful collaborations in treatment more difficult and is an exceptionally troubling impediment to improvement. Increasing adherence and insight may enhance the potential for recovery. At present, there are few cost-effective strategies to improve insight in psychosis. We developed the Levels of Recovery from Psychotic Illnesses Scale (LORS) as a teaching tool for patients with psychotic illnesses. It is designed to identify strengths and weaknesses in insight in order to provide the basis for an intervention to enhance and promote change and recovery. The State of Massachusetts Department of Mental Health Treatment Guidelines for Schizophrenia (1999) cites the LORS as an example of an educational tool for this population. The most clinically compelling use of the LORS was using it as an intervention with patients, what we have defined as the LORS Enabled Dialogue or LED. Design and Methods: The purpose of this study is to assess an intervention that increases insight into mental illness, promotes adherence to medications and enhance recovery. The study is being done over four months for each of 90 inpatient and outpatient subjects with psychotic illnesses in which we are performing the LED intervention. We measure insight using the discrepancy index of clinician and subject LORS scores. Assessment is being measured through changes in the scores of 5 psychometric scales as well as hospitalizations one year after completion of the study. Forty-five subjects are assigned to LED intervention and 45 to treatment as usual. The LED intervention utilizes principles of motivational interviewing as a therapeutic method to begin the process of educating subjects

about mental illness. The LED asks the patient a number of open-ended questions related to their overall goals. The LED communicates with the subject about overall recovery goals and current symptoms that may interfere with theses goals. Discrepancies between the clinician's assessment of functions on the LORS and the subjects' own understanding of symptoms on the LORS are emphasized, which serves to help motivate more helpful participation in treatment in order to attain goals. This abstract will present the preliminary results of this study to date. This study is funded by Lilly Pharmaceuticals.

AN OBSERVATIONAL STUDY OF INTRAMUSCULAR OLANZAPINE TREATMENT IN ACUTELY AGITATED PATIENTS WITH BIPOLAR I DISORDER OR SCHIZOPHRENIA

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The objective of this study was to evaluate intramuscular olanzapine treatment of acute agitation in usual clinical practice, allowing study of more severely agitated patients than in prospective, controlled clinical trials. This was an open-label, multi-center, 1-week, observational study of intramuscular olanzapine treatment in acutely agitated patients (n=74) with bipolar I disorder, manic or mixed (n=22) or schizophrenia/schizoaffective disorder (n=52) who were inpatients or presented to emergency departments. The primary measure was the change in Positive and Negative Syndrome Scale-Excited Component scores during the first 2 hours after the first IM injection of olanzapine. Categorical response was a rating of mild or less on each item (tension, uncooperativeness, hostility, impulsivity, and excitement) of that scale. Sedation was assessed by the Agitation Calmness Evaluation Scale. At 2 hours after the first injection of olanzapine (mean dose=9.9 mg), agitation was significantly reduced by 19.2 ± 0.98 points ($p<.001$) from baseline (mean=29.0) with a mean level of sedation consistent with mild calmness. Over 90% of the patients received only 1 injection in the first 24 hours, and 50% of patients had a categorical response within 30 min. While both patients with schizophrenia and bipolar disorder had significant reductions in agitation within 15 minutes ($p<.05$), the response pattern differed between the two disorders. Treatment-emergent adverse events that occurred in ≥4% of patients included insomnia (9.5%), arthralgia (7.9%), and headache (6.3%). Severely agitated patients with bipolar I disorder or schizophrenia experienced a rapid reduction in agitation with a single injection of intramuscular olanzapine without excessive sedation or serious treatment-emergent adverse events. Funded by Eli Lilly and Company

CARDIAC RISK FACTORS AND SCHIZOPHRENIA: AN ANALYSIS OF 18,094 PATIENTS ENROLLED IN AN INTERNATIONAL COMPARATIVE TRIAL OF OLANZAPINE AND ZIPRASIDONE

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Ziprasidone has modest QTc-prolonging effects, but it is not known if this translates to increased risk of cardiovascular events. The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), a large (N>18,000), international, open-label, randomized, post-marketing study, has been conducted to address this issue. To describe baseline characteristics, including cardiac risk factors, of patients with schizophrenia enrolled from a variety of psychiatry practice settings in an international large simple trial of ziprasidone and olanzapine. A physician-administered questionnaire collected baseline information on demographics, medical and psychiatric history, and concomitant medication use. Data were self-reported by patients or reported by enrolling physicians. Selected baseline data on 18,094 patients are presented here. ZODIAC enrolled a total of 18,240 schizophrenia patients (mean age, 41.6 years; 55.1% male; 60.0% white), primarily from the United States or Brazil (73.0%). Approximately 18% of patients had hypertension, 14.8% hyperlipidemia, 46.5% currently smoked, 28.9% had a body mass index of ≥30 kg/m^2, and 7.7% had diabetes at baseline. Mean time since schizophrenia diagnosis was 10.4 years, and average Clinical Impression Score was 5.2 (range, 1-8). At baseline, 71% of patients were using antipsychotics. Almost 80% of patients were using concomitant medications, yet less than 3% were using antihypertensives or statins. In conclusion, the ZODIAC baseline data suggest that this study population has a substantial prevalence of cardiovascular risk factors and that, hyperlipidemia and hypertension may be undertreated.

POSITION OF OLDER ANTIPSYCHOTICS IN TMAP

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For treatment of individuals with chronic (multi-episode) schizophrenia we reviewed evidence regarding the use of older antipsychotics (i.e., antipsychotics available before clozapine was approved for use in the U.S. in 1989). We did not find strong evidence to support classifying antipsychotic drugs into "atypical" and "typical" categories or considering them as distinct drug classes. Except for clozapine in individuals with poor response to previous drug trials, there was no strong evidence of an efficacy advantage for any drug. Antipsychotic drugs seem to distinguish themselves mainly in the incidence and severity of adverse effects, including extrapyramidal side effects, weight changes, sedation, sexual dysfunction, anticholinergic effects, hypotension, and effects on lipid and glucose metabolism. Current evidence indicates lower rates of tardive dyskinesia with newer antipsychotics, but use of higher than needed doses of the older medications may have contributed to this disparity. For individuals in need of a new antipsychotic drug trial, we recommend treatment with a single antipsychotic selected collaboratively. Drugs with a high risk of undesired side effects should be avoided. Higher doses of older drugs should be avoided. If poor adherence to oral medication regimens is a concern, long-acting injectable medications should be considered.

EFFECTS OF RISPERIDONE LONG ACTING INJECTION (RLAI) ON BRAIN ACTIVATION DURING WORKING MEMORY EXPERIMENTS IN PATIENTS WITH SCHIZOPHRENIA

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There are indications that switch from conventional depot medication to risperidone long acting injection (RLAI) is associated with

psychiatric and neurologic improvements in people with schizophrenia. The aim of this study was to determine the effect of RLAI on brain functioning and cognitive performance during the working memory task. Method. 16 schizophrenia patients on RLAI, 16 schizophrenia patients on conventional depot medication (CONV) and 8 healthy control volunteers (NC) entered the study. Patient groups did not differ in terms of their positive and negative symptoms as well as quality of life scores. All subjects participated in a functional MRI study of working memory during which they performed experiments with increasing difficulty of task (1-, 2-, 3-back) vs. an active baseline. They have also completed off-line experiments on letter-digit span, verbal learning memory, block design, implicit face recognition memory. Results. Repeated measures 3 x 3 ANOVA for the whole brain activation with memory load (1-back, 2-back, 3-back) as a within-subjects variable and group (NC, CONV, RLAI) as between-subjects variable was performed to examine possible main effects and interactions. This analyzis produced a differentially activated cluster (x = -11/+14, y = 22/52, z = -13/-9) located bilaterally in Ventro-medial prefrontal cortex (VMPFC). This cluster was accounted for by significantly greater activation in CONV in 3-back condition, compared with RLAI: Mann-Whitney U=51; p=0.004. RLAI and NC tended to deactivate this cluster, whereas CONV had an opposite (positive) trend of the activation. The three groups did not differ in their on-line performance in any of three working memory tasks. The CONV group performed significantly worse than NC and RLAI in off-line experiments with letter-digit span task. Conclusions. An abnormally increased activation in VMPFC in CONV patients may reflect their inefficient cognitive strategy during working memory task with the high memory load. Patients on RLAI demonstrated a brain activation pattern which did not differ from that detected in NC. This may indicate a normalization of functioning of neural structures implicated in working memory in patients receiving RLAI.

AKATHISIA IN SCHIZOPHRENIA PATIENTS TREATED WITH ARIPIPRAZOLE, HALOPERIDOL, OR OLANZAPINE - ANALYSES OF THE FIRST 12 WEEKS OF THREE DOUBLE BLIND, LONG TERM TRIALS

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Atypical antipsychotics (AAs) have an improved tolerability profile compared to typical drugs (TAs). Most AA clinical concerns focus on changes in metabolic parameters induced by some drugs in this class. Akathisia is an EPS less frequent with AAs compared to TAs. Aripiprazole has a unique mode of action compared to other AAs; its partial D2 agonism and lack of histaminergic and cholinergic receptor affinities account for its clinical characteristics, including a benign metabolic profile. Clinical experience has suggested that akathisia may be more frequently associated with aripiprazole than with other AAs. A post hoc analysis was conducted to assess akathisia characteristics in schizophrenia patients receiving aripiprazole (Ari), olanzapine (Olz), or haloperidol (Hal), in the first 12 weeks of treatment. Three double-blind randomized trials were included: a 52-week comparison of Ari 30mg/d vs Hal 10mg/d and pooled data from 2 trials (26- and 52-week) of Ari 15-30mg/d vs Olz 10-20mg/d. The following akathisia parameters were assessed: incidence, time to onset, duration, severity, and scores on the Barnes Akathisia Rating Scale (BARS). Most patients reported akathisia in the first 12 weeks of treatment with severity usually rated as mild/moderate (≥ 80% of cases). The percentage of patients with akathisia (BARS) at week 12 was significantly higher for Hal vs Ari ($p<0.0001$) and did not differ between Olz and Ari ($p=0.1$). Consistent with previous reports, the TA haloperidol was associated with higher rates of akathisia than the AAs aripiprazole and olanzapine. Under double-blind conditions, for all drugs, akathisia occurred early, was time-limited, of mild to moderate severity, and associated with high rates of concomitant BZD use. Contrary to other reports, akathisia was not associated with high rates of discontinuation. The high use of BZD in all groups may have influenced its clinical presentation, as this class of drugs have been successfully used to manage akathisia.

	Aripiprazole versus Haloperidol		Aripiprazole versus Olanzapine Trials	
	Aripiprazole	Haloperidol	Aripiprazole	Olanzapine
Incidence at endpoint (%)	12.5	24.1	10.7	6.1
% of patients reporting akathisia in first 12 weeks	89.6	92.5	94.4	90.2
Median day of onset	16.5	11.5	13	15.5
Median duration (days)	13	17	7	7
Discontinuation due to akathisia (%)	0.9	2.8	1.2	0.2
Benzodiazepine (BZD)use among patients reporting akathisia	77.1	86.5	86.3	75
% of patients with BARS Global Assessment ≥ 2	9	25.5	9.4	6.6

THE PHARMACOLOGY OF PSYCHOSIS

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Psychosis is a dimensional symptom profile characterized by disorganization of thought, delusions and hallucinations. It can be seen in multiple diagnostic classifications, including schizophrenia (SCZ), bipolar-1 disorder (BD-1), schizoaffective disorder (SAD), dementia, and even in primarily medical conditions. The phenomenology of psychosis as well as its pharmacology is relatively common across diagnostic categories. Psychosis responds either partially or wholly to antipsychotic treatment with a 1st or 2nd generation drug (APD). These are dopamine receptor antagonists or low intrinsic activity partial agonists; in addition, APDs have affinities and activities at other monoamine receptors, particularly at the serotonin-2a receptor. In SCZ and SAD, because the psychosis is chronic, APDs are prescribed chronically. Here, APDs reverse the psychotic symptoms, but generally leave the primary cognitive and negative symptoms untouched. In BD-1, where psychosis may be episodic, their use is more targeted; however, APDs during acute manic episodes are often necessary for good response in BD-1 with psychosis. Mood stabilizers are important to overall good outcome over time in BD-1. Curiously, mood stabilizers are often used in SCZ and even more in SAD for concurrent mood symptoms, but with only a slim published literature to support it. The use of other pharmacological probes, including partial dopamine agonists, glutamatergic drugs, and other monoamine ligands, will be reviewed.

A 6-WEEK PLACEBO-CONTROLLED STUDY OF THE SAFETY AND TOLERABILITY OF FLEXIBLE DOSES OF ORAL PALIPERIDONE EXTENDED-RELEASE TABLETS IN THE TREATMENT OF SCHIZOPHRENIA IN ELDERLY PATIENTS

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Paliperidone ER has a demonstrated efficacy and favorable side effect profile in schizophrenia patients aged ≥18 years. The purpose of the study was to evaluate the safety and tolerability of paliperidone extended-release tablet (paliperidone ER), an investigational psychotropic agent delivered using OROS® technology over a 24-hour period, in elderly patients with schizophrenia. In this international, 6-week, double-blind, placebo-controlled study, patients with schizophrenia (age ≥65 years; mean Positive and Negative Syndrome Scale [PANSS] total score=70—120) randomly received placebo (n=38) or 6mg/day paliperidone ER (n=76; with increase to 9mg/day after 7 days if tolerated, thereafter flexible dosing of 3—12mg/day in 3mg dose increments). All randomized patients who received ≥1 dose of study medication were included in the safety analysis set. Safety assessments included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), laboratory tests, vital signs, physical findings and bodyweight. Major efficacy measurements included change in PANSS total score at end point. The safety analysis set=114 patients, mean age=70 years, baseline mean PANSS total score=92.6±9.5 and mean modal paliperidone ER dose=8.3mg/day. Study completion rates=84% and 68% for paliperidone ER and placebo, respectively, while treatment discontinuations due to AEs=7% and 8%, respectively. The TEAE incidence was comparable for paliperidone ER (67%) versus placebo (71%). Movement disorder related AEs occurred at equal rates in both treatment groups (13%). SAEs were reported in the paliperidone ER (3%) and placebo (8%) groups. Two patients died in the placebo group (cardiac arrest and intracranial hemorrhage). No prolactin or glucose treatment-related AEs were observed. Mean±SD weight change (kg) at end point in the paliperidone ER group was –0.05±2.10 versus –0.01±2.34 in the placebo group. An increase in bodyweight of ≥7% was only experienced with placebo (3%). The mean±SD change in PANSS total score at endpoint was –14.6±14.6 (paliperidone ER) and –9.9±15.0 (placebo) (LSM difference: –5.5; 95% CI: –9.85 to –1.12). In elderly patients with schizophrenia, a population that may be more vulnerable to medication side effects, paliperidone ER (3—12mg/day) was generally well tolerated and safe and appeared effective over this 6-week study period. Supported from funding from Johnson & Johnson Pharmaceutical Services, LLC and Johnson & Johnson Pharmaceutical Research and Development.

COGNITIVE TRAINING INTEGRATED IN OPUS TREATMENT OF PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA

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The study examines the effect of cognitive training on cognitive functioning and everyday competencies of patients with schizophrenia. 120 patients are expected to be included in this randomized controlled trial running at two sites in Denmark starting October 2006. The effect of a 16-week, manualized program of cognitive training integrated in a comprehensive psychosocial treatment (OPUS) for first-episode schizophrenia patients is compared with the effect of standard treatment (OPUS). A six month follow-up assessment is conducted to investigate a possible long-term learning effect of cognitive training. Blinded assessments include the MATRICS Consensus Cognitive Battery and a co-primary outcome measure of cognitive improvement: A translated version of the UCSD Performance-based Skills Assessment (UPSA) adjusted to a Danish context. The cognitive training consists of four modules focusing on the domain of attention, executive functioning, learning and memory. Module 1 and 2 are based on computer-assisted training tasks, and the following modules focus on more practical everyday tasks and calendar training. Cognitive training takes place twice a week and every other week the patient and trainer engage in a dialogue on the patient's cognitive difficulties, motivational goals and his/her progress in competence level. The use of errorless learning principles, scaffolding and attentional externalisation aims at improving the patients' performance on cognitive and everyday tasks by learning to apply compensation techniques as well as limiting dysfunctional uses of available cognitive ressources (i.e. excessive self-focus, rumination). The study will provide MATRICS Consensus Cognitive Battery results from a relatively large Danish sample of first-episode schizophrenia and contribute with valuable normative data on the UPSA. It is hypothesized that cognitive training integrated in OPUS treatment enhances both cognitive and everyday competence of patients more than OPUS treatment alone. Expectations are that cognitive training will demonstrate a small to moderate effect on cognitive functioning and a moderate effect on everyday functioning as measured with the UPSA. Moreover, patients allocated to cognitive training are expected to show an improvement in self-esteem.

FOR HOW LONG CAN WE TREAT A PATIENT WITH THE SAME ANTIPSYCHOTIC DRUG?

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Introduction: Overall treatment effectiveness in patients suffering from schizophrenia can be measured by the duration of antipsychotic treatment. Several recent studies found olanzapine to be associated with significantly longer continuation of treatment relative to a range of other antipsychotic drugs of the second generation (AP2). The duration of follow-up in these studies was usually relatively short, the longest being about two years. This is a report about an attempt to find the most successful antipsychotic drug using the duration of its administration in routine private out-patient practice as criterion of success. Method: all medical records of patients fulfilling the criteria for the diagnosis of schizophrenia (F20 according to ICD 10) during the last ten years were examined and the drugs prescribed to these patients for the longest periods were recorded. Results: 56 patients suffering from schizophrenia were identified. One patient was treated with clozapine for 31 years. Compared to other AP2, sertindol was taken for the longest periods: in two patients for 9 years, in one for 8 years, in two for 7 years and in six patients for 5 years. The next AP2 with longest treatment time was risperidon with four patients treated for 5 years. Discussion: The data obtained by an examination of medical records of one private out-patient psychiatric clinic could not bring unequivocal evidence that the choice of sertindol is the most reliable way of maintaining a patient on the same antipsychotic drug for the longest time. The bias which might be involved in the design of this study does not permit such a conclusion. Nevertheless, the method, the strict naturalistic setting and

the long time of follow-up can be considered a contribution, when trying to find differences in the efficacy of antipsychotic drugs. Conclusion: sertindol was detected as the antipsychotic which schizophrenic patients have taken for the longest period as compared to other antipsychotic drugs in one routine out-patient clinic.

EARLY-ONSET ANTIPSYCHOTIC ACTION IN THE TREATMENT OF AGITATED PATIENTS

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Objective: To evaluate early response (within the first 24 hours) in psychosis and agitation symptoms with ziprasidone IM treatment. Methods: In two 24-hour, double-blind studies, hospitalized patients with psychotic disorder and acute agitation were randomized to treatment with fixed doses of ziprasidone 2 mg IM (N=94), 10 mg IM (N=64, Study 1), or 20 mg IM (N=40, Study 2). Efficacy evaluation was based on the PANSS scale at baseline, 4 hours, and 24 hours. Improvement in psychosis was evaluated by the PANSS positive subscale and an additional early psychosis factor score (conceptual disorganization, hallucinatory behavior, and unusual thought content) used in previous research.1 Results: Ziprasidone IM showed a significant ($p<0.05$) dose-related effect (20 mg vs. 2 mg) on the PANSS early psychosis factor (EPF) score (conceptual disorganization, hallucinatory behavior, and unusual thought content)1 and PANSS positive subscale, at the first post-baseline time point (4 hours) and at 24 hours. Dose-related response in overall psychopathology ($p=0.02$) and reduction of acute agitation symptoms ($p=0.02$) were also observed as early as 4 hours. No statistically significant difference in these outcome measures was observed between the 10 mg and 2 mg groups during the first 24 hours of treatment. Mediator analyses suggest this early response in psychosis (ERF or PANSS positive symptoms) with ziprasidone treatment can be partially explained by improvement in agitation (assessed by the PANSS-EC) ($p<0.001$, mediator effect). Conclusions: Ziprasidone produced a rapid (within 4 hours) and significant dose-related response in the treatment of subjects with psychotic disorders, as measured by changes in psychosis measures (EPF or PANSS positive subscale), agitation (PANSS EC factor score), and overall psychopathology (PANSS total score). Our findings suggest that in addition to reduction in acute agitation, ziprasidone IM may be associated with a more rapid improvement in psychotic symptoms than has been previously reported. These results support the early onset of antipsychotic action hypothesis by demonstrating the potential for rapid drug effects on both psychosis and agitation.

IMPROVING ANTIPSYCHOTIC ADHERENCE IN SCHIZOPHRENIA: A RANDOMIZED PILOT STUDY OF A BRIEF CBT-BASED INTERVENTION

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Background: Most medication adherence strategies can assume that patients accept a diagnoses. However, many schizophrenia patients disagree with their diagnoses. Such patients might benefit from adherence strategies that bypass a diagnostic label. Cognitive Behavior Therapy (CBT) relies on a symptom rather than diagnosis-based approach and works with patients' personal beliefs and goals. We used a CBT platform to develop and pilot a new intervention to improve antipsychotic medication adherence. Methods: Recently relapsed schizophrenia patients who responded to oral antipsychotic therapy were invited to participate in a pilot study of CBT-Adherence Intervention (CBT-AI). Consenting subjects were randomized to either continue with Treatment as Usual (TAU), or to add a 12-session CBT intervention, based on the CBT Insight Programme(CBT-IP)developed by DT and adapted to address medication adherence. Therapists, initially trained in CBT-IP, received weekly supervision by PJW for the adherence focus and DT for CBT techniques. CBT sessions were recorded. Primary outcome measures were adherence attitude measured by the Rating of Medication Influences (ROMI) and adherence behavior defined by time until first episode of nonadherence. Other outcomes included changes in symptoms, "insight", and satisfaction with CBT-AI. Results: 88 patients were screened between 10/04-3/05; 41 were eligible, 19 consented and 16 were randomized (CBT n=9, TAU n=7). Subjects were relatively young (mean 33.2 years), 58% men, and had been ill for 8.1 years. Four of 9 CBT subjects completed 12 sessions, (range 1-12), mean/SD 7/4.8. Sessions were consistent with the original CBT platform; all therapists achieving passing CBT fidelity scores based on review of audiotaped sessions (mean score 37.7; comparable to CBT-IP therapists certified in the UK with "passing" > 30). CBT-AI subjects were significantly more likely to endorse reasons for both adherence and nonadherence. There was a trend suggesting that time to nonadherence was longer in the CBT group; at the 4 month assessment, 5 of 6 TAU subjects had stopped medication compared to 3 of 9 CBT subjects. Conclusion: This study cannot separate nonspecific effects of increased therapist attention from the specific effects of CBT-AI. The changes in adherence attitudes as well as a trend in improved adherence behavior in the CBT group support the hypothesis that a CBT platform can be adapted to improve medication adherence.

A COMPARISON OF BUPROPION SR AND PLACEBO FOR SMOKING CESSATION

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Schizophrenia patients have a higher rate of smoking than the general population and are less likely to receive smoking cessation interventions. Cigarette smoking places them at higher risk of serious lung and cardiac disease, contributing to the premature death rate observed in people with schizophrenia. This poster will report on the use of combined group therapy and adjunctive bupropion SR for the treatment of cigarette addiction in patients with schizophrenia. Of 58 patients who signed consent, 42 were included in the study, and of those, 32 completed the treatment phase. All subjects participated in a 9 session supportive/educational group and received either bupropion 150mg twice daily or placebo for a total of 14 weeks. Outcome measures that will be reported, include a comparison of baseline to end of study change in end-expired carbon monoxide levels, urine cotinine levels, and scores on the Fagerstom Test for Nicotine Dependence. Secondary outcomes measures will include changes in symptom ratings, motivational assessments, and neuropsychological measures of memory and attention. One-year smoking follow-up for five subjects will be described.

THREE-YEARS REHOSPITALIZATION RATES OF PATIENTS DISCHARGED: A COMPARISON BETWEEN HALOPERIDOL, RISPERIDONE AND CLOZAPINE

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A major indicator of drug effectiveness in patients with schizophrenia is prevention of relapse and hospitalization. It is well established that maintenance treatment with antipsychotic drugs decreases relapse rates which is important for improving outcomes for people with schizophrenia. The literature is sparse in terms of the evaluation of the risks of relapse and rehospitalization of patients with schizophrenia receiving conventional antipsychotic or second generation antipsychotic, although evidence suggest derived from meta-analyses that second generation antipsychotics are associated with a lower risk for rehospitalization than conventional antipsychotics. Objetive: The purpose of this study was to compare the rehospitalization rates of patients discharged from a university hospital while being treated with conventional antipsychotis (haloperidol) or atypicals (risperidone or clozapine). Method: This study evaluates the risk of readmission in patients discharged from the Institute of Psychiatry of Clinical Hospital of University of São Paulo School of Medicine between Jan. 1, 1997 and Dec. 31, 1999 on haloperidol (N = 43) or risperidone (N = 22) or clozapine (N = 31). Time to readmission over the course of 3 years was measured by the product-limit (Kaplan–Meier) method. Results: The readmission rate at 12 months was 16% for patients discharged with haloperidol, 27% with risperidone and 10% with clozapine. At 24 months such rates were 21% for haloperidol, 41% for risperidone and 16% for clozapine. The readmission rate for risperidone and clozapine treated patients appeared to be steady up to 36 months and it raised to 26% for haloperidol treated patients. The rate of rehospitalization was significantly lower for the group treated with clozapine compared to the rate for the group treated with risperidone, and that difference is maintained at 24 months (log rank=4,98, dif=1, p=0,0256) and 36 months (log rank=4,95, dif=1, p=0,0261). Conclusion: This study demonstrates that the rehospitalization rates of patients taking clozapine and risperidone are similar to those reported in previous studies, whereas the rehospitalization rates of patients taking haloperidol are lower than those previously reported.

EFFECTS OF RISPERIDONE MICROSPHERES ON POLYPHARMACY AND COGNITIVE FUNCTION

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Background: When a patient with a psychotic disorder has an incomplete therapeutic response to an antipsychotic, the treating clinician may add a second antipsychotic or adjunctive medication (mood stabilizer, antidepressant, etc.) in an effort to better control the psychopathology. However, incomplete therapeutic response has been shown to be associated with poor medication adherence, a problem that is not corrected by additional medications. We examined whether assured antipsychotic treatment through risperidone microspheres allowed for a discontinuation of other antipsychotics and adjunctive medications. We also examined whether continued treatment was associated with improvement in cognitive function. Methods: We switched patients with a psychotic disorder and incomplete adherence and/or polypharmacy to treatment with Risperdal Consta. Over a one year follow-up, we attempted to reduce polypharmacy by reducing the number of antipsychotics, adjunctive medications or both, and assessed clinical course (Brief Psychiatric Rating Scale) and change in cognitive function (Brief Assessment of Cognition in Schizophrenia). Results: Of 54 subjects, 30 completed one year, 9 completed 6 months, 9 completed 4 months, and 6 completed 2 months. A total of 27 (50%) had a reduction in the number of antipsychotics and/or adjunctive medications. Analysis of time to dropout by whether the subject had a reduction in number of medications indicated no differential dropout rate. Improvement in psychopathology (BPRS ratings) reached maximum at 6 months, with no significant change thereafter. Components of cognitive function (BACS) showed gradual improvement over the 12 months, reaching significance for verbal memory and symbol coding. Discussion: These results support the hypothesis that assured treatment with risperidone microspheres may permit a reduction in polypharmacy. Subjects continuing on risperidone microspheres also showed improvements in cognitive function.

GUIDED DISCONTINUATION VERSUS MAINTENANCE TREATMENT IN REMITTED FIRST EPISODE PSYCHOSIS: RELAPSE RATES AND FUNCTIONAL OUTCOME

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Alternative strategies to maintenance treatment, including guided discontinuation, have not been prospectively studied in first episode patients yet. Remitted first episode patients (n=128) were randomly assigned to guided discontinuation of antipsychotic treatment (n=65) or maintenance treatment (n=63). In guided discontinuation, if symptoms recurred, treatment was resumed. In discontinuation strategy 21.5% of patients successfully discontinued antipsychotics, against 4.8% in maintenance strategy. However relapse rates in discontinuation strategy were twice as high compared to maintenance treatment: 42% vs. 21% during 18 months of follow-up. Relapses had a benign course, rarely leading to hospitalization or other consequences beyond the resumption of antipsychotic medication. The discontinuation group spent less days in hospital, although not statistically significant. There were no advantages, but also no disadvantages of the discontinuation strategy regarding outcome of psychopathology, social functioning, quality of life or side effects. We conclude discontinuation strategy is not to be universally applied in remitted first episode patients, because of high relapse rates and associated risks. However, if patients and their families feel inclined to try it, and if close monitoring can be guaranteed, discontinuation strategy is worthwhile to demonstrate either the need for further antipsychotic treatment, or to find out – in about 20% – that antipsychotic treatment is no longer necessary.

CHANGES IN SAFETY PARAMETERS IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH BIFEPRUNOX, PLACEBO, OR RISPERIDONE

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(a) To evaluate potential alterations in body weight, prolactin and EPS associated with bifeprunox in patients with acute exacerbations

of schizophrenia. (b) In this 6-week randomized, double-blind, placebo (PBO)-controlled, risperidone-referenced safety and efficacy study of bifeprunox, subjects were randomly assigned to once-daily treatment with bifeprunox 30 mg (n=148), 40 mg (n=148), PBO (n=149) or risperidone 6 mg (n=154). Bifeprunox doses were titrated, beginning with a dose of 0.25 mg on day 1 and approximately doubled every day until 30 or 40 mg (day 8) were reached; risperidone was titrated over 3 days. Weight and body mass index (BMI) were evaluated at endpoint. Prolactin levels and EPS were assessed at weeks 1–4, and endpoint. (c) Bifeprunox 30 and 40 mg treatment was associated with significant mean weight loss (-1.0 kg, P=0.0008; -0.86 kg, P=0.0018, respectively) compared to PBO (+0.23 kg) at endpoint; some decreases occurred independent of nausea and vomiting. Patients receiving risperidone experienced significant mean weight gain (+1.2 kg, P=0.0004) vs. PBO during the same period. In addition, more bifeprunox-treated patients (30 mg, 8%; 40 mg, 7%) had >7% decrease in body weight compared to PBO (4%) and risperidone (2%). Conversely, 11% of risperidone-treated patients had >7% elevation in weight vs. PBO (5%), while only 3% of patients treated with 30 or 40 mg bifeprunox had such increases at endpoint. Similarly, bifeprunox 30 and 40 mg were associated with mean reductions (-0.3 kg/m2 and -0.4 kg/m2, respectively) in BMI compared to PBO (no change from baseline). Patients treated with risperidone had a +0.5 kg/m2 mean increase in BMI versus PBO. Patients receiving bifeprunox 30 mg experienced significant (P=0.0156) decrease in prolactin vs. PBO, while patients receiving risperidone demonstrated significant (P<0.0001) increase in prolactin. Bifeprunox-treated patients showed incidence of EPS similar to PBO, as measured by BAS, SAS, and AIMS, while risperidone-treated patients demonstrated significant increase in SAS scores vs. PBO at all timepoints. (d) In this study, a decrease in body weight, BMI and prolactin, and an EPS profile similar to PBO was seen consistently in bifeprunox-treated patients. These findings are consistent with other bifeprunox studies. This is noteworthy given that weight gain and hyperprolactinemia are problematic issues in patients treated with atypical antipsychotics

PROPOSAL FOR DEFINITION OF UNIQUE CLINICAL PHENOMENON (TENTATIVE TERMS ARE 'VITALIZATION' OR 'ACTIVATION') WHILE PATIENTS WERE MEDICATED WITH DOPAMINE D2 PARTIAL AGONIST, ARIPIPRAZOLE (ABILIFY®)

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Aripirazole is a recently introduced effective antipsychotic and the first D2 receptor partial agonist. Aripiprazole has a unique pharmacologic profile.Clinical response of patients to aripiprazole, such as symptomatic changes and side effects profiles, are also unique and different from previous antipsychotics. Actually, many clinicians already familiar with previous antipsychotics, would be confronted frequently with patient's behavioral and psychological changes which were unique when aripiprazole was medicated, especially initial period. Until now, most clinicians thought a tendency to this unique phenomenon as just a simple adverse effect like akathisia or symptom aggravation. Therefore, when this unique phenomenon (like 'Vitalization' or 'Activation' phenomenon) appears during treatment, most clinician would withdrawal or decrease dosage of aripiprazole, even though aripiprazole is effective for controlling psychotic symptoms. However, this unique clinical response could be used as an indicator of the clinical effectiveness and a method for dosage titration of aripiprazole. This 'Vitalization' or 'Activation' phenomenon is described when patients become more or less talkative, energetic, alert and smart and show subjective ego-syntonic feeling which could be controlled by patients themselves to some extent. Therefore, patients look like 'vitalized' or 'activated'. This phenomenon can not be controlled by anticholinergics or beta blockers. Moreover, an increase the dosage of aripiprazole should be considered when patients who haven't shown this phenomenon in many cases. Therefore, this phenomenon could be used as an indicator of dosage titration and effectiveness. It can be differentiated readily from akathisia, agitation, psychotic aggravation and mood elation. These are summerzed in the table. This 'Vitalization' or 'Activation' phenomenon is also shown in patients with major depression, bipolar disorder, senile dementia (BPSD) and other psychotic disorder, but the incidence of this 'vitalization' is less obvious in some psychiatric disorder, such as, BPSD. Therefore, new criteria and definition for this 'Vitalization' or 'Activation' phenomenon is required and further study, because this phenomenon maybe essential features of a series of D2 receptor partial agonist antipsychotic medications. In-depth studies about the cause of this phenomenon, including its partial agonistic property or intrinsic activity of aripiprazole, are also required.

THE NUMBER NEEDED TO TREAT (NNT) FOR ALL-CAUSE MEDICATION DISCONTINUATION IN CATIE COMPARED TO A LONG-TERM OBSERVATIONAL STUDY

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In the treatment of schizophrenia, time to all-cause medication discontinuation is considered a global measure of a medication's effectiveness, reflecting treatment efficacy, safety, and tolerability. This was the primary outcome measure in the CATIE trial. Our study compared CATIE, a randomized double blind study, and a long-term observational study (US-SCAP) on the Number Needed to Treat (NNT) for all-cause medication discontinuation. NNTs are clinically meaningful measures of effect size representing the number of patients needed to be treated with one treatment instead of another to prevent one negative outcome, defined here as one additional medication discontinuation for any cause. We used data from a 3-year prospective non-randomized observational U.S. study of schizophrenia-related disorders in usual care (US-SCAP) to calculate NNTs for all-cause medication discontinuation and to compare with NNTs reported for CATIE. Comparisons of NNTs on this measure were made under similar conditions, using 18-months following medication initiation, and the same comparators (olanzapine, risperidone, quetiapine, ziprasidone, and perphenazine). To account for selection bias occurring in usual practice, logistics models were employed to adjust for group differences at the time of medication initiation. NNTs with their 95% confidence intervals were calculated and compared with published NNTs for CATIE (phase 1). The NNTs for all-cause discontinuation of olanzapine vs. each studied atypical antipsychotic during the 18 month following medication initiation in US-SCAP were comparable to CATIE: 7 for olanzapine vs. quetiapine (6 in CATIE); 12 for olanzapine vs. risperidone (10 in CATIE); and 6 for olanzapine vs. ziprasidone (6 in CATIE). The NNT for olanzapine vs. perphenazine in US-SCAP (4) was, however, smaller (better) than the NNT in CATIE (9). Findings were essentially

unchanged when sensitivity analyses included only patients diagnosed with schizophrenia. The NNTs for all-cause medication discontinuation based on an industry-sponsored non randomized observational study (US-SCAP) appeared comparable to the NNTs based on an independent randomized double blind study (CATIE) – when comparing among the atypical antipsychotics, but not when comparing to perphenazine. The NNTs for olanzapine therapy were consistently the lowest (best) when compared to each studied atypical antipsychotic and when compared to perphenazine. Funded by Eli Lilly and Company

17. Therapeutics: Pharmacologic Probes

SERTINDOLE REVERSES COGNITIVE IMPAIRMENT INDUCED BY PCP IN TWO RAT MODELS AND IMPROVE COGNITIVE PROCESSING IN PATIENTS WITH SCHIZOPHRENIA

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Sertindole (SER) is a novel antipsychotic with potent effect on D2, 5-HT2A,2C,6 and α1-adrenergic receptors but no effect on histaminergic and muscarinic receptors. SER has placebo level extrapyramidal symptoms in schizophrenic patients. We examined whether SER may improve cognition in rats impaired by acute or subchronic treatment with the NMDA receptor antagonist phencyclidine (PCP). We also report results of a clinical study investigating the effects of sertindole versus haloperidol on cognitive performance in schizophrenic patients. Methods: In a water maze task PCP was injected daily (1.3 mg/kg SC), beginning 3 days before the first acquisition trial and throughout the experiment; SER was dosed on the 3 acquisition days. In an extradimensional set shifting task PCP 5 mg/kg was injected IP BID for 1 week, followed by 10 days withdrawal. Set shifting was studied after acute treatment with SER (Rodefer et al, Eur J Neurosci, 21, 1070, 2005). Clinical study: 34 patients with schizophrenia randomly received SER (10-24 mg/ day) or haloperidol (5-15 mg/day) for 12 weeks. Cognitive performance was measured at baseline, after 4 and 12 weeks' treatment, using Reaction Time Decomposition and Wisconsin Card Sorting Tests. Results: SER (0.63-2.5 mg/kg) reversed PCP-induced impairment of spatial learning in the water maze on test day 2 and 3. In the set shifting model of executive function SER (0.63-2.5 mg/kg) reversed the impairment induced by previous PCP treatment. In patients sertindole improved cognitive processing in tasks of executive function versus haloperidol, independently of motor function. The improvement was observed after 4 weeks of sertindole treatment and continued to improve at 12 weeks. Discussion: The results show that SER exerts a robust cognitive-improving effect in two rat models of PCP-induced impairment of relevance for the cognitive deficits in schizophrenia. Importantly, improved cognitive performance was also confirmed in schizophrenic patients in a task assessing executive function, depending on cortical function. The precise mechanism(s) behind the effects remain(s) to be demonstrated, but the high affinities for 5-HT2A and 5-HT6 receptors may be of importance: 5-HT2A antagonists are known to enhance cortical NMDA function and, a selective 5-HT6 antagonist was recently shown to reverse PCP-induced deficits in the rat set shifting model (Rodefer et al, Int J Neuropsychopharm, 9, S140, 2006)

A SCALE TO ASSESS FIDELITY TO EVIDENCE-BASED PRINCIPLES OF MEDICATION MANAGEMENT FOR SCHIZOPHRENIA

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Medication Management Approaches in Psychiatry (MedMAP) is a systematic application of evidence-based principles to the pharmacological treatment of schizophrenia. Adapted from the Texas Medication Algorithm Project, MedMAP was developed in response to surveys finding large discrepancies between well-accepted treatment recommendations and usual practice in routine settings. MedMAP originated in the work of the National Evidence-Based Practice Project, which recognized the need for practical tools for implementing these practices. One such tool is a fidelity scale, which measures the degree of adherence to a program model. Fidelity scales are used for both research and quality improvement purposes. Studies suggest that attainment of high fidelity leads to better patient outcomes. Feedback to clinicians in the form of fidelity reviews has proven to be an effective tool for quality improvement. The current study examined the psychometric properties of two newly-developed scales for assessing fidelity of MedMAP implementation. A 17-item organizational scale assesses agency infrastructure (e.g., policies, structures, and standardized forms), and a 22-item prescriber scale assesses actual prescriber behavior, as documented in patient charts. Ratings are guided by a detailed protocol. Our sample consisted of 50 prescribers in 26 outpatient clinics located in 4 states. After receiving systematic training in the procedures, pairs of assessors conducted the 2-day fidelity assessments at each site. Test-retest reliability was assessed one month later in 12 clinics. Monthly teleconferences were used to refine the scales and protocol. Interrater and test-retest reliability for both scales was very good. Mirroring earlier research, we found fundamental gaps in routine practice, including poor documentation of medication history and infrequent monitoring of symptoms and side effects. Rational sequencing of medications was hampered by these gaps. Organizational fidelity was moderately correlated with prescriber fidelity, suggesting the role clinics play in facilitating quality medication management. One next step is the development of a brief version of the prescriber scale, which our analyses suggest is feasible. In addition, an insight from our study was recognizing that our procedures permit assessment of fidelity at the individual patient level, which provides more precise feedback to prescribers regarding medication management.

TMAP AND TREATMENT-REFRACTORY SCHIZOPHRENIA: SO WHEN SHOULD I TRY CLOZAPINE?

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The treatment of patients with treatment refractory schizophrenia has become increasingly complex with frequent switching and combining of medications, such that the selection of clozapine is further deferred as a "last ditch" option. Paradoxically, the accruing scientific literature, including 2 new, government sponsored trials CATIE (in the US) and CUTLASS (in the UK), reaffirms clozapine's superior efficacy over other anti-psychotic medications. On the other hand, the adverse effect profile of clozapine is very unfavorable and the use of this drug is further curtailed by administrative burden and perceived concerns about compliance. Thus, for patients and clinicians, the question of when to try clozapine is now very challenging. In the TMAP Expert Consensus conference, it was recommended that clozapine continue to be a treatment reserved for patients who had not responded to prior antipsychotics. An adequate trial of (no more than) 2 prior antipsychotics was endorsed. Additional recommendations were given to time limitations wherein a patient with persistent positive symptoms for 2 years should receive consideration for clozapine therapy with 5 years of inadequate response being mandate for a trial of clozapine. Factors (based on a variable evidence base) that would prompt earlier consideration for clozapine included comorbid substance abuse, persistent violent

behavior and (with a firmer evidence base) suicidality. Consumer participants who readily appreciated the complexity of decision making between the patient and clinician when choosing clozapine, endorsed these recommendations.

ROLIPRAM, A PDE4 INHIBITOR, SHOWS EFFICACY IN ANIMAL MODELS OF ANTIPSYCHOTIC-LIKE ACTIVITY: STUDIES USING PDE4B AND PDE4D KNOCKOUT MICE

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Recent studies have shown an association of several single nucleotide polymorphisms (SNPs) in PDE4B that are associated with an increased incidence of schizophrenia in the general population (King et al., Society for Neuroscience, 2006). The aim of the present studies was to use pharmacological and genetic techniques to elucidate the therapeutic potential of targeting PDE4B for the treatment of schizophrenia. We have assessed the activity of rolipram in several animal models predictive of antipsychotic-like efficacy and side-effect liability. Rolipram antagonized both PCP- and d-amphetamine-induced hyperactivity with ED50 values of 0.14 and 0.46 mg/kg, respectively. Rolipram also inhibited conditioned avoidance responding (CAR) in male CD rats and DBA1Lac/j mice (ED50 = 0.25 and 0.49 mg/kg, respectively). Both PDE4B wild-type and knockout mice (C57BL/6 background) were able to quickly acquire the CAR task, reaching 80% avoidance criteria within 3 days of training. In the PDE4B wild-type mice, rolipram produced a dose-dependent suppression of the conditioned avoidance response (ED50 = 2.4 mg/kg), with a complete blockade of the response at the highest dose of 3.2 mg/kg. In the PDE4B knockout mice, rolipram also suppressed conditioned avoidance responding (ED50 = 7.3 mg/kg), however, even at the highest doses used, there was never more than a partial suppression (approximately 50%) of the CAR suggesting PDE4B is involved, at least in part, with the activity of rolipram in this model. In contrast, clozapine, was equally effective in suppressing CAR in both PDE4B wild-type and knockout mice (ED50 = 1.8 and 2.1 mg/kg, respectively). Furthermore, rolipram was equally effective in PDE4D WT and KO mice (C57BL/6N/1290la background, ED50 = 0.52 and 0.53 mg/kg, respectively). Rolipram was not effective in reversing an MK801 induced PPI deficit. No catalepsy was observed at doses of rolipram up to 1.0 mg/kg, however, the highest dose (3.2 mg/kg) produced a modest, but significant degree of catalepsy. The present results demonstrate that rolipram has a pharmacologic profile which is similar to that of the atypical antipsychotics and has low extrapyramidal symptom liability. These results suggest that PDE4B mediates, at least in part, the antipsychotic effects of rolipram in the conditioned avoidance test and that the PDE4B-regulated cyclic adenosine monophosphate signaling pathway may play a role in the pathophysiology and pharmacotherapy of psychosis.

VALPROIC ACID REGULATES THE EXPRESSION OF PGC-1α AND PGC-1α-RESPONSIVE GENES IN NEUROBLASTOMA CELLS AND PRIMARY NEURONS

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Abnormalities in metabolism and synaptic plasticity have been implicated in the pathogenesis of schizophrenia. Current evidence indicates that chromatin hypermethylation in GABAergic neurons contributes to a decrease in gene transcription of the GABA-producing enzyme glutamic acid decarboxylase (GAD67) in schizophrenia. In animal models, the mood stabilizer valproic acid (VPA) can prevent hypermethylation-induced changes in GAD67 expression, and this effect has been hypothesized to be due to VPA's actions as a histone deacetylase (HDAC) inhibitor. In muscle cells, HDAC inhibitors can influence metabolism by upregulating the expression of the transcriptional coactivator peroxisome proliferator activated receptor g coactivator 1a (PGC-1α), a protein concentrated specifically in GABAergic neurons in the rat brain. To determine whether PGC-1α is similarly regulated in neurons by VPA, we treated SH-SY5Y neuroblastoma cells or primary hippocampal and cortical neurons with varying doses of VPA (0, 1, 2, 5 mM) for 18-48 hours and collected the cells for RNA isolation and real-time RT-PCR. The ability of VPA to inhibit HDAC activity was confirmed by Western blot for acetylated H3. Basal PGC-1α expression was very low in the neuroblastoma cells; VPA increased PGC-1a expression over 200 fold. In hippocampal and cortical neurons, which had higher basal levels of PGC-1α expression, PGC-1α was increased 2-fold. To determine the relevance for the VPA-mediated increase in PGC-1α, we measured the expression of a panel of putative PGC-1α-responsive genes in VPA-treated cells. In SH-SY5Ys, the largest increase in gene expression was seen in glucose transporter 4 (GLUT4; 5-fold) and carnitine palmitoyl transferase 1α (CPT1α; 11-fold). Synaptophysin expression increased 2-fold. In primary neurons, GLUT4 increased 30-fold, while there was no change in synaptophysin. Overexpression of PGC-1α in SH-SY5Y cells resulted in a 12-fold increase in GLUT4 expression and a 3-fold increase in CPT1α and synaptophysin expression, suggesting that PGC-1α may mediate VPA's effects on gene expression. This is the first evidence that VPA can regulate the expression of PGC-1α and PGC-1α-responsive genes in neuronal cells. These results indicate that VPA may exert its effects by influencing neuronal metabolism and that PGC-1α may be a good pharmacological target for counteracting the detrimental effects of chromatin hypermethylation in schizophrenia. Supported by: NS049863 (RMC) and NS42056 (JWR).

RISK FOR DIABETES AND PRIMARY CHD IN SCHIZOPHRENIC PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS: AN ANALYSIS OF CATIE DATA USING NNH METHODOLOGY

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A published study using baseline fasting laboratory values from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study indicated increases in coronary heart disease (CHD) risk among patients receiving treatment with antipsychotic agents compared with age- and sex-matched controls.[1] We used a simulation model that was based on the Framingham risk equations and national epidemiologic studies of diabetes risk to determine whether metabolic changes observed in CATIE following treatment with atypical antipsychotic agents translated into further long-term increases in CHD and diabetes risk. Risk equations were used to estimate 10-year rates of diabetes and CHD using baseline and follow-up data from CATIE. Exposure-adjusted mean change from baseline was used to estimate the increase in risk relative to treatment with ziprasidone or no treatment. Results: Relative to ziprasidone, olanzapine, and quetiapine substantially elevated the risk for diabetes and for a primary CHD event among men and women (range of relative risk

= 1.06–1.26 for men and 1.03–1.09 for women). To a lesser extent, risperidone elevated the risk for diabetes and CHD in men and for CHD in women. Ziprasidone treatment did not increase risk for diabetes or CHD for patients in the CATIE study. In conclusion, olanzapine and quetiapine substantially increased the risk for diabetes and CHD above that of ziprasidone and above that of the patients' baseline risk, as calculated using exposure-adjusted metabolic changes observed in the CATIE study. These results suggest serious long-term safety concerns for olanzapine, quetiapine, and, to a lesser extent, risperidone. Reference 1. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res.* 2005;80:45–53.

EXPERIMENTAL EVIDENCE OF ENHANCED SENSITIVITY TO THE EUPHORIC EFFECTS OF ALCOHOL IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia have higher rates of alcohol use disorders than the general population. The purpose of this study was to determine whether schizophrenia was associated with alterations in alcohol response that might explain the elevated risk for AUDs in this population. Methods: In a randomized, double-blind, placebo-controlled, counter-balanced 3 test day laboratory study, the effects of alcohol were compared in 23 subjects with schizophrenia (without any previous alcohol use disorder but with some alcohol exposure) and in 14 healthy subjects matched for age, gender, education and lifetime exposure to alcohol. Standard alcohol drinks in a scheduled design were administered to produce blood alcohol levels of 0, 0.02-0.04 mg%, or 0.06-0.08 mg%. Schizophrenia symptoms, perceptual alterations, stimulant and depressant subjective effects of alcohol, and "high" were measured prior to alcohol administration and at several postdrug timepoints. Verbal learning and recall, vigilance and distractibility, and motor function were assessed once per test day. RESULTS: Relative to healthy subjects, subjects with schizophrenia reported greater euphoria and stimulatory effects in response to alcohol. Alcohol produced small transient increases in positive psychotic symptoms and perceptual alterations without affecting negative symptoms. Alcohol also impaired several aspects of immediate and delayed recall, and vigilance and distractibility. CONCLUSIONS: Schizophrenia patients showed increased euphoric and stimulatory responses to alcohol. These exaggerated positive responses to alcohol doses may contribute to the increased risk for alcohol use disorders associated with schizophrenia. The absence of beneficial effects of alcohol does not support a self-medication hypothesis of alcohol use in schizophrenia.

PSYCHOPHARMACOLOGICAL EVIDENCE OF CANNABINOD AND DOPAMINE RECEPTOR INTERACTIONS IN HUMANS: IMPLICATIONS FOR THE LINK BETWEEN CANNABINOIDS AND PSYCHOSIS

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Cannabinoids produce psychotomimetic effects, memory and attentional impairments, and euphoria in humans. There is growing preclinical evidence of cannabinoid-dopamine interactions, though this has not been adequately studied in humans. Methods: The effects of pretreatment with various doses of a dopamine receptor antagonist, on the behavioral and cognitive effects of the cannabinoid d-9-THC were studied in humans. Under double-blind conditions, healthy human subjects completed 2 test days during which active or placebo oral haloperidol was administered in random order followed 1.5 h and 3.5 h by intravenous administration of placebo (vehicle) and active d-9-THC administration (0.035 mg/kg over 5 minutes), respectively in a fixed order. In the first study of 10 subjects, haloperidol (0.05 mg/kg or placebo) and d-9-THC (0.035 mg/kg or placebo over 5 minutes) were administered. In the second study of 27 subjects, a higher dose of haloperidol (0.057 mg/kg or placebo) and lower/slower dose of d-9-THC (0.0286 mg/kg or placebo over 20 minutes) were administered. Results: In both studies, d-9-THC produced positive and negative-like symptoms of psychosis, perceptual alterations, and feeling states associated with the cannabis response including anxiety, "high", panic, and tired. Haloperidol did not reduce any of the behavioral effects of d-9-THC. While haloperidol did not have any effects on verbal recall, consistent with other studies, d-9-THC impaired several aspects of verbal recall. Haloperidol and d-9-THC interacted to worsen recall. Further, haloperidol increased omission and commission errors on a distractibility task and interacted with d-9-THC to further increase omission and commission errors. Haloperidol also increased omission errors on a vigilance task and interacted d-9-THC interacted to further increase omission errors. Conclusions: These data provide the first evidence in humans that we are aware of that cannabinoid and dopamine systems have interactive effects on attention and memory. Interestingly, haloperidol did not reduce the psychotomimetic effects of d-9-THC. The results of these studies will be discussed in the context of the preclinical evidence of cannabinoid dopamine interactions. In particular, how these results relate to the proposed dopaminergic mechanism underlying the psychotomimetic effects of cannabinoids will be discussed.

BRATTLEBORO RATS DISPLAY SCHIZOPHRENIA-RELEVANT COGNITIVE DEFICITS THAT ARE REVERSED BY CLOZAPINE AND A NEUROTENSIN-1 RECEPTOR AGONIST

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Background: Brattleboro (BRAT) rats differ from "wild type" Long Evans rats by a single gene mutation. Our laboratory demonstrated that BRAT rats exhibit natural deficits in prepulse inhibition (PPI) similar to those exhibited by schizophrenia patients. More recently, we demonstrated that BRAT rats exhibit deficits in a social discrimination test, which is an ethologically relevant test of memory and attention pertinent to the cognitive deficits seen in schizophrenia. This makes the BRAT rat a strong model of the sensorimotor gating deficits and cognitive deficits associated with schizophrenia. We have shown that antipsychotics and a neurotensin-1 receptor agonist reverse PPI deficits in BRAT rats. In this study, we investigated whether clozapine and a neurotensin-1 receptor agonist that enters the CNS could also reverse social discrimination deficits in BRAT rats. Methods: We administered subcutaneously to BRAT rats either saline, one of several doses of clozapine (0.1, 1.0 10 mg/kg) or PD149163 (0.1, 0.3, 1.0 mg/kg) a selective neurotensin-1 receptor agonist designed to enter the CNS after systemic administration.

Immediately after drug injections a juvenile rat was placed in the home cage of test rats for 4 minutes. After a 30 minute period in which test rats were alone in their cage, the previously presented juvenile rat and a novel juvenile were reintroduced for a four minute period. The amount of time the test rat spent investigating the familiar and novel rat was recorded. A group of Long Evans rats were also tested with saline as comparators. Results: Saline-treated Long Evans rats spent less time exploring pre-exposed juveniles compared to novel juveniles indicating intact social discrimination. In contrast, saline-treated BRAT rats did not display social discrimination. Clozapine and PD149163 restored social discrimination in these rats in a dose-dependent fashion. Discussion: These results provide further support for the BRAT rat as a genetic animal model with strong relevance to schizophrenia and strong utility for antipsychotic drug development. These results also add to the existing evidence that neurotensin-1 receptor agonists are good candidates for potential novel antipsychotic drugs and in addition to their general antipsychotic efficacy they may have therapeutic benefit for the cognitive deficits associated with schizophrenia.

CATECHOLAMINE REGULATED PROTEIN (CRP40), AS A POSSIBLE THERAPEUTIC AGENT IN SCHIZOPHRENIA

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The overall objective of this proposal study will establish whether knockdown of the CRP40 mRNA in the prefrontal cortex leads to the development of behavioural abnormalities in a putative animal model; and second, we will concentrate on recombinant human CRP40 fusion protein as a therapeutic agent, using chitosan nanoparticles in the prefrontal cortex of the rat brain. Specifically, human CRP40 will act as a neuroprotective agent to retard the excess dopamine and their metabolites in rat models. Previous studies from our laboratory have described a new class of central nervous system proteins known as catecholamine-regulated proteins that are capable of coupling to catecholamines, including dopamine. Recently, we have also cloned a human homologue of CRP40 and the fusion protein is functionally similar to bovine CRP40. The various characteristics and functions of CRP40 are: (1) recent molecular cloning of human CRP40 shows that it is an isoform of the 70 kDa mitochondrial heat shock protein, mortalin-2; (2) and a reduction of CRP40 expression was observed in the nucleus accumbens and the prefrontal cortex of post mortem brain specimens with schizophrenia relative to controls. In addition, this novel protein was normalized by antipsychotic medications. Experimentally we used Sprague Dawley rats that were implanted with bilateral 26-gauge stainless steel guide cannulae above the prefrontal cortex (stereotaxic coordinates: 3.0mm anterior to bregma, 0.7mm lateral to midline and 2.5mm below the surface of the skull). CRP40 antisense solution (n=6) or cerebral spinal fluid controls (n=6) were infused continuously for 3 weeks via implanted osmotic mini-pumps connected by separate catheters to respective cannulae. Animals were then subjected to the determination of behavioural abnormalities by a specific schizophrenic test known as Prepulse Inhibition Startle (PPI), which measures the sensorimotor gating deficit in these animals. The results showed the antisense rats displayed a significant deficit ($p<0.05$, students t-test). All rats were sacrificed and Western blotting confirmed a significant reduction in CRP40 levels in the CRP40 antisense knockdown rats. Next, the rats will be implanted with nanoparticles containing CRP40 plasmids in the same cannulaes, to determine if the reversal of the cognitive deficits will be seen. If the hypothesis is correct, CRP40 may be used as a natural alternative for the treatment of some symptoms of schizophrenia. CIHR Funded

PHARMACOLOGY OF A NEW ATYPICAL ANTIPSYCHOTIC AGENT, EGIS-11150/S36549

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EGIS-11150/S36549 is a new atypical antipsychotic agent developed by EGIS Pharmaceutical Plc. The compound exerted strong antipsychotic activity in a series of models of the negative and positive symptoms of schizophrenia. EGIS-11150/S36549 blocked conditioned avoidance response in rats (ID_{50} = 0.7 mg/kg p.o.) and apomorphine-induced stereotypy and climbing in mice (0.2 and 0.06 mg/kg respectively). In the phencyclidine (PCP) interaction tests, the compound showed similarity to other atypical neuroleptic agents. The PCP-induced social withdrawal thought to be the best animal test modelling both the positive and negative symptoms of schizophrenia. EGIS-11150/S36549 abolished the effects of phencyclidine on locomotion, ataxia, and social investigation. The larger dose (1 mg/kg p.o.) had a stronger effect on locomotion-related behaviours (locomotion and ataxia), while the lower dose (0.1 mg/kg p.o.) affected social investigation more strongly. EGIS-11150/S36549 is a potent antagonist of the locomotor effects of PCP (antagonism at 0.015 mg/kg orally in mice). EGIS-11150/S36549 was active in the dose range studied in reducing startle response in the prepulse inhibition (PPI) model of schizophrenia. The highest dose of EGIS-11150/S36549 (0.3 mg/kg ip.) achived positive effects (that suggest antypsychotic properties: this dose) and significantly opposed the PPI-disruptive effects of the NMDA antagonist, ketamine. In receptor binding studies EGIS-11150/S36549 showed affinity for α_1 adrenoceptors (Ki: 0.5 nM), 5-HT_{2A} receptors (Ki: 3.1 nM), D_2 receptors (Ki: 120 nM) and 5-HT_7 receptors (Ki: 9.1 nM). However, it is unlikely that these effects alone are responsible for the antagonism of PCP because α_1 and 5-HT_2 antagonists do not fully antagonise the effects of PCP even at high doses. EGIS-11150/S36549 shows low cataleptogenic potential in the therapeutic dose range. According to present studies EGIS-11150/S36549 is a potential third generation antipsychotic compound with the remarkable properties of controlling both the positive and negative symptoms of the disease (in some models at extremely low dose), while basically free of extrapyramidal and other side effects, apart from those anticipated from α_1 adrenoceptor blockade.

DROSOPHILA MELANOGASTER AS A MODEL SYSTEM TO EVALUATE DRUG INDUCED CENTRAL NERVOUS SYSTEM ADVERSE EFFECTS

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Antipsychotic medications used in the treatment of schizophrenia have a number of CNS adverse effects; such as CNS depression or stimulation. There is a clear need to develop time efficient and cost effective screening systems to evaluate drug induced CNS adverse effects. In research and development of pharmaceutical compounds, the majority of animal behavioral testing is done using mice as the

model system. This system is time-consuming and costly. The approach to model the phenotypical effects of drugs on the central nervous system in Drosophila melanogaster offers many advantages in efficiency. The purpose of this study was to create a high-throughput screening method to evaluate drugs with known impact on the CNS. Comparisons between the fly and human genomes indicate a high degree of conservation in fundamental biological pathways. Large-scale pharmacological screens of drugs are possible since flies have a complex nervous system. The purpose of this presentation is to discuss the methodologies that we developed to efficiently test the effects of drugs on the central nervous system in Drosophila melanogaster. Different dosages of modafinil, lamotrigine, and propofol were tested for any significant correlations in mating success. Courtship in Drosophila is a very complex process in which the two sexes exchange stimuli of different modalities: visual, chemosensory (olfactory and gustatory), and auditory. Due to the complexity and precision of the process, any changes in the CNS could potentially affect the mating success rate. Dose-response data of modafinil demonstrates that the drug was effectively up-taken by the fruit flies and the CNS was perturbed. Lamotrigine showed a dose-response of CNS depression while propofol demonstrated significant CNS depression at one dose. These results offer great motivation in further developing the model system using Drosophila melanogaster for high-throughput testing and creating a system to cost-effectively screen compounds for their impact on CNS.

POTENTIAL FOR ALLOSTERIC ACTIVATORS OF M1 MUSCARINIC AND MGLU5 RECEPTORS IN THE TREATMENT OF SCHIZOPHRENIA

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Growing evidence suggests that NMDA receptor (NMDAR) hypofunction may contribute to the symptoms observed in schizophrenics. Direct activation of NMDAR function, however, is associated with an increased risk of excitotoxicity, receptor desensitization and tolerance. One alternative approach to the direct stimulation of NMDARs involves the activation of other receptors that indirectly enhance NMDAR signaling. Both M1 muscarinic and metabotropic glutamate subtype 5 (mGlu5) receptors have been shown to enhance the function of NMDARs and it is hypothesized that selective activators of either receptor may be useful in the treatment of schizophrenia. Developing compounds with selectivity for each of these receptors versus related family members, however, has remained challenging and has limited use of these receptors as therapeutic targets. Here we describe the pharmacological characterization of TBPB (1-[1'-(2-Tolyl)-1,4'-bipiperidin-4-yl]-1,3,-dihydro-2H-benzimidazol-2-one), a recently reported novel M1-selective agonist. In recombinant systems, TBPB robustly increased intracellular calcium in cells expressing M1 receptors (EC_{50} of 140nM). Encouragingly, TBPB was without effect at any of the other muscarinic subtypes (M2-M5) at concentrations up to 10μM. TBPB also activated a mutant M1 receptor (Y381A, which is insensitive to orthosteric agonists) with a potency similar to that observed at wildtype M1, suggesting that this compound is not acting at a site identical to the orthosteric binding site. In rodent models predictive of antipsychotic activity, TBPB also exhibited many of the antipsychotic-like actions of the M1/M4-preferring muscarinic agonist xanomeline and clinically available antipsychotic drugs. Using a similar approach for the development of selective mGluR5 activators, our group and others have characterized several selective mGluR5 allosteric potentiators, compounds that do not activate mGluR5 directly but dramatically potentiate the response of the receptor to glutamate. These compounds are represented by 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (CDPPB), which induces a robust potentiation of mGluR5-mediated responses in vitro (EC_{50} ~25 nM) and shows efficacy in rodent models predictive of antipsychotic activity. These studies suggest that M1 and mGluR5 selective activators may have beneficial properties in the treatment of schizophrenic symptoms.

A 26-WEEK OPEN-LABELED PROSPECTIVE STUDY OF ARIPIPRAZOLE IN THE TREATMENT OF SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER IN KOREA

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OBJECTIVE: The objective of the current study is to investigate the long-term efficacy and tolerability of aripiprazole therapy in patients with schizophrenia or schizoaffective disorder in Korea. METHOD: The current study was an extension of multicenter, single group, 8-week study of patients with schizophrenia or schizoaffective disorder. Two hundreds and one patients who completed 8-week acute aripiprazole therapy, participated in this extension study. The primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS) total score, and secondary efficacy measures included Clinical Global Impression (CGI), social functioning scale, and emotional factors. Safety was evaluated by recording treatment-emergent adverse events and measuring vital signs, weight, and laboratory test RESULTS: One hundred and forty eight patients completed 26-week aripiprazole therapy. An intent-to-treat, last-observation-carried-forward analysis demonstrated a significant reduction in all subscale scores of PANSS, and responder rate (decrease > 30% on the PANSS) of approximately 60% was found after 26-week of aripiprazole treatment. The most common side effects for aripiprazole were nausea, insomnia, and akathisia. Significant weight gain rate (increase > 7% of baseline weight) was 26 %, although there were no significant elevation in glucose level and lipid profile after 26-week of aripiprazole treatment CONCLUSION: Aripiprazole is an effective antipsychotics in the long-term treatment of both positive and negative symptoms of schizophrenia without serious side effect in Korean patients with schizophrenia

ANTIPSYCHOTICS AND QUALITY OF LIFE, SOMETHING TO WORRY ABOUT?

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Introduction: Diminishing antipsychotic symptoms but also improvement of quality of life is an important aim in antipsychotic treatment. Antipsychotics show desired but unfortunately also undesired treatment effects, the latter related to different pathophysiological mechanisms. We present a study on antipsychotic treatment effects and quality of life. Design: A multi-centre cross-sectional study among patients with a schizophrenia spectrum disorder treated with antipsychotics was carried out. Treatment effects were evaluated using the Subjects' Response to Antipsychotics questionnaire (SRA, Wolters

et al. 2006). Quality of life (QoL) was evaluated using the WHO-QoL-Bref (WHOQoL-group 1998). The SRA evaluates antipsychotic treatment attributed to the medication from a patients' perspective and is divided into desired responses (24 items) and undesired responses (weight gain (4 items), sexual anhedonia (3 items), sedation (6 items), affective flattening (3 items), movement disorders (5 items), diminished sociability (6 items), and increased sleep (3 items)). Results: 234 men and 86 women agreed to participate, mean age was 35 (SD=11.5) years, 74.5% atypical antipsychotics. Undesired treatment effects predicted Qol more than the desired treatment effects (Pearson correlation undesired r=-49**, desired r=+25**). Undesired treatment effects predicting QoL were sedation r-41**, diminished sociability r=-40**, affective flattening r=-38**, movement disorders r=-30**, increased sleep r=-26**, sexual anhedonia r=-21**). Weight gain as well as age, gender, atypical versus typical, depot versus oral and duration of medication did not predict QoL. Corrected for demographic and medication variables (multiple linear regression, enter method), undesired responses predicted a lower (r=-50**), desired responses a higher QoL (r=+27**). Conclusion: Treatment effects of antipsychotics evaluated by patients with the SRA predict patients' evaluation of there quality of life, undesired effects predict a lower quality of life, desired treatment effect predict to a lesser extent a higher quality of life. To optimize clinical guidance and to set targets for future drug development understanding the influence of antipsychotics on quality of life is very important. (**p<0.01) Reference: Wolters HA., Knegtering H., Wiersma D., van den Bosch, RJ (2006). The evaluation of the Subjects' Reaction to Antipsychotics (SRA) questionnaire. Int Clin Psychopharmacol. 21(1):63-9.

PALIPERIDONE IMPROVES COGNITIVE BUT NOT SOCIAL DEFECTS IN ANIMAL MODELS OF SCHIZOPHRENIA

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Paliperidone is the 9-hydroxylated metabolite of the second-generation antipsychotic drug, risperidone. Risperidone has been shown in animal studies to improve prepulse inhibition deficits in the neonatal rat ventral hippocampal lesion model (Le Pen and Moreau, 2002) and rat social interaction behavior following repeated dosing with the psychotomimetic ketamine (Becker and Grecksch, 2004). Pharmacokinetic studies suggest, however, that paliperidone has a slower clearance rate from brain tissues and, therefore, maybe a more effective antipsychotic medication. However, there are almost no data on the behavioral effects of paliperidone in animal models of schizophrenia. Therefore, we evaluated paliperidone in two animal preparations of schizophrenia exhibiting cognitive and social deficits in order to gain more information about the in vivo actions of paliperidone. The two model systems we employed were male rats repeatedly treated with phencyclidine (PCP, Lee et al., 2005) and male rats exposed to a prenatal stress paradigm during in utero development (Koenig et al, 2005). Adult male rats treated for 7-days with a low dose of PCP display marked social withdrawal and cognitive impairment when tested in the novel object recognition task. A single injection of paliperidone (0.25 – 1.0 mg/kg, ip) failed to improve the behavioral impairments induced by PCP. However, administration of paliperidone over the same dose range for 7 days improved performance on the novel object recognition task without significantly improving the social interaction deficits induced by PCP. In the prenatally stressed rat preparation, a single injection of paliperidone was also ineffective in improving the social behavior deficit or the impaired object recognition behavior. Studies in the prenatally stressed rats using repeated dosing with paliperidone are underway and will also be presented. Repeated but not acute exposure to paliperidone restores cognitive function in an animal model of schizophrenia. Additional work is underway to determine whether paliperidone improves social behavior in animal model of schizophrenia. This work was supported by a grant from Janssen Pharmaceutica LP.

LIMBIC RCBF PATTERNS PREDICT TREATMENT RESPONSE IN SCHIZOPHRENIA

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Background: Using PET with ^{15}O, we sought to evaluate whether drug-free and antipsychotic-induced rCBF patterns would be predictive of treatment response in patients with schizophrenia. We had hypothesized that drug-induced rCBF changes in limbic regions would predict treatment response. Methods: Patients with schizophrenia were initially scanned during a resting state after withdrawal of all psychotropic medication (two weeks), and then blindly randomized to treatment with haloperidol (n=12) or olanzapine (n=17) for a period of 6 weeks. Patients were scanned again after 1 and 6 weeks of treatment. All assessments, including scanning sessions, were obtained in a double-blind manner. To evaluate if drug-free rCBF patterns were predictive of treatment response, we generated pixel-by-pixel correlations between the drug-free scans and the BPRS Psychosis change scores after 6 weeks of treatment. Likewise, to evaluate whether rCBF changes after one week would predict treatment response, we generated correlations between the rCBF changes after one week and the BPRS Psychosis change scores at the end of treatment. Results: There was a significant correlation (r= 0.4, p=0.05) between rCBF in the ventral striatum and the BPRS Psychosis change scores with treatment. Low ventral striatum in drug-free subjects was predictive of good treatment response. In both treatment groups, there were significant correlations between rCBF changes in both the ventral striatum (Olanz, r= -0.76, p=0.01, Hal, r= -0.85, p=0.01) and the hippocampus (Olanz, r= 0.72, p=0.01, Hal, r=0.79, p=0.02) and the BPRS Psychosis change scores with treatment. Increased ventral striatum and decreased hippocampal activity as the result of one week of treatment were predictive of treatment response. Discussion: Blockade of dopamine D2 receptors in the ventral striatum is a likely first step into antipsychotic action and appears to be followed by neuronal events affecting limbic regions. We propose that treatment response is characterized by an improved neuronal transmission starting in the ventral striatum and relayed to limbic regions through efferent projections. rCBF patterns in ventral striatum and hippocampus may represent imaging markers indexing treatment response to psychosis. A clear understanding of the biological correlates of treatment response to positive symptoms could provide a solid base for the development of more effective and specifically targeted drugs.

POLYPHARMACY AND PRESCRIBING PATTERNS IN PATIENTS WITH SCHIZOPHRENIA IN AN ACUTE UNIT IN SPAIN

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Introduction. Antipsychotic Monotheraphy is consider as the gold Standard in pharmacological treatment of Schizophrenia and other psychotic disorders. Only two of the main clinical guides are recomending the employment of polipharmacy (PA) for those refractory patients to monotherapy. Nonetheless, there is a large rate of studies, made in many different settings, showing PA as more frecuent that would be expected attending expert's recommendations. Method. We review, in this retrospective study, all the psychotropic drugs dispensed to inpatients in a short-time psychiatric ward in 2005 year diagnosed as Paranoid Schizophrenia (ICD-9) at the time of discharge. There were included a total 209 patient more than eighteen (18) year old. Results. Of these total 209 patient studied 55,5% were discharged under PA treatment. Inpatient were given 3,06 psychotropic drugs and 1,61 on average at discharge. A mean 33,2% of patients studied were given anticholinergic drugs and 66,2% were given benzodiazepines. The most prevalent combination drugs was constant released Risperidone plus atypical antipsichotic. Amisulpiride was the most used antipsychotic as adyuvant treatment. Conclusions. Despite of different clinical guidelines, antipsichotic PA is a commonly pharmacologic strategy as is showed in our study and in the reviewed literature. Data in our study point that these rates of PA are not only claimed to refractory patients to treatment.

ANXIOLYTIC PROPERTY OF ATYPICAL ANTIPSYCHOTICS: A PRECLINICAL INVESTIGATION

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Atypical antipsychotics have been increasingly used to treat anxiety-related disorders, but the clinical and preclinical evidence supporting their intrinsic anxiolytic property has been mixed. It is also not clear how atypicals such as clozapine differ from the classical anxiolytics such as benzodiazepines in the treatment of anxiety. The present study investigated the possible antipsychotic and anxiolytic properties of typical haloperidol, atypical clozapine and anxiolytic chlordiazepoxide in a rat conditioned avoidance response model (CAR). We concurrently compared their effects on the acquisition of avoidance responding (an index of antipsychotic efficacy) and various fear responses (e.g. body temperature increase, defecation, and 22 kHz ultrasonic vocalization, index of anxiolytic efficacy) in this model. Forty-four rats were randomly assigned to 5 groups: Haloperidol (0.05 mg/kg, sc, n=9), Clozapine (20 mg/kg, sc n=10), Chlordiazepoxide (10 mg/kg, ip, n=10), Vehicle (sc, n=9) and Control (ip, n=6). The first 4 groups were trained in a 20-trial CAR session/day for 7 consecutive days, whereas the control group was just exposed to the CAR boxes for 20 min during the same period. Before each daily session, the rats were injected with one of the drugs or vehicle. The number of avoidance responses, 22 kHz ultrasonic vocalizations, and amount of defecations were also recorded daily. Body temperatures were taken before and after each CAR session. The results suggest that at the clinical relevant doses, haloperidol, clozapine and chlordiazepoxide exhibit distinct antipsychotic and anxiolytic profiles in this model. Haloperidol and clozapine, but not chlordiazepoxide, significantly disrupted the acquisition of avoidance responding, confirming the antipsychotic efficacy of both antipsychotics. Clozapine and chlordiazepoxide, but not haloperidol, also suppressed the number of 22 kHz ultrasonic vocalizations, the fear-induced body temperature increase and amount of defecations. Clozapine also differs from chlordiazepoxide in its time course of anxiolytic action. Clozapine seems to have an immediate onset, whereas chlordiazepoxide seems to exhibit a progressive improvement effect with repeated treatment. In conclusion, the present findings provide strong supportive evidence for the dual (antipsychotic and anxiolytic) property of clozapine and suggest that it may be beneficial to use clozapine to treat anxiety disorders and psychotic fear/anxiety in schizophrenia.

DEVELOPMENT OF NOVEL, CENTRALLY ACTIVE GLYT1 INHIBITORS THAT FURTHER VALIDATE THE NMDA HYPOFUNCTION HYPOTHESIS OF SCHIZOPHRENIA IN PRECLINICAL ANIMAL MODELS

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In an effort to develop new antipsychotics based on the NMDA receptor hypofunction hypothesis of schizophrenia, our laboratory initiated an effort to discover potent, non-sarcosine-derived GlyT1 inhibitors. A high-throughput screening (HTS) campaign, employing a [14C] glycine uptake SPA assay, identified a novel [4-phenyl-1 (propylsulfonyl)piperidin-4-yl] methyl benzamide as a potent, reversible inhibitor of GlyT1 (IC50 = 135 nM) with high selectivity against GlyT2. In this presentation, we report on the lead optimization, pharmacology and *in vivo* efficacy of advanced analogs of the screening lead that further validated the NMDA receptor hypofunction hypothesis in a preclinical behavioral model of prepulse inhibition where known antipsychotics provide similar, positive results. Furthermore, the development and *in vitro* characterization of a novel radioligand will be discussed.

EFFECT OF FOOD ON ABSORPTION OF ZIPRASIDONE

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Oral ziprasidone shows increased bioavailability in the presence of food, therefore, administration with food is recommended.[1] In this report we describe pharmacokinetic (PK) studies conducted to quantify the impact of food on ziprasidone absorption under various conditions. The effect of food on ziprasidone absorption was examined in 2 clinical PK studies. The first, an open-label, nonrandomized, 6-way crossover study, investigated ziprasidone absorption in 8 healthy male subjects. Subjects received oral ziprasidone 20-, 40-, and 80 mg single doses after an 8-hour fast or immediately following consumption of an FDA standard meal (ie, 60% fat content). The second, an open-label, randomized, 3-way crossover study, explored the impact of dietary fat content on ziprasidone absorption in 14 healthy subjects. Subjects received ziprasidone 40 mg using a steady-state regimen under 3 conditions: fasting, with an FDA standard meal (60% fat content), and with a lower-fat meal (30% fat content). In the first study, $AUC_{0\text{-inf}}$ was greater in fed than fasting states at each dose tested (20 mg, +48%; 40 mg, +87%; 80 mg, +101%). Increases in $AUC_{0\text{-inf}}$ and C_{max} with dose were nonlinear in the fasting

state but linear in the fed state. Nonlinearity was attributed to dose-limiting absorption at the higher doses owing to fasting conditions during administration. In the second study, decreasing the fat content from 60% to 30% in test meals (using the 40-mg dose) had a modest impact on ziprasidone absorption. Compared with the fasting state, AUC increased 100% for the high-fat meal and 80% for the lower-fat meal. These increases are attributed to enhanced ziprasidone solubilization secondary to food consumption leading to greater intestinal absorption.[2] Less variability of AUC and C_{max} values was observed in the fed state, suggesting more consistent absorption of ziprasidone when taken with food. These results demonstrate that administration of ziprasidone with food is crucial to ensure linear PK and optimal absorption for consistent systemic exposure to ziprasidone. Food also reduced PK variability in drug absorption indicating that coadministration of ziprasidone with food will also provide greater consistency in daily systemic exposure to ziprasidone and, thus, symptom control and tolerability. References 1. Geodon® (ziprasidone) [prescribing information]. New York, NY: Pfizer Inc; 2005. 2. Lebel M, et al. *Clin Invest Med.* 1993;16:B18.

PRECLINICAL PROFILE OF SCA-136 (VABICASERIN): BROAD SPECTRUM PSYCHOTHERAPEUTIC FOR SCHIZOPHRENIA, DEPRESSION AND BIPOLAR DISORDER

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The 5-HT_{2C} receptor subtype has been implicated in a wide variety of psychiatric conditions and as a consequence has received considerable attention as a target for drug discovery. The current studies evaluated the preclinical behavioral, electrophysiological and neurochemical properties of SCA-136, a novel 5-HT_{2C} receptor selective agonist. SCA-136 was tested in models predictive of antipsychotic (antagonism of apomorphine-induced behaviors, conditioned avoidance responding (CAR), prepulse inhibition (PPI)) and antidepressant (forced swim test, resident-intruder, and olfactory bulbectomy models) efficacy. These data were further amplified by neurochemical and electrophysiological studies. The results of these studies show that SCA-136 produced a dose-dependent decrease in apomorphine induced climbing (MED = 5.4 mg/kg, ip) without affecting apomorphine-induced stereotypy (>30 mg/kg, ip). In this dose range, SCA-136 did not produce significant levels of catalepsy in mice. In the rat CAR model, SCA-136 dose-dependently decreased avoidance responding (MED = 1.7 mg/kg, ip; 5.4 mg/kg, po). SCA-136 blocked the deficits in PPI produced by both DOI (MED = 17 mg/kg, ip) and amphetamine (MED = 3 mg/kg, ip). Acute and chronic (21 day) treatment with SCA-136 produced dose-dependent decreases in the number of spontaneously-active A10 (MED ≦ 3 mg/kg, ip), but not A9, dopamine neurons (>30 mg/kg, ip), and a dose of 17 mg/kg, sc produced a selective decrease in nucleus accumbens dopamine relative to striatal dopamine. SCA-136 significantly decreased immobility with an MED of 17 mg/kg ip in the forced swim test in WKY rats. Acute treatment with SCA-136 selectively reduced the aggressive behavior of resident rats during social encounters at doses that do not result in motor impairment (MED ≦ 0.3 mg/kg, sc) and increased aggressive behavior following short-term treatment (effective by Day 2-3). Furthermore, SCA-136 decreased the hyperactivity associated with olfactory bulbectomy (MED = 0.3 mg/kg, ip) without affecting levels of activity in sham-operated rats following both short-term (3-day) and long-term treatment (21-day), consistent with rapid onset antidepressant-like effects. In summary, SCA-136 produces a behavioral, electrophysiological and neurochemical profile consistent with potential therapeutic activity in schizophrenia, depression, and bipolar disorder.

METABOTROPIC GLUTAMATE RECEPTOR 5 (MGLUR5) MODULATION OF PREFRONTAL CORTEX FUNCTION: REVELANCE TO SCHIZOPHERNIA

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Suboptimal activation of NMDA receptors in corticolimbic regions may play a role in cognitive deficits associated with schizophrenia. Although direct manipulation of regulatory sites on the NMDA receptor has been the primary approach for pharmacological enhancement of NMDA receptor function, targeting metabotropic glutamate receptors (mGluR) may be a more practical strategy for regulation of abnormal glutamate neurotransmission. Evidence suggests that modulation of NMDA receptors may be achieved by targeting the mGluR2 or mGluR5 subtype of mGluRs. We studied the effects of mGluR5 antagonist MPEP and the allosteric mGluR5 modulator CDPPB, alone or in combination with an NMDA antagonist on cognitive measures such as working memory, instrumental learning, set shifting, dopamine release in prefrontal cortex (PFC) and nucleus accumbens, and neuronal activity in the PFC of awake rats. MPEP or CDPPB did not impair working memory or set-shifting abilities, but MPEP dose-dependently exacerbated MK801-induced cognitive deficits. Both drugs were devoid of a major effect on the dopamine system. CDPPB exerted a dose-dependent influence on spontaneous activity of PFC neurons. CDPPB also affected the pattern of firing of PFC neurons by increasing the percentage of spikes in bursts. Pre-treatment with CDPPB blocked the effect of MK801 on PFC neuronal activity. These findings suggest that CDPPB reduces some of the disruptive effects of NMDA receptor deficiency. MPEP decreased the spontaneous burst activity of most mPFC neurons. This inhibition was selective for the most active cells because greater decreases were observed in neurons with higher baseline firing rates. MPEP augmented the effects of MK801 on burst activity, variability of spike firing and random spike activity. These findings demonstrate that in awake animals mGlu5 receptors tonically regulate the function of PFC neurons by two related mechanisms: (1) activity-dependent excitatory influence on spontaneous burst activity and, (2) potentiation of NMDA receptor mediated effects on firing rate and burst activity. These mechanisms support the idea that modulation of mGlu5 receptors may provide a pharmacological strategy for fine-tuning the temporal pattern of firing of cortical neurons.

DIFFERENTIAL EFFECTS OF SERTINDOLE AND RISPERIDONE ON EXTRACELLULAR DOPAMINE AND GLUTAMATE IN THE FRONTAL CORTEX OF CONSCIOUS RATS

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The 2nd generation of antipsychotics are characterized by a lower incidence or absence of extrapyramidal side effects compared with

conventional antipsychotics, as well as by variable effects on negative symptoms and cognitive deficits. A well-known effect that distinguishes 2nd generation from conventional antipsychotics is an increase in extracellular dopamine (DA) in frontal cortex. However, in recent studies in rats a differential effect of 2nd generation antipsychotics has been shown on impairment in a cognitive task depending on frontal cortex. Deficits were induced by subchronic phencyclidine in an extradimensional set shifting task (Rodefer et al, Int J Neuropsychopharmacol, 9, S140, 2006): Sertindole (SER) induced a significant reversal of impairment in extradimensional set shifting, while risperidone (RIS) had a numeric, but non-significant effect. The selective 5-HT2A antagonist, M100.907, mimicked the effect of RIS, while the 5-HT6 antagonist, SB-271046, was as effective as SER. This is in agreement with in vitro profiles indicating high and low 5-HT6 receptor affinities of SER and RIS, respectively, while both drugs have high affinities for 5-HT2A and D2 receptors (Leysen, 2000, In: Atypical Antipsychotics, p 57; eds BA Ellenbroek & AR Cools Birkhäuser). In the present studies we looked for effects on frontal cortical neurotransmitter levels that may differentiate between sertindole and risperidone. Male Sprague Dawley rats were prepared for standard microdialysis studies. Guides were implanted using Hypnorm/Dormicum anaesthesia 2-3 days before and dialysis probes were inserted 3 hrs before the experiments. SER (2.5-10 mg/kg, PO) or RIS (1.0 mg/kg, SC) were administered to awake rats, and dialysates were sampled in 20 min intervals for 4-7 hrs and analysed for DA and glutamate (GLU) using HPLC with electrochemical and fluorescence detections, respectively. Both drugs approximately doubled extracellular DA levels, while SER (10 mg/kg), but not RIS (1 mg/kg) induced a modest increase (40 %) in cortical GLU. This effect may be of importance for the cognitive improvement observed with SER. Furthermore, the results will be supplemented with analysis of extracellular levels of acetylcholine in cortex. Other ongoing studies explore the effects of selective 5-HT2A and 5-HT6 antagonists to further examine the hypothesis that enhancement of GLU and acetylcholine levels (perhaps in concert with increased DA) may correlate to effects on cognition.

BLUNTED "NEGATIVE" BUT NOT "POSITIVE" EFFECTS OF THC IN CANNABIS ABUSERS: IMPLICATIONS FOR CANNABIS ABUSE IN SCHIZOPHRENIA

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There is increasing recognition of a link between cannabis and schizophrenia. While cannabis exposure may be a risk for schizophrenia, cannabis use is also a common co-morbidity. Individuals with schizophrenia have higher rates of cannabis use relative to the general population and although cannabis use has a negative impact on the course and expression of schizophrenia, patients often report deriving "benefits" from its use. In attempting to reconcile this discrepancy, we first compared the effects of delta-9-tetrahydrocannabinol (THC) in schizophrenic patients and controls (both of whom did not abuse cannabis); relative to controls, schizophrenic patients exhibited greater THC induced cognitive impairments and psychotomimetic effects. However, whether cannabis abusing schizophrenic patients also show this vulnerability has not been studied. Recent data suggest that innate i.e., genetic factors influence the response to cannabis and the risk of cannabis addiction. We therefore examined the possibility that individuals who abuse cannabis may be protected from its "negative" effects by comparing the effects of THC in cannabis abusers and healthy controls. METHODS: In a 3-day, double-blind, randomized, placebo-controlled study, the behavioral (measured by PANSS,CADSS and VAS), cognitive (measured by HVLT), and physiological effects (heart rate) of 0 mg, 2.5 mg, and 5 mg intravenous THC were compared in 30 cannabis abusers and 22 healthy subjects (non-abusers). RESULTS: As expected, THC produced transient perceptual alterations and psychotomimetic effects, increased feelings of "high" and "anxiety" and impaired immediate and delayed recall in both groups. However, while abusers experienced the "positive" effects of cannabis such as "high" as much as non-abusers, they had significantly lower "negative" effects such as perceptual alterations, psychotomimetic effects, cognitive impairments and "anxiety". There were no differences between groups in the tachycardiac response to THC. CONCLUSIONS: Lower "negative" and/or greater "positive" drug effects have been associated with a greater likelihood of future drug use/abuse. This profile of THC effects in cannabis abusers suggests that innate differences in response to THC might explain why some but not others go on to abuse cannabis. The results of our study may also offer an explanation for the high rates of cannabis abuse in schizophrenia.

ZIPRASIDONE IN THE TREATMENT OF SCHIZOPHRENIA: EVIDENCE FOR A LINEAR DOSE-RESPONSE RELATIONSHIP

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The objective of this study was to examine the dose-response relationship of ziprasidone in patients with acute exacerbations of schizophrenia or schizoaffective disorder. Data were pooled from two 6-week, fixed-dose, placebo-controlled trials of ziprasidone.[1,2] Patients with acute exacerbations of schizophrenia or schizoaffective disorder received ziprasidone 40 (n = 86), 80 (n = 104), 120 (n = 76), or 160 mg/day (n = 103) or placebo (n = 71). Change from baseline to end point in Montgomery-Åsberg Depression Rating Scale (MADRS) and Positive and Negative Symptom Scale (PANSS) total score, subscales, and items were analyzed by group. A treatment effect size for each group was obtained and statistical testing for dose-response relationship applied. There was a significant linear dose-response relationship for MADRS (subjects with baseline MADRS ≥14) and PANSS total score, subscales, and items. Treatment effect sizes were consistently greatest in the 120 and 160 mg/day groups. Analysis of PANSS items showed linear dose-response relationships for 28 of 30 items, with the greatest treatment effect size in the 160 mg/day group for 19 items and in the 120 mg/day group for 9 items. In conclusion, an analysis of MADRS and PANSS scores demonstrated a significant linear dose-response relationship for ziprasidone in the management of schizophrenia and schizoaffective disorder, with the largest clinical benefits observed with 160 mg/day dosing. References 1. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology (Berl).* 1998;140:173–184. 2. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. *Neuropsychopharmacology.* 1999;20:491–505.

ACUTE EFFECTS OF THE AMPAKINE FARAMPATOR ON MEMORY AND INFORMATION PROCESSING IN HEALTHY ELDERLY VOLUNTEERS

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Introduction: Ampakines act as positive allosteric modulators of AMPA-type glutamate receptors and facilitate hippocampal long-term potentiation (LTP), a mechanism associated with memory storage and consolidation. The present study investigated the single dose effects of farampator (Org 24448) on memory and information processes in healthy elderly volunteers. Methods: A double-blind, placebo-controlled, randomized, cross-over study was performed in 16 healthy, elderly volunteers (8 male, 8 female; mean age 66.1, sd 4.5 years). All subjects received farampator (500 mg) and placebo. Testing took place one hour after drug intake, which was around Tmax for farampator. Subjects performed tasks assessing episodic memory (wordlist learning and picture memory), working and short-term memory (N-back, symbol recall) and motor learning (maze task, pursuit rotor). Information processing was assessed with a tangled lines task, the symbol digit substitution test (SDST) and the continuous trail making test (CTMT). Results: Farampator (500 mg) unequivocally improved short-term memory but appeared to impair episodic memory. Furthermore, it tended to decrease the number of switching errors in the CTMT. Drug-induced side effects (SEs) included headache, somnolence and nausea. Subjects with SEs had significantly higher plasma levels of farampator than subjects without SEs. Additional analyses revealed that in the farampator condition the group without SEs showed a significantly superior memory performance relative to the group with SEs. Conclusions: The positive results on short-term memory and the favorable trends in the trail making test (CTMT) are interesting in view of the development of ampakines in the treatment of Alzheimer's disease and schizophrenia.

NEW DIRECTIONS IN THE TREATMENT OF SCHIZOPHRENIA: MODULATORS OF MGLU2 AND/OR MGLU3 RECEPTORS

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Glutamate is the major excitatory neurotransmitter in the mammalian CNS responsible for mediating excitation in the majority of synapses and also plays a key role in long-term processes such as synaptic plasticity. In spite of the introduction of atypical antipsychotics and dopamine stabilizers, disability from schizophrenia is still a very high unmet medical need and thus exploration of these novel mechanisms may be the key to better understanding of the illness as well as future therapeutic advances. Glutamatergic drugs have potential to treatment certain features of schizophrenia depending on which processes are involved and the circuits that specific agents might correct. Evidence favoring this hypothesis includes the observation that drugs such as phencyclidine and ketamine which act via blockade of NMDA ion channel receptors for glutamate disrupt glutamate neurotransmission and exacerbate psychosis in schizophrenic patients. Metabotropic glutamate (mGlu) receptors (mGlu1-8) are coupled to G-proteins and, depending their expression and subtype, function to regulate glutamate neurotransmission via presynaptic, post-synaptic, and glial (production of second messengers that regulate glial function and expression of receptors, transporters and glial factors) mechanisms. With regard to the potential to treat schizophrenia, agonists for mGlu2/3 receptors and allosteric potentiators of mGlu2 receptors block the effects of psychomimetics (such as PCP, amphetamine, 5HT2A agonists) in animals and/or humans. These agents appear to work by preventing glutamatergic hyperexcitations in limbic circuits that has been associated with the actions of psychotogens and possibly in the symptoms of schizophrenia. In essence they will be useful to test the clinical relevance of glutamate hyperexcitability to the etiology of schizophrenia. Their usefulness either alone or in combination with other agents such as atypical antipsychotics needs further study in animals and possibly humans. Overall, the effectiveness and long-term safety of all these agents needs further exploration in animals and humans. Nevertheless, these mGlu receptor active agents represent novel approaches for schizophrenia treatment in a field where monoaminergics are essentially the only agents shown to be effective clinically. This presentation will present the progress made on the discovery and development of mGlu2 and/or receptor active agents for treating schizophrenia.

SOCIAL COGNITION AND NEUROCOGNITION: EFFECTS OF RISPERIDONE, OLANZAPINE, AND HALOPERIDOL

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This study examined the effects of first- and second-generation antipsychotic medications on social cognition and neurocognition. One hundred patients with schizophrenia or schizoaffective disorder participated in an eight week, double blind study of risperidone, olanzapine, and haloperidol. Participants were administered multiple measures of social cognition, neurocognition, and clinical symptoms at baseline, end of week 4, and end of week 8. Seventy three patients completed the baseline assessment and at least one other assessment. Their data were analyzed (N = 73) using mixed effects ANCOVAs. For data reduction, the social cognitive measures were clustered into a summary score, and the neurocognitive measures were clustered into two summary scores. There were no treatment-related differences on any of the three summary scores. One neurocognitive score, general neurocognitive ability, increased during the study period for patients receiving all three medications. The present findings did not find evidence of differential treatment effects on social cognition.

ASENAPINE SHOWS HIGH AFFINITY AND POTENT ANTAGONIST ACTIVITY AT AN ENSEMBLE OF HUMAN 5-HT RECEPTOR SUBTYPES

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Modulation of central serotonergic function may be beneficial in terms of improved effectiveness and tolerability in the treatment of patients with schizophrenia. Asenapine is a novel psychopharmacologic agent in development for the treatment of schizophrenia and bipolar disorder. The goal of this research is to compare the antag-

onist effects of asenapine binding at cloned human 5-$HT_{1A/1B}$, 5-$HT_{2A/2C}$, 5-HT_6 and 5-HT_7 receptors versus the effects of olanzapine and risperidone. Receptor binding and functional activity results were determined using membranes and whole cells, respectively, from cell lines expressing cloned human receptors. Asenapine was tested for effect on basal and stimulated activity. Changes in intracellular cAMP (5-HT_6 and 5-HT_7) or Ca2+ (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}) levels, induced at submaximal agonist concentration, were used to assess functional activity. Affinity at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors was higher with asenapine (pKi 8.6, 8.4, 10.2, 10.5, 9.6, 9.9) than with olanzapine (5.8, 6.6, 8.9, 8.4, 8.5, 7.4) or risperidone (6.8, 7.3, 9.7, 8.2, 5.7, 9.1). Asenapine showed no agonist activity at any of these receptors under the assay conditions used. In tests for antagonist activity, asenapine demonstrated potent blockade of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors (pKB 7.4, 8.1, 9.1, 9.0, 8.0, 8.5) whereas olanzapine (<5.5, 6.7, 8.6, 7.7, 7.4, 6.9) and risperidone (6.4, 7.7, 9.2, 6.6, <5, 8.5) showed generally lower potency and a different rank order of antagonist activity across these receptors. In addition, asenapine showed similar affinity and comparably potent antagonist effects at 5-HT,sub>6 and 5-HT^7 receptors, whereas olanzapine and in particular risperidone showed more disparate results for binding affinity and for antagonist activity at these 2 receptors. In this study, asenapine showed greater binding affinity as well as a more potent and distinct antagonist signature than olanzapine and risperidone at an ensemble of serotonin receptor subtypes. Potent and concerted modulating effects at these key central receptors may contribute towards a more favorable efficacy and tolerability profile in patients with schizophrenia or bipolar disorder.

NOVEL POTENT AND SELECTIVE PDE10A INHIBITORS SHOW ACTIVITY IN ANIMAL MODELS OF PSYCHOSIS AND ANXIETY

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PDE10A is a dual-substrate phosphodiesterase highly expressed in the primary projection neurons of the striatum, nucleus accumbens and the olfactory tubercle (Seeger et al. 2003). We have previously reported that inhibition of PDE10A with papaverine produces activity in several models predictive of antipsychotic activity (Siuciak et al., 2006). Here we characterize novel, chemically distinct and potent inhibitors (PQ10, MP10 and TP10; IC50 for rat recombinant PDE10A = 6.0. 0.48, and 0.32 nM, respectively), highly selective for PDE10A versus other PDE gene family members and CNS receptors. These inhibitors suppress conditioned avoidance responding (CAR) in wild-type but not PDE10A knockout mice, consistent with this activity being mediated through PDE10A inhibition. They also inhibit PCP and amphetamine-stimulated locomotor activity and show only a partial, modest induction of catalepsy. In two animal models of anxiety, the elevated plus maze and fear potentiated startle, anxiolytic activity is also observed. PDE10A inhibition resulted in a dose-dependent elevation of striatal cGMP (4-5x) compared to D2 antagonists (2x). Striatal pCREB, a marker of the cAMP signaling pathway, was also elevated. Unlike D2 antagonists, the elevation of both cGMP and pCREB was not prevented by MK-801. The effect of PDE10A inhibition on striatal cAMP was confirmed using in vivo microdialysis in the rat. MP-10 and TP-10 increased extracellular concentrations of both striatal cGMP and cAMP. Reverse dialysis with the NOS inhibitor, L-NAME, prevented the increase in cGMP produced by MP-10 without affecting the elevation of extracellular cAMP. The present studies are the first to describe the development of potent, selective and brain-penetrant PDE10A inhibitors and confirm both biochemical and behavioral evidence of striatal activation. These data provide additional evidence that PDE10A inhibitors may produce a clinical profile very different from the currently used D2 therapies.

S 36549 (EGIS 11150) PREVENTS STRESS-INDUCED IMPAIRMENT OF SYNAPTIC PLASTICITY

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The hippocampus to ventromedial-prefrontal cortex (H-PFC) pathway plays a major role in the executive control of context, and may be disrupted in schizophrenia. Drugs which restore transmission in this pathway may be novel antipsychotic agents. We screened a series of 20 compounds on three parameters in this pathway : 1) theta coherence, 2) antagonism of phencyclidine (PCP, Sebban et al., 2002), 3) antagonism of stress-induced inhibition of plasticity (LTP). EEG: PFC power spectra (1 - 30 Hz) were obtained from conscious rats. S 36549 was found to increase 8-9 Hz spectra (and H-PFC coherence) from 2 µg/kg ip in a dose-dependent manner and was >30x more potent than clozapine, > 100x olanzepine >risperidone, haloperidol. From 10 µg/kg ip S 36549 was the only of these drugs to completely antagonise the effects of PCP on PFC EEG, and to antagonise PCP-induced behaviour. LTP: Acute platform stress inhibits H-PFC LTP induced in vivo in the rat (Rocher et al, 2004): clozapine (0.3 mg/hg ip) administration restores LTP. S 36549, at the same dose (10 µg/kg ip) which induces H-PFC theta coherence and fully antagonises the effects of PCP, fully restored stress-inhibited LTP (and had beneficial effects in memory paradigms). S 36549 has a unique profile as a potential antipsychotic agent, which is not readily explained by its receptor profile. C. Rocher, et al., (2004) Cereb Cortex. 14, 224-229 C. Sebban, et al., (2003) Br J Pharmacol, 135, 65-78

AN INITIAL ANIMAL PROOF-OF-CONCEPT STUDY FOR CENTRAL ADMINISTRATION OF CLOZAPINE IN SCHIZOPHRENIA PATIENTS

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The recent NIH sponsored CATIE 2 study has highlighted the superiority of clozapine for the treatment of schizophrenia symptoms. Clozapine is also one of the few antipsychotics to improve the sensory inhibition deficit common in schizophrenia, and the only one which spontaneously suppresses smoking behavior in this population. Unfortunately, its oral usage is limited due to its side effect profile including agranulocytosis, a systemic bone marrow disorder. A reduction in the circulating levels of clozapine while still maintaining the CNS effectiveness could allow greater use of this drug while reducing the risk of the life-threatening side effect. The DBA/2 mouse has a deficit in sensory inhibition that

models that seen in schizophrenia patients. This mouse model has proven efficacy for both mechanistic studies and the development of new therapeutics. We administered clozapine directly into the anterior lateral ventricle of the DBA/2 mouse at a dose of 0.5 or 1 μg in 1 μl of saline. Both doses showed improved sensory inhibition through a reduction in TC ratio ($F(23,184)=3.07$, $p<0.001$, $F(23,184)=3.07$, $p<0.001$, respectively) with the 1.0 μg dose showing both statistically significant suppression of the test amplitude and increase in conditioning amplitude. This dose is 1/1000th the intraperitoneal systemic dose which improved sensory inhibition in this mouse model. Clozapine is difficult to maintain in solution at physiological pH, but we have demonstrated stable solutions for 2 months with the addition of β-cyclodextrin. This combination of clozapine/β-cyclodextrin was not shown to be toxic to primary neuronal cell cultures until the concentration of clozapine reached 10 μg/ml and β-cyclodextrin itself was not shown to be toxic at concentrations up to 0.1%. These data suggest that central administration of clozapine via a chronically implanted pump and catheter system, similar to that used for intrathecal administration of pain medication, may be a viable alternative approach for the treatment of medically refractive schizophrenia patients. This work supported by a University of Colorado POC Grant to TJA.

SCHIZOPHRENIA ENDOPHENOTYPES AS TREATMENT TARGETS

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Until recently, the development of drug treatment in schizophrenia has mostly focused on models of psychosis and dopaminergic function. Thus the available treatments in schizophrenia are mostly ineffective against primary negative symptoms as well as cognitive and information processing deficits associated with the disorder. Previous research has identified several neurophysiological deficits in schizophrenia that are enduring, frequently occurring before psychosis, and marking the disease liability. These include deficits in the smooth pursuit eye movements, antisaccade, memory saccade, pre-pulse inhibition (PPI), evoked P50 sensory gating, and cognitive functions including attention, memory, and executive functions. Most of these impairments are not improved by the traditional drug treatments. These schizophrenia endophenotypes provide important targets for novel treatment development as they represent the core deficits of the disorder, occur in closer proximity to the genetic effects than the clinical symptoms, can be modeled in laboratory animals, and may have relevance for early intervention and preventative treatment strategies. Preliminary data from an ongoing schizophrenia family studies show that these endophenotypes are mostly independent of each other and are associated with different candidate genes. This suggests that different treatments will affect different endophenotypes and symptom domains. This is demonstrated by two proof-of-concept studies using a gamma amino butyric acid (GABA) agonist, tiagabine, and nicotine. Earlier studies have shown that pursuit initiation deficit marks deficit syndrome liability, while predictive pursuit abnormality occurs in relatives of all schizophrenia patients thus marking psychosis liability. A drug probe study using nicotine showed that nicotinic agonist normalize initiation deficit in schizophrenia patients ($n=17$; $p < 0.01$) without affecting the predictive pursuit measure. Pilot data from tiagabine showed that the GABA agonist improved predictive pursuit.

SUBJECTIVE ATTITUDE TOWARDS ANTIPSYCHOTICS AND NEUROCOGNITIVE FUNCTIONS IN SCHIZOPHRENIC INPATIENTS

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Objective: This study aimed to examine the relationships between subjective attitudes towards antipsychotics and objective cognitive function in schizophrenia patients. Method: The subjects of study were clinically stable schizophrenic patients (N=55) who were hospitalized in Naju National Hospital. They were grouped into positive (N=35) and negative drug attitude groups (N=20) by Drug Attitude Inventory (DAI-10). They were assessed using Positive and Negative Syndrome Scale, Calgary Depression Scale for Schizophrenia, Extrapyramial Symptom Rating Scale, UKU side effect rating scale, Social and Occupational Functioning Assessment Scale and Subjective Well-being Under Neuroleptic Treatment. A battery of neurocognitive tests were also administered using Seoul Computerized Neurocognitive Function Test. Results: Patients between positive and negative drug attitudes did not differ in social demographic and clinical characteristics. They also showed no differences in neurocognition tests except a subset of verbal auditory learning test. Conclusions: These findings may indicate no associations between subjective drug attitudes and objective neurocognitive dysfunctions in schizophrenic inpatients. It suggests that subjective aspects measured by DAI may be a distinct dimension from objective neurocognitive profiles in terms of compliance.

18. Health Economics & Services Research

EVALUATING EARLY PSYCHOSIS TREATMENT SERVICES WITH PERFORMANCE MEASURES

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Objective: The purpose of this research was to apply a previously identified set of consensus derived performance measures in order to evaluate an early psychosis treatment service. Methods: This study was conducted in three phases. First a literature review, then a multi-stakeholder Delphi process to identify essential measures. In the third phase operational definitions were developed and measures were scored from a variety of sources including corporate data bases, clinical data bases and chart review. Results: Forty one measures were scored including 12 effectiveness measures. The measures covered 7 of 8 domains recommended for service level evaluation by the Canadian Institute for Health Information. Effectiveness results included 62% of patients being admitted to the program as outpatients, 86% remaining in the program after one year, 2.5% attempting suicide in their first year and cumulative inpatient admissions of only 14% at two years. Discussion: The set of measures proved feasible to collect and provides a performance framework that assesses key processes and outcomes. It also documents achievement of program objectives. The outcomes achieved in this real life clinical service are comparable to those achieved in clinical trials of specialized early psychosis treatment services. The measures were considered feasible and useful for evaluation of early psychosis services and may hold promise for similar programs.

FOOD CHOICES AND POTENTIAL FOR WEIGHT LOSS IN PATIENTS ON SECOND GENERATION ANTIPSYCHOTICS

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It has now been well documented that patients taking second generation antipsychotic medications, in particular olanzapine and clozapine, are at much greater risk for weight gain, obesity, and the development of the Metabolic Syndrome. What still needs to be determined is the mechanism for the weight gain and what, if any, appropriate interventions can be implemented to minimize the health consequences faced by these patients. Factors common in people with schizophenia, such as a sedentary lifestyle and poor nutrition may contribute to the development of the Metabolic Syndrome. There has also been speculation that overactivity of the hypothalamic-pituitary-adrenal axis, leading to hypercortisolemia, may result in excessive visceral fat accumulation (Ryan & Thakore, 2002). The current investigation includes an evaluation of food choices made by patients on clozapine and olanzapine, measurement of weight and waist to hip ratios, and the differential weight loss of these two groups when participating in a Weight Watchers program. Both groups were compared with a control group taking no medication in a study that sought to observe the behavioral component of satiety after a standardized meal. As part of this study, subjects were asked to rate the importance of the following variables: taste, fullness, cost, looks, prep time, and eat time. Patients on olanzapine (m=3.62) and patients on clozapine (m=3.08) felt that fullness was significantly more important than controls (m=1). Olanzapine patients rated the importance of flavor when consuming a meal or snack as significantly less important than both clozapine and control groups. This could indicate that olanzapine patients are not as discriminating in what they choose to eat. Both patient groups in this study had larger waist to hip ratios than controls, though all three groups were overweight. Preliminary analyses comparing a group of olanzapine patients (n=11) to a group of clozapine patients (n=6) participating in a Weight Watchers group revealed that patients on olanzapine lost a mean of 3.12 pounds, whereas patients on clozapine lost a mean of 5.4 pounds after 8 weeks. While both groups were able to benefit from a standardized intervention and group differences were not statistically significant, the differentially greater success of one group may further inform us regarding the mechanism for the initial weight gain. Some support provided by Eli Lilly and Company and ACISR pilot project funding.

BASIC EMOTIONS AND POSITIVE SYMPTOMS IN NEEDS FOR ACTIVATION AND SOCIAL ADAPTATION IN SUBJECTS SUFFERING FROM SCHIZOPHRENIA

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Background. It is often assumed that positive symptoms are of primary relevance in subjects suffering from schizophrenia. Basic emotional functioning is often insufficiently assessed. Emotions might be relevant for clinical practice. Method. All severe mental illness patients in a 650.000 inhabitant catchment area in the South of the Netherlands are assessed repeatedly for psychopathology (BPRS rated anxiety, depression, hallucinations and delusions) and need for care (CAN rated needs for activation and social contact) using a Cumulative Need for Care Monitor. Results. 1350 subjects were assessed. The relation between needs for activation was related to the level of depression and delusions but not to anxiety and hallucinations (Chi2=113.57 p<.0001). Both were also related to the success of interventions for these SMI patients (Chi2=137.23 p<.0001). Needs for social contact were related to anxiety, depression and delusion but not hallucinations, treatment success only to the emotions (Chi2=182.86 p<.0001). Conclusion. Monitoring the patient's emotions seems to be more important than focussing on positive symptoms to attain success in psychiatric rehabilitation. Delusions are more important than hallucinations.

STATISTICAL METHODS FOR COMPARING ANTIPSYCHOTIC TREATMENT COSTS: CONCERNS WITH LOG TRANSFORMATIONS

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Due to the chronic nature and early onset of schizophrenia, treatment costs for schizophrenia patients can have high impact on health care payer budgets. Cost comparisons of various antipsychotic treatment regimens are thus extremely important to health care payers and researchers. Statistical comparisons are complicated by highly skewed cost distributions and the need to assess means (not medians)

to estimate, say, per-member-per-month costs. Some common statistical methods, such as utilizing ranked or log-transformed data, require strong assumptions to yield valid estimates of arithmetic means. Focusing on the total cost of schizophrenia care, we first review the assumptions necessary for valid cost comparisons using either rank or log transformed data. Second, using actual data from three schizophrenia naturalistic trials, we demonstrate that alternative approaches can yield contradictory cost differences between conventional and atypical medications. The assumptions required for rank and log transformed analyses to yield valid estimates of mean costs are typically not satisfied when comparing costs of conventional with atypical antipsychotics. In particular, the assumption that variances of log costs are equal within subsets of patients treated with either conventional or atypical antipsychotics can be particularly unrealistic. Failure of this assumption was so dramatic that log-transformed analysis suggested statistically significant treatment differences ($p<.05$) in two studies, while bootstrapping suggested no hint of any difference ($p>.90$) in one study and statistical significance in the opposite direction in another study! Comparisons of costs within the atypical class were more consistent across alternative statistical analyses. Given the dramatically different results obtained utilizing three alternative statistical approaches, it is critical that authors, reviewers and consumers of antipsychotic cost comparisons fully disclose and understand the implications of the basic assumptions behind alternative methods. The assumption (homoskedasticity) necessary for log-transformed cost data to yield valid comparisons of conventional antipsychotics with atypical antipsychotics should not be made without verification. Given the importance of treatment cost differences to healthcare payers, we recommend using robust methods requiring fewer distributional assumptions, such as non-parametric bootstrapping. Funded by Eli Lilly and Company

INDIVIDUAL PLACEMENT AND SUPPORT (IPS) IS EFFECTIVE ALSO IN EUROPE

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The effectiveness of IPS in helping people with severe mental illness into open employment has been demonstrated in several North American studies. There is little evidence to determine whether IPS will be equally effective in European countries with very different welfare provisions and conditions of employment. A randomised controlled trial was conducted in six European centres. Patients with psychotic illnesses (n=312) were followed up for 18 months. One-hundred-fiftysix were treated with IPS, while 118 received traditional vocational rehabilitation treatments. The primary outcome was the difference between the proportion of people entering competitive employment in each service. The heterogeneity of IPS effectiveness was explored using prospective meta-analyses to determine the impact of socio-economic context. Associations between working and clinical and social functioning were explored using multi-level regression modelling. IPS was more effective than the Vocational Services for every vocational outcome, with IPS patients twice as likely to get a job. Vocational Service patients were significantly more likely to have dropped out of the service and to have been hospitalised. Local unemployment rates explained a significant amount of the heterogeneity in IPS effectiveness. National welfare systems explained overall employment rates. Working was associated with better clinical and social functioning and with better overall quality of life and greater satisfaction with job situation, although the differences were small. IPS clearly increases dramatically the access to work of people with psychotic illnesses, without any corresponding clinical deterioration. Its effectiveness varies in different European centres and is affected by context, in particular it seems to work better in contexts with higher long-term unemployment rates.

Outcome	N	IPS	Vocational	Difference	95% CI
Worked for at least 1 day	312	85	43	26.9%	16.4%/ 37.4%
Number of hours worked	281	428.8	119.1	308.7	189.22/ 434.17
Number of days employed	306	130.3	30.5	99.8	70.71/129.27
Job tenure (days)	122	213.6	108.4	104.9	56.03/ 155.04
Drop-out from service	312	20	70	-32.1	-41.5/-22.7
Hospitalized	273	28	42	-11.2	-21.5/-.90
Time in hospital (%)	273	4.6	8.9	-4.3	-8.40/-.59

CULTURAL AND REGIONAL DIFFERENCES IN THE PANSS

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Background There are numerous potential cultural and ethnic factors that may influence the outcome of international schizophrenia trials. Cultural perspectives and related symptom interpretation have been shown in previous studies to influence ratings on some commonly used rating instruments such as the YMRS for mania and PANSS for schizophrenia. Previous studies on the PANSS have suggested that a 5-factor structure be applied when analyzing data collect on the PANSS. This structure divides the PANSS into 5 symptom groups: Positive, Negative, Excitement, Cognitive and Depression/Anxiety. However this structure has not been widely validated across multiple cultures and languages. This study evaluates differences among PANSS raters across 6 regions of the world and accesses their scoring of all 30 items in a videotaped patient interview. Methods Raters from 6 regions (Eastern Europe, Western Europe, South America, North America, Asia and South Africa) were required to rate a videotape PANSS subject interview as part of the rater qualification process to rating in a Schizophrenia trial. Data was collected from multiple investigators' meetings from 2004 – 2005. The video was of an English speaking, African-American patient that was subtitled into the 12 non-English languages used in the study. The video was shown to 396 trained clinician raters. Raters were asked to review the videotaped interview and score all 30 PANSS items. All raters' scores were compared to the scores of an expert consensus panel for overall concordance on each item. A factor analysis was conducted on the PANSS for each region to compare it to the 5-factor structure. Additionally, we examined the internal consistency of the 5-factor structure for each region. Results Preliminary data suggests that there may be cultural/ regional variability in the 5-factor structure for analyzing data for the PANSS. A detailed analysis of PANSS items and the 5- factor structure by region will be presented in the paper. Discussion The PANSS is the most widely used instrument to assess efficacy in schizophrenia trials. While this data does not contradict the use of the PANSS, it does suggest that scoring of the PANSS may be affected by culture and/or region. This does suggest the need for additional cross-cultural studies for the PANSS, which may result in alteration of the 5-factor structure that has been previously employed when analyzing data for the PANSS.

BRAIN BANKING FOR NEUROSCIENCE: HELPING SCIENTISTS FIND CAUSES AND CURES FOR NEUROPSYCHIATRIC DISORDERS

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The NSW Tissue Resource Centre (TRC) was established in 1994 at the Department of Pathology, University of Sydney (Australia) with the aim to collect, store and distribute fresh-frozen and fixed post-mortem brain tissue for neuropsychiatric research. The TRC focuses on schizophrenia and allied disorders and other neuropsychiatric conditions. Tissue requests received by the NSW TRC from researchers are evaluated and approved by scientific advisory committees. An annual evaluation questionnaire is sent to all researchers who use TRC material. The evaluation form requests information on publications and presentations resulting from research projects, other information on quality and availability of tissues, TRC performance and any suggestions to the TRC. Over the past decade the TRC has collected 445 cases. Tissues have been sent to 108 researchers (84 national and 24 international) for 260 different projects, which resulted in 94 peer-reviewed publications. In 2004/05, the last evaluation period, there were 35 research projects compared to a total of 34 projects in the first 5 years. The most popular research methodologies are genomics (37%) and proteomics (31%), requiring fresh-frozen brain tissue. This is different to the 1994/99 period where 85% of tissue requests were for neuropathological studies (fixed tissues). The size of tissue samples required has decreased dramatically from blocks of 5-10 grams in the 1990's down to 0.1g of tissue today. Thus one brain can be used for multiple research projects. This increases the value and potential outcomes from each case. Data from different studies on the same cases can be cross-correlated – a value-added outcome. All researchers surveyed indicated that tissue samples were critical for their projects and the quality of tissue was satisfactory. Approximately 70% of researchers asked for additional information including clinical, neuropathological and life style. More than half indicated that they plan to approach the TRC with new tissue requests for further projects. The TRC is highly responsive to research demands and modifies protocols and procedures to accommodate new technologies and optimize tissue quality and availability. The TRC is a key resource facility for research into the biological basis of alcohol use disorders, schizophrenia and other neuropsychiatric diseases. It is not only a Brain Bank but also a centre for research, education and community awareness.

BELGIAN SCHIZOPHRENIA OUTCOME SURVEY

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Objective: The Schizophrenia outcome survey (SOS) compared psychopathology, adverse events and medical cost in out-patients with schizophrenia in Belgium during 2 years following hospitalization for an acute psychotic episode. Methods: Patients older than 18 and stabilized with haloperidol(H), olanzapine(O) or risperidone(R) entered this observational study at discharge from the hospital and were assessed at baseline, after 3, 6, 12, 18 and 24 months using Brief Psychiatric Rating Scale (BPRS), CGI, and spontaneous adverse events reporting. Results: 323 patients were included (H32, O149, R142). At the start of the study, the patients were stabilized on their treatment for about 6 months. The O and R group were comparable except for more first episode patients in the R group. (H6%, O17%, R27%). H patients had more residual schizophrenia, were more frequently hospitalized, were evaluated as less treatment resistant and had more EPS. Overall 68% (219/323) of the patients completed the 2 years follow up (H59%, O66%, R71%). Treatment continuation (patients who didn't drop out and without antipsychotic medication change or addition) was 31%(H), 50%(O) and 43%(R). The mean duration of haloperidol treatment was 476 days at a mean dose of 8.9 (±9.6) mg/day, of olanzapine 545 days at a mean dose of 14 (±6) mg/day and of risperidone 513 days at a mean dose of 4.2 (±1.9) mg/day. The mean duration of hospitalization was H 94 days (±166), O 48 days (±91), R 55 days (±122). Total medical costs over 2 years were H 30484 [lHl] (± 36332), O 20897 [l)l] (± 27863), R 20916 [l8l] (± 31776) The CGI improved during the first 3 months, the BPRS deteriorated in the first year and then remained stable. The percentage of patients with at least 1 EPS (LOCF) at the last visit was: H66%, O48% and R49% and at least 1 sexual problem was H69%, O40%, R44%. Weight gain was H 0.53 (± 5.0) kg, O 3.3 (±8.3) kg and R 3.2 (±8.4) kg. Conclusion: Patients stabilized on antipsychotic monotherapy and discharged from hospital were followed up for 2 years. Even in this group of stabilized patients, treatment continuation was poor: only in 1 out of 3 haloperidol patients, treatment was not changed during the 2 years follow up. The fewest treatment change was in the olanzapine group (1 out of 2). Although not significantly different, treatment cost was higher in the haloperidol group and similar in olanzapine and risperidone group as hospitalization was the main cost driver.

CAN SPECIALIZED EARLY PSYCHOSIS PROGRAMS REDUCE SUICIDE RATES IN FIRST EPISODE PSYCHOSIS?

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This study examined the impact of a specialized early psychosis (EP) treatment program on suicide risk following first contact with mental health services. The study setting was all public mental health services in the state of Victoria, Australia. The study used a retrospective cohort design, with a variable maximum follow-up period of up to 8.5 years. A cohort of 7,760 individuals (59.7% males) with a psychotic disorder, aged 15 to 29 years at inception, was ascertained from a statewide psychiatric case register containing patient-level socio-demographic, clinical and treatment information. Suicides were identified by linking the psychiatric register to a coronial register of unnatural deaths. Psychiatric service activity data were used to determine which members of the cohort had received treatment at the Early Psychosis Prevention & Intervention Centre (EPPIC), a specialized EP treatment program offering an 18-month episode of care. Cox proportional hazards (PH) models were used to investigate potential risk factors, including specialized EP treatment, for suicide. Univariate analyses were used to select potential predictors for inclusion in multivariate models. The median follow-up period was 4.2 years; 154 suicides were identified. The cumulative suicide rate was 0.7% by the end of the first year, 1.5% after 3 years, 2.3% after 5 years, and 4.2% over the entire follow-up period. Over the entire period, the survival functions did not differ significantly between the EP and No EP Treatment groups (logrank χ^2=0.04, df=1, p=0.84). However, the results of the multivariate Cox PH

analysis indicated that, after adjusting for the effects of other variables, the risk of suicide in the first 3 years of treatment was 50% lower for the EP Treatment group (adjusted hazard ratio=0.52, 95% confidence interval=0.27-0.99). Beyond 3 years, the EP Treatment group was exposed to greater risk, although this was not statistically significant. History of inpatient treatment, larger quantum of treatment, and shorter time to establish a psychotic diagnosis were associated with increased suicide risk. Being outside the labor force exerted a protective effect. Results suggest that the EP treatment model affords substantial protection from suicide while the EP intervention is delivered, and for a limited period afterwards. The topography of suicide risk suggests that longer periods of EP care, possibly 5 years, may be required to sustain a positive impact on suicide rates.

PREVALENCE OF SCHIZOPHRENIA AND BIPOLAR DISORDER IN A STATE MEDICAID SYSTEM

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The purpose of this study was to determine the annual prevalence of schizophrenia and bipolar disorder in a state Medicaid population during the period between 1998 and 2002. Patients were identified by at least 1 inpatient or 2 outpatient claims with an ICD-9-CM (295.00–295.99) diagnosis of schizophrenia or at least 2 or more paid claims with an ICD-9-CM (296.00-296.19, 296.40-296.89) diagnosis of bipolar disorder. Annual prevalence rates were calculated using all patients with a diagnosis of schizophrenia or bipolar disorder for a specific year as the numerator and the number of people eligible for state Medicaid within the specified year (obtained from Health Care Financing Administration [HCFA] 2082 Reports) as the denominator. The eligible population comprised people with paid claims in the Medicaid claims database as well as those people eligible for Medicaid who had never used or claimed any services. Among the state Medicaid population, total annual prevalence rates for schizophrenia and bipolar disorder ranged from 0.9% to 1.6% and 0.7% to 1.7%, respectively, between 1998 and 2002. The annual prevalence of bipolar disorder among patients between 20 and 64 years of age increased from 1.3% in 1998 to 3.3% in 2002. Similar increases in annual prevalence rates for schizophrenia were observed in this age group (from 2.2% to 3.2%). In younger patients (up to 14 years of age), annual prevalence rates were 0.02% to 0.04% and 0.02% to 0.06% for bipolar disorder and schizophrenia, respectively, between 1998 and 2002. In this state Medicaid patient population, annual prevalence rates for schizophrenia and bipolar disorder demonstrated a steady increase from 1998 to 2002. These findings highlight higher prevalence rates for schizophrenia in the Medicaid population compared with the general population, and may be of particular importance for health services planning. Supported by funding from AstraZeneca Pharmaceuticals LP.

FOSTERING UNDERGRADUATE ENGAGEMENT IN SCHIZOPHRENIA SERVICES AND RESEARCH

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The George Washington University undergraduate curriculum includes Dean's Seminars, limited-enrollment classes led by full-time faculty, to provide an in-depth introduction to issues of particular significance. In an effort to increase awareness of schizophrenia as a significant public health problem and to encourage students to develop an interest in schizophrenia services and research, a seminar that focuses on schizophrenia is offered. This seminar explores the history of the diagnosis and subsequently on advances in reliable and valid characterization of the antecedents, onset and psychopathological features of schizophrenia; although schizophrenia as a diagnostic entity is over 100 years old, controversy remains regarding the boundaries of the syndrome, its course and treatment. In addition, the important role of public health policies in affecting service availability for severe mental illness is reviewed. While long-term outcome for seminar students is pending, immediate outcomes include significant student interest and action in pursuing careers in schizophrenia services and research.

ASSOCIATIONS BETWEEN NEGATIVE SYMPTOMS, SERVICE USE, AND COSTS FOR PATIENTS WITH SCHIZOPHRENIA IN FIVE EUROPEAN COUNTRIES

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We analyzed the use and cost of clinical services in the presence or absence of negative symptoms in patients with schizophrenia from Amsterdam, the Netherlands; Copenhagen, Denmark; London, England; Santander, Spain; and Verona, Italy. Negative symptoms were documented using the Brief Psychiatric Rating Scale and assessed in terms of presence, severity scores, and component scores. Other data were collected using the Global Assessment of Functioning, Camberwell Assessment of Need, Lancashire Quality of Life Profile, and Verona Service Satisfaction Scale. Multiple regression models were used to analyze the impact of negative symptoms on the utilization and costs of inpatient, outpatient, and community-based services, controlling for the influence of age, gender, marital status, employment status, race, education, psychiatric history, and study center. The sample comprised 404 patients (mean age, 41 y) from the five study centers; 57% were men, 65% were single, 85% were white, 69% were living alone or with relatives, and 70% were unemployed or on pension. Negative symptoms were present in 247 patients (63%), with the lowest incidence in Verona (50%) and the highest in Amsterdam (79%). Patients with negative symptoms incurred higher mean costs for inpatient care, day care, community services, residential care, and total costs but lower costs for outpatient care. After adjusting for sociodemographic and clinical variables, the only statistically significant difference was annual total costs, which were higher for patients with negative symptoms. Analysis by center showed no significant correlations between negative symptoms and costs in Amsterdam or Copenhagen; in London, presence of negative symptoms and higher symptom scores were both related to increased inpatient and total costs, and component scores were related to total costs; in Santander, component score was inversely related to outpatient costs; and in Verona, symptom score was associated with higher inpatient and total costs while component score was associated with higher outpatient and total costs. In this survey, the most consistently seen correlations were between negative symptoms and higher inpatient and total costs. The lower outpatient cost associated with negative symptoms merits further investigation.

ONE YEAR ESTIMATE OF DEPOT ANTIPSYCHOTIC ADHERENCE AND READMISSION IN AUSTRALIAN COMMUNITY MENTAL HEALTH SETTINGS

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This study aimed to (1) To establish the actual or 'found' depot adherence rate in typical community psychiatric settings, (2) To describe the sociodemographic associations with depot adherence, (3) To investigate the relationship between the degree of depot adherence and admission rate to hospital. Patients treated with depot antipsychotics were sampled from CCT settings in two AMHSs in urban Melbourne. Depot adherence was defined as patients receiving their injection ± 7 days from the due injection date. Sociodemographic data was acquired from relevant administrative databases. The study finds that there is a high mean adherence rate (93%) and the rate of complete adherence is 54%. Patients' adherence was not related to: gender, being subject to a community treatment order (CTO), being of non-English speaking background, long durations of illness nor, time on depot treatment. Twenty-eight percent were admitted in the study year and admission was significantly inversely proportional to depot adherence ($p < .001$). The risks of readmission increase significantly when patients are less than 85 percent adherent having a relative risk of readmission of 2.63 and for those with less than 75% adherence, a relative risk of 4.32 ($p < .01$) To our knowledge this is the first study to report on the FDAR in community-treated patients. The finding that below 85% adherence, readmission is significantly more likely suggests that there may be a role for carefully and progressively monitoring depot adherence in community services. Reduction in relapses from enhanced adherence will have clinical, social, and economic benefits.

Logistic regression of readmission by adherence rate controlling for centre and age

Predictor	B	SE	p-value	RR
Adherence (full=ref)				
<75	3.07	0.974	0.002	4.32
75-85	1.469	0.742	0.048	2.63
85-93	0.861	0.67	0.199	1.87
93-99	0.085	0.873	0.923	1.07
Centre	1.11	0.56	0.047	2.10
Constant	-1.08	0.341	0.002	

Model $\chi 2$ (5) = 15.055, p= .010; Nagelkerke R Square .193

COSTS OF SCHIZOPHRENIA DURING FIVE YEARS

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The early onset and chronic nature of schizophrenia result in major cumulative direct costs from medication, hospitalization and sheltered living, but also large indirect costs due to inability to participate fully in the work force. To explore the direct and indirect costs in we followed a cohort of 158 risperidone-treated patients with schizophrenia, and schizophrenia-related disorder, annually over five years. The study describes costs for medication, hospitalization, sheltered living, and productivity losses, as well as degree of social isolation. Results: The direct costs were dominated by hospitalization and sheltered living expenses, while drug costs only represented 6% of the direct costs. Indirect costs represented 43% of the total costs during the five years. About 12% worked full-time, and 12% worked part-time, resulting in large productivity losses. Conclusion: As a consequence of the national mental healthcare reform, a dramatic shift of costs from hospitalizations to sheltered living took place, and a high degree of social isolation was seen, with about 20% completely without social contacts and about 30% seeing friends less often than once a week.

SWITCHA - AN INTERACTIVE UTILITY FOR NEUROLEPTIC SWITCHING, DOSING, ADJUSTMENT & STABILIZATION

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This paper describes a computer decision support software (CDSS) instrument designed as an efficient mechanism for switching between neuroleptics. Developed in-house by our research team using a variety of object-oriented software, we demonstrate how it operates in a streamlined fashion to aid clinical activities within mental health research and clinical programs. Optimal patient selection and planned switches ensure long-term stability of prescribing. 'Switcha' has been developed to provide a structured guide to switching with embedded teaching and training modules that allow broader pharmacological principles to be acquired for application in many switching settings. Psychiatrists and residents often report failures in switching and, often erroneously, attribute the outcome to the new drug. This CDSS utility explicates the reasons why switching failure may occur, often for reasons unrelated to the efficacy of the introduced agent. When discussing clinical experiences with doctors involved in the treatment of patients with psychoses, this utility has been found to improve confidence in reviewing the processes involved in initiating switching and may enhance appropriate use of successful switching strategies. When switching, the initial dose of the new agent is calculated from published equivalencies, all such referenced material can be searched for in the utility's Reference Library. The utility takes into account numerous moderating factors that can have significant pharmacological recourse when planning an effective switch for the patient. Such factors include endogenous anticholinergic (Ach) properties of the pre-switch agent, as well as anticholinergic antidote medication status, age, episode status, ethnicity, gender, and recent adherence. This paper describes how the utility selects the most optimal switch titration curve and starting dose of the new agent as well as an overall switch protocol encompassing adjustment and stabilisation of the new agent. Recommended time-frames are advised and access to embedded educational content is available for further information. The whole CDSS is presented in a newmedia format and runs on hospital networks and the internet.

SCHIZOPHRENIA TREATMENT IN CUBA:A RESEARCH AGENDA FOR THE U.S

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Problem:An unknown number of Cuban residents suffer from schizophrenia and because of the U. S. blockade and other economic reasons, medications for treatment are scarce and often unavailable. The

worst, unremitting cases are undoubtedly confined in hospitals that are difficult to access by non-Cubans. However, a large number of people with schizophrenia are able to function in the community with minimal interventions from health professionals. This phenomenon warrants investigation, as there are likely to be lessons to be learned from the Cuba experience with schizophrenia treatment. Method: Observations of patients and interviews with psychiatrists, psychologists and other health clinicians working with schizophrenia patients took place during 2005-6. These interviews took place in clinic settings, neighborhoods in Havana and at the University of Havana. Observed patients ranged from teens to middle-aged adults. Findings: People with schizophrenia lived with their families and were well tolerated in the community. They often were involved in art and music projects that gave them a degree of status in a society where the arts are highly valued and economic contribution is less important. Clinics treat family members for the stress they endure as adjunctive to schizophrenia treatment. Clinics often have facilities for "sleepovers" for the patient and the family when they are needed. Therapies include cognitive, group, and family treatment as well as art and music therapy and have been shown to be effective, according to Cuban clinicians. Clinicians visit homes and are on-call 24 hours for patients and families and social workers visit homes on a regular basis without being called. Discussion: Research agenda emanating from the Cuba experience:1)What are the clinical effects of stigma? Does a reduction in stigma increase patients' abilities to function in the community; 2)To what degree is assertive treatment of familial stress effective for family and patient well-being;3)Can home visits be demonstrated to effectively and efficiently reduce symptoms and increase functioning for patients; and,4)How can progress in patient functioning in the community best be measured?

EDUCATIONAL INFORMATION CAMPAIGNS ARE CRITICAL TO REDUCING DURATION OF UNTREATED PSYCHOSIS

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Purpose and Method: The TIPS study in Norway and Denmark comparatively and significantly reduced the duration of untreated psychosis (DUP) in a sample of first episode schizophrenia from one catchment area (Rogaland County, Norway) by adding two early detection teams (DTs) to the area's psychiatric services and by engineering an information campaign (IC) that educated clinicians, educators, and the general public about the early signs of psychosis (Melle et al, 2004). After this initial study conducted between 1997-2000, the Rogaland psychiatric services stopped the IC but retained the DTs in their healthcare system. A second "no-IC" sample of first episode schizophrenia was recruited between 2002 and 2004 (N=75) from the same catchment area and evaluated using the same assessment instruments and virtually the same clinical research assessment team as in the original 1997-2000 study. This study compares the DUP and baseline clinical characteristics between the samples recruited with and without the information campaign (IC vs no-IC). Results: The 2002-2004 no-IC sample's DUP rebounded from a median of 5 weeks in the 1997-2000 IC sample to a median of 15 weeks (p<0.005, see Table). This was mainly accounted for by a subgroup of long-DUP cases. Fewer no-IC patients were detected through the detection teams. Patients were also less frequently diagnosed with schizophreniform disorder, had more PANSS positive and total symptoms, and poorer GAF symptom scores. Conclusion: Intensive education campaigns targeting the general public, the primary health services, and schools appear to be necessary to reduce DUP. When such campaigns were stopped, DUP increased, as did the severity of presenting baseline symptoms and functional compromise in first episode patients.

Patient Characteristics at Admission

	No-IC (n=75)		IC (n=108)	
Recruitment periods, months	30		48	
DUP, weeks, mean/median (SD)	105/15	(275.8)	26/5	(58.6)**
Age, mean, years	26.4		24.4	
Females, No. (%)	28	(37.0)	42	(39.0)
Single Marital Status, No. (%)	52	(75.5)	83	(80.6)
Education: length, mean years	11.7		11.9	
Referred by Detection Team, No. (%)	11	(14.7)	34	(31.5)*
Schizophreniform Disorder, No. (%)	6	(8.0)	27	(25.0)*
PANSS positive symptom, mean (SD)	20.3	(48)	18.7	(5.3)**
PANSS total symptom, mean (SD)	69.3	(14.9)	64.6	(15.9)**
GAF symptom, mean (SD)	28.5	(7.1)	30.6	(6.5)**

* P=0.009 Pearson Chi-Square
** P=<0.005, Mann-Whitney U-test (2-tailed)

SELF-REPORTED MEDICAL COMORBIDITY AND RESULTING INTERACTIONS WITH HEALTH CARE PROVIDERS IN A SAMPLE OF US PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

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Schizophrenia and bipolar disorder are associated with high rates of medical comorbidity, in particular obesity, diabetes, and cardiovascular disorders. However, little is known about patients' level of awareness of medical comorbidities and resulting long-term health consequences. The primary objective of this investigation was to assess patient awareness of comorbidities associated with their mental illness; knowledge of long-term health risks associated with, and treatment for, their mental illness; and interaction with health care providers regarding comorbid conditions. A secondary objective was to assess the validity and reliability of internet-based surveys in patients with schizophrenia or bipolar disorder. An internet-based survey was conducted in 11 countries. Subjects were patients currently receiving pharmacological treatment for schizophrenia or bipolar disorder. The following results are based on a US sample of 135 patients with schizophrenia and 135 with bipolar disorder. Among subjects with schizophrenia, 29% self-reported obesity, 32% reported diabetes, 28% reported hypertension, and 18% reported other cardiovascular disease. Similarly, 29% of patients with bipolar disorder reported obesity, 14%, reported diabetes, 21% reported hypertension, and 8% reported other cardiovascular disease. BMI >30 was reported by 71% of respondents with schizophrenia and 51% of respondents with bipolar disorder. BMI >25 was reported in 87% and 76% of respondents with schizophrenia or bipolar disorder, respectivelyAccording to the respondents, health care providers discussed the potential long-term consequences of weight gain with 61% of subjects with schizophrenia and 42% of

subjects with bipolar disorder, and discussed the impact of psychotropic medication on comorbidities with 60% of subjects with schizophrenia and 40% of subjects with bipolar disorder. However, only 20% of subjects with schizophrenia and 24% of subjects with bipolar disorder reported receiving a physical examination, 35% and 42%, respectively, reported being weighed, and 28% and 36%, respectively, reported ever having any blood test done. The results of this internet-based survey of US patients with schizophrenia or bipolar disorder suggest that subjects in this nonclinical sample are suboptimally informed about the issues surrounding comorbidity and its long-term consequences despite high rates of medical comorbidity.

REMISSION IN SCHIZOPHRENIA: A COMPARISON OF THE COST-EFFECTIVENESS OF 2 DOSE REGIMENS OF ZIPRASIDONE VERSUS HALOPERIDOL TREATMENT IN A 3-YEAR DOUBLE-BLIND EXTENSION STUDY

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Long-term cost-effectiveness in the treatment of schizophrenia has not been well studied for second-generation (atypical) antipsychotics, despite questions from US managed care and other payers on their value in comparison with conventional agents. We compared the cost effectiveness of 2 dose regimens of ziprasidone (80-160 mg/d given BID, n = 72; 80-120 mg/d given QD, n = 67) and haloperidol (5-20 mg/d, n = 47) in terms of cost per patient achieving full remission according to consensus-based operational criteria. Data used in this analysis were collected in a 40-week core trial and 156-week continuation study. One hundred eighty-six subjects completed the 40-week core phase and entered the 3-year double-blind extension study. Efficacy variables included remission rate, defined according to recently proposed criteria[1] and Quality of Life Scale (QLS) scores, and were analyzed over time using generalized estimating equations. A resource utilization questionnaire was administered to obtain data on direct medical costs, social services, criminal justice, and caregiver out-of-pocket costs. Costs were assessed from a payer perspective and were discounted over 4 years. Thirty-seven percent of subjects completed the full 3-year continuation phase. Ziprasidone treatment was associated with a significantly greater likelihood of achieving full remission in the 6 months preceding the last visit (Week 196 or early termination; $P < .05$). Longitudinal assessment of cross-sectional remission and QLS scores in the continuation phase demonstrated superior improvement (slope or trends) for QD and BID ziprasidone regimens compared with haloperidol. Results of the cost analyses will be presented in terms of cost per patient achieving remission and the cost per quality-adjusted life-year gained.In this double-blind, long-term study, ziprasidone was associated with continued improvement in remission rate and quality of life, in contrast to haloperidol. The results of this study will address the long-term cost-effectiveness of ziprasidone compared with haloperidol in the treatment of schizophrenia. Reference 1. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus.*Am J Psychiatry.* 2005;162:441–449.

ARE THE SHORT-TERM COST SAVINGS AND BENEFITS OF AN EARLY PSYCHOSIS PROGRAM MAINTAINED AT 8-YEAR FOLLOW-UP?

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Despite considerable interest and investment in early psychosis services over the past 1-2 decades, scant attention has been paid to the economic evaluation of such services. A one-year evaluation of the cost-effectiveness of the Early Psychosis Prevention & Intervention Centre (EPPIC) model in Melbourne, Australia, concluded that EPPIC was a dominant intervention compared to historical care in that it was cheaper and more effective, however no published studies have evaluated the longer term effects of a model of early intervention in terms of both outcomes and costs. This study examined whether the cost savings and benefits associated with EPPIC persist beyond the one year timeframe. The study used a historical control design. A sample of 51 participants who presented to EPPIC in 1993 was individually matched (on age, sex, diagnosis, premorbid adjustment and marital status) with 51 participants admitted to the precursor service (the 'pre-EPPIC' service) between 1989 and 1992. Participants were followed up at one year, then again approximately 8 years after inception. A representative subsample of 65 participants was interviewed at 8-year follow-up. Data describing psychiatric service use, medication type, duration and dosage were collected via interviews with patients and informants, electronic databases, and medical records. Standard economic methods will be used to assess the costs, benefits and incremental cost-effectiveness ratios of the two interventions. The economic perspective will be that of the health sector. The previous cost-effectiveness analysis found that the EPPIC sample incurred lower health service costs (largely due to reduced use of inpatient services) and had better outcomes (improvements on measures of symptomatology and quality of life) compared to the pre-EPPIC control group. This study will help answer whether the EPPIC model of care maintains 'value for money' over a longer period. The longer time frame of the current study will also help to resolve some of the methodological issues of historical matching faced by the first study in that the both the service use and outcome data of the two samples were collected over distinctly different periods of time, therefore issues of confounding and bias could not be unequivocally dismissed. During the longer term follow-up a significant proportion of service use in both cohorts will have occurred over a similar time frame, therefore reducing the potential effects of bias and confounding.

AN INVESTIGATION OF PATIENT EXPERIENCES WITH EMPLOYMENT SERVICES

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Hypothesis: Employment is a primary goal of many individuals with serious mental illnesses, yet the vast majority remain unemployed (Drake 1998). Research has shown that vocational outcomes are improved when mental health and vocational services are closely integrated (Bond 1997, Cook 2005). Supported employment (SE) is an evidence-based employment intervention for people with mental illness that emphasizes rapid job placement, integrated mental health and vocational services, follow-along vocational supports, and an

emphasis on client choice (Drake 1996, Bond 1997). Despite the vast body of evidence supporting its effectiveness, SE is far from widely implemented (Torrey, 2001). This project hypothesizes that individuals wish to be employed at a higher rate than employment is achieved. Further, it is expected that more information will be gathered related to the barriers to employment, which will assist the development of more comprehensive programs. Methods: Participants will be solicited by contact with clinicians who directly work with mentally ill people. Clinicians will be asked to consider for participation patients who have been referred for any type of vocational services in the last six months, regardless of the outcome of the service. Patients will be contacted by phone by the investigators, and an interview will be conducted, which will last approximately 10-15 minutes. Questions during the interview will ascertain the participant's current job status. Information regarding the effectiveness of employment services as well has what types of employment services they received will be elicited. The information will be maintained on a confidential data base for further evaluation. Results: The results of this study are pending. Conclusions: Data suggests that mentally ill patients desire employment, but are underemployed. Patient feedback regarding community vocational services will likely be instrumental in forming an integrated mental health treatment plan that includes vocational training. Though it is well-established that considering patient/consumer preferences should be a part of service development, direct client feedback can be used as a tool in the service development process.

ATYPICAL AND TYPICAL ANTIPSYCHOTIC DOSING TRENDS IN A LARGE US MANAGED CARE PLAN

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This study examined antipsychotic dosing patterns according to provider specialty within a large US managed care plan. Patient enrollment, medical, and pharmacy claims data were extracted, and prescription fills for atypical and typical antipsychotics between January 1, 2001 and December 31, 2004 were studied. The days supply and total dose from filled prescriptions were used to calculate average daily dose. Provider specialty was also identified from filled prescriptions. Periods in which prescriptions were not filled were not included in calculations of average daily dose. Mental health diagnoses were obtained from ICD-9-CM diagnostic codes within medical claims. Among the total group of patients with antipsychotic prescriptions (N=142,069), treatment group sample sizes ranged from n=839 (clozapine) to n=54,120 (olanzapine). Average daily doses of atypical antipsychotics prescribed for patients with schizophrenia were less than or in the lower range of recommended dose levels (mean [SD] dose [mg/day] of 345.9 [186.3] for clozapine, 3.0 [2.2] for risperidone, 12.5 [7.5] for olanzapine, 289.1 [224.8] for quetiapine, 18.2 [8.8] for aripiprazole, and 105.3 [65.1] for ziprasidone). Although overall antipsychotic doses were low, psychiatrists prescribed higher average daily doses for all atypical antipsychotics than providers from other specialties. Average daily doses of atypical antipsychotics generally decreased from 2001 to 2004 (ranging from -3% to -28%). Atypical antipsychotics were used in less than or in the lower ranges of recommended dose levels in this managed care population. From 2001 to 2004, average daily doses for atypical antipsychotics decreased. Supported by funding from AstraZeneca Pharmaceuticals LP.

FUNCTIONAL, CLINICAL, AND ECONOMIC RAMIFICATIONS OF EARLY NON-RESPONSE TO ANTIPSYCHOTICS IN THE NATURALISTIC TREATMENT OF SCHIZOPHRENIA

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Naturalistic comparison of the functional, clinical, and economic outcomes of individuals who did and did not have early response to antipsychotic medication evident at 2 weeks into the treatment of schizophrenia. This post hoc analysis used data from a 1-year, multi-site, randomized open-label study of antipsychotics in the treatment of schizophrenia, conducted in the U.S. between May 1998 and September 2002. "Response" was defined as at least 20% improvement on the PANSS total score from baseline; "Early Response" as at least 20% improvement at 2 weeks. Patients with early response were compared to patients without early response ('early non-responders") on several standard psychiatric outcome measures following 8 weeks of treatment. These measures included SF-36, Lehman Quality of Life Inventory (QOLI), and the Rating of Medication Influence (ROMI). Systematic abstraction of medical records provided resource utilization data for calculating total direct treatment cost for each patient for the first 8 weeks of treatment. Statistical comparisons were made both unadjusted and adjusted for a set of patient characteristics, identified a priori. Early response/non-response at 2-weeks predicted subsequent response/non-response at 8-weeks with high overall level of accuracy (73%). Almost all (90%) of non-responders at 8 weeks were correctly identified at 2 weeks (high specificity). Compared to early responders (N=108, 22%), early non-responders (N=389, 78%) were significantly more likely to experience, at 8 weeks, poorer levels of functioning, were less likely to perceive adherence with medication as beneficial (per ROMI), and incurred significantly higher total treatment costs. Early non-responders were twice as costly as early responders ($4,264 vs. $2,017 following 8 weeks of treatment, $p<.01$). In the naturalistic treatment of schizophrenia, early non-response to treatment with antipsychotics appears to accurately predict subsequent non-response to treatment. Compared to early responders, early non-responders appear to have poorer clinical and functional outcomes, to perceive their medication as less beneficial to them, and to incur substantially higher total treatment costs. Findings suggest that early non-responders may benefit from change in antipsychotic regimens to minimize prolonging exposure to suboptimal or ineffective treatment alternatives. Funded by Eli Lilly and Company.

COST EFFECTIVENESS OF A PREVENTIVE INTERVENTION FOR YOUNG PEOPLE AT ULTRA HIGH RISK OF DEVELOPING PSYCHOSIS

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Recent research has shown that the provision of specific treatment to young people identified as being at 'ultra high risk' of developing a psychotic disorder may delay, or even prevent, the onset of disorder. Moreover, UHR individuals are 'in better shape' psychologically

after they have received treatment than before (McGorry et al., 2002, McGlashan et al., 2006; Morrison et al., 2004). However, there are obvious costs associated with identifying and treating UHR individuals and the question of whether such intervention provides value for money is important in the context of scarce health resources. This study aimed to determine the health sector costs associated with a randomised controlled trial for UHR participants attending the PACE Clinic in Melbourne, Australia. Treatment was either a Specific Preventive Intervention (SPI: neuroleptic medication and cognitively oriented psychotherapy) or Needs Based Intervention (NBI: supportive psychotherapy alone). The second aim was to determine whether SPI resulted in cost savings over short (12 months) and long (12-36 month) follow-up periods. During the treatment phase, the SPI group incurred significantly higher Therapy and Total costs compared to the NBI group, but Hospital and Medication costs did not differ between the groups. There were no significant treatment cost differences between the SPI and NBI groups over the first-follow-up phase. However, over the second follow-up phase, the SPI group incurred significantly lower Therapy and Total costs compared to the NBI group. Members of the NBI group who did not develop psychosis incurred significantly higher Therapy and Total costs compared to the SPI sub-group who did not developed psychosis. There were no significant cost differences in treatment of the psychotic subgroups of the NBI and SPI groups over the long-term follow-up period. This preliminary study has demonstrated long-term cost savings associated with specific treatment for young people at UHR for psychosis. Although the treatment for the SPI group was more expensive while it was being provided- primarily due to increased therapy costs- there were lower treatment costs for members of that group who did not develop psychosis three years later.

PATHWAYS TO CARE FOR PATIENTS AT RISK OF PSYCHOSIS AND RELATIONSHIP TO DIAGNOSIS

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We set out to measure the pathways to care for patients at risk of developing psychosis and their relationship to consequent diagnosis. The data presented here is drawn from the OASIS (Outreach and Support in South London) service, a prodromal psychosis service seeking to engage people aged 16-35 years at ultra-high risk of developing psychosis. Referrals are made by primary care health services and other health professionals, by social welfare agencies, by friends and relatives, or by self-referral. The pathway to care of all referrals (n=367) to our service from June 2001 to March 2006 was analysed by number and type of services involved prior to referral. At Risk Mental State for psychosis was diagnosed via the Comprehensive Assessment of At Risk Mental State criteria (Yung et al 2002). A sub-analysis of pathway to care in those involved with only one service prior to referral revealed that in both the ARMS and non-ARMS populations the majority of referrals were made by General (Family) Practitioners. In the ARMS population (n=100), 45% of patients were referred after involvement with one service only, 30% after involvement with two services, and the remainder after involvement with three or more services. This analysis shows that although the most common pathway to care for people at risk of developing psychosis is by a one-step referral, for a high proportion of referrals the pathway entails the involvement of multiple services prior to referral for ARMS assessment. This suggests scope for optimising awareness of the At Risk Mental State in services at the first point of contact, thereby reducing the need for a multi-step referral process, and consequently, minimising the delay in intervention. Where referral is one-step, there is variation within referring groups of referrals which meet At Risk Mental State criteria and those which do not. Thus within referral groups, appropriate referral is still a "hit and miss" process: this indicates further need for education about ARMS, and has implications for the development by prodromal psychosis services of health promotion strategies and education programmes aiming to assist referring services in identifying At Risk Mental State for psychosis.

RECURRENT PSYCHIATRIC INPATIENT HOSPITALIZATION

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Background The purpose of this study was to determine if an interagency treatment planning process could be effective in engaging patients in their treatment and to determine what differences distinguished those who were recurrently readmitted to the hospital in contrast to those who were not. In the literature, we noted that the consensus definition for "recidivism" seems to be someone who is admitted to a psychiatric inpatient service three or more times within an eighteen month period (Casper & Pastva, 1990; Kent et al., 1995). Methods Design. We performed two studies, the first of which was a prospective, experimental pilot study comparing before and after experience of readmission to psychiatric hospital after an administrative intervention, the High User Treatment Planning Group (HUTPG) designed to increase the quality of treatment planning and to ensure the availability of resources. A second study was a retrospective chart review with a matched pair design of recurrently admitted vs non-recurrently admitted patients admitted to Yale New Haven Psychiatric Hospital from Sept, 2005 through June, 2006. We extracted demographic, clinical and utilization data. Both studies have IRB approval. Results Retrospective Chart Review. From the retrospective chart review, we compared those recurrently admitted (N=69) and those not (N=47), found the following statistically significant differences at the $p < .05$ level or better: those who were recurrently admitted to the psychiatric hospital were more likely to be male (53.6% vs. 40.4%), single (73.9% vs 59.6%), caucasian (50.7% vs 12.7%), and carry a diagnosis of schizophrenia (24.6% vs 4.3%), schizoaffective disorder (23.2% vs 4.3%), or bipolar (34.7% vs 19.1%). Furthermore, the recidivist patients were less educated (23.2% with some college or more vs 42.5%), more likely to be unemployed (90% vs 72.3%) and more likely to have a family history of mental illness (42% vs 27.7%). Prospective Study. The HUTPG was not associated with any effect on mitigating the readmission experience. We did find that that if there were problems with housing, shelter, food, or security at the one month follow-up, the patient was more likely to be re-admitted by 6 months. These findings were significant at $p < .05$ level or better. Conclusion. New approaches for collaborative engagement are needed in order to reduce the re-hospitalization experience for those who are prone to return.

LINKS BETWEEN VIOLENCE, ADDICTION, AND PSYCHOPATHY TRAITS: FINDINGS FROM A FIRST EPISODE OF PSYCHOSIS COMMUNITY SAMPLE

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Although there is evidence that those who suffer from psychosis are at higher risk for both criminal and violent behavior, few studies have looked at this relationship in a first episode community sample. In fact, it has been suggested that variables such as personality may mediate this relationship. 116 first episode psychosis participants from Canada were evaluated. In terms of violence, the MOAS detected that 48.6% of the sample had a history of physical aggression and 40.5% had a history of verbal aggression. Overall, combining verbal and physical violence 69.6% of the sample had a history of one or both of these types of violence. Forty-five percent of the sample reported having been in trouble with the law at some point in their lives, 44.5% had been arrested and 36.1% had spent at least one night in jail. Substance use for the last 30 days was assessed using the ASI. In this sample, marijuana was the most commonly used substance. Fifty-seven point eight percent of the sample reported marijuana use, 49.1% reported alcohol use, 30.2% used cocaine, 24.1% used amphetamines, 16.4% used ecstasy, 14.7% used hallucinogens and 13.8% reported heroin use. In addition, 16.5% of the sample reported that they had overdosed in the past on some type of drug or alcohol. Further analyses revealed no significant differences between the number of individuals who did or did not use drugs regularly at any time in their life in terms of violence history ($\chi 2 = 1.08$, $p = .298$). There was, however, a relationship found at trend level between regular alcohol use and the likelihood of having a history of violence ($\chi 2 = 3.26$, $p = 0.054$). The t-test was significant when those with and without a history of violence were compared on total BPRS scores ($t(99) = 2.02$, $p < .05$), with more severe symptoms present in those with a history of violence. No significant differences were found for the positive symptoms subscale. A significant difference was found between those with a history of violence and those without in terms of abuse history ($t(99) = 2.01$, $p < .05$), with more childhood abuse having been experienced by those presenting with violent behaviours. With respect to psychopathy, the t-test did not reach significance when comparing those with and without a history of violence (verbal and physical) on the SRP-II. Additional variables and statistics will be investigated and presented and implications for treatment will be discussed.

A SYSTEMATIC REVIEW OF CAREGIVER BURDEN IN THE RELATIVES OF SCHIZOPHRENIC PEOPLE

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Background: Schizophrenia often imposes a considerable burden on the people who suffer from it, as well as on their family members and the society. Studies have consistently shown that approximately one-third of caregiving relatives have elevated levels of anxiety or depression. Aims: To critically review the literature on family burden and schizophrenia and to provide evidence based information to design future caregiver research in schizophrenia. Method: Articles were identified by the Medline search (1990-2006), manual searching of the bibliographic articles, and an in-house bibliographic database. The review was conducted using the search terms of family burden and schizophrenia. Hand searching of journals was not performed. So, there is potential a publication bias. Results: Forty-two studies met the inclusion criteria. Most of the studies conducted in primary family caregivers and mainly assessed the parental caregivers. Many studies investigated the affected relatives' problems such as behavior, quality of life, symptoms, daily living, medication side effects and duration of the illness. The caregivers were mainly assessed for burden of care, psychological morbidity, expressed emotion, coping, general health, educational status, quality of life, their needs, service use, and level of stress. Few studies investigated the stigma in family caregivers. Most of the studies used cross-sectional designs and conducted in the developed countries. Conclusions: There has been relatively little research on spousal and sibling caregivers in schizophrenia. Most of the research studies conducted in primary caregivers and investigated the negative aspects of caregiving. There is a future need for longitudinal studies, focusing on multiple caregivers, and investigating the positive aspects of caregiving in schizophrenia.

ASSERTIVE COMMUNITY TREATMENT VERSUS STANDARD PSYCHIATRIC TREATMENT FOR SEVERELY MENTALLY ILL PATIENTS IN DENMARK

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Background: Assertive Community Treatment (ACT) is a well established service model in several countries for people with severe and enduring mental health problems who do not engage with psychiatric services. Community mental health teams based on the ACT model have only recently been introduced in Denmark. It is unclear how models of community care translate to a Danish culture and the degree of adaptation that may result. Method: This investigation assesses the effect of ACT in Denmark. The effect of ACT is compared with the effect of Standard Psychiatric Treatment (SPT) through a quasi-experimental design with matched control groups. 198 severely mentally ill patients have been allocated to two ACT teams (case-load 10-12 per case manager) and 200 severely mentally ill patients have been allocated to two matching SPT teams (case-load 30-35 per team manager). Social functioning, clinical symptoms, and contact with psychiatric services are measured at baseline, and 2 years. Outcome measures at 2 years also include quality of life (Lancashire Quality of Life Schedule (LQLS)), patient satisfaction (Patient Satisfaction Questionnaire (PSQ), Verona Service Satisfaction Scale (VSSS)) positive symptoms, (Scale for the Assessment of Positive symptoms (SAPS)), negative symptoms, (Scale for the Assessment of Negative symptoms (SANS)), perceived experience of coercion, and semi-structured qualitative interviews. Results: Results at baseline and 2 years will be presented for the following measures; social functioning, contact with psychiatric services, SANS & SAPS, LQLS, PSQ, VSSS, perceived experience of coercion and semi-structured interviews.

FACTORS INFLUENCING HOSPITALIZATION DURING THE FIRST THREE YEARS OF TREATMENT FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Purpose: Studies of administrative databases have identified multiple factors, including site of initial diagnosis (inpatient versus outpatient), residence (urban versus rural) and sex, which influence hospitalization in the first year of treatment for schizophrenia (Whitehorn et al, Can J Psychiatry. 49:635-8:2004). We now report on the first three years of treatment and a comparator sample diagnosed with bipolar disorder. Methods: Three administrative databases that record all inpatient and outpatient contacts in the province of Nova Scotia (population 900,000) were used to identify presumed first diagnosis cases with a diagnosis of schizophrenia (SC) or bipolar disorder (BP) in 1998-2000 and no SC or BP diagnosis in the previous 5 years. Site of initial diagnosis, (inpatient versus outpatient), location of residence (urban versus rural), sex and all hospitalizations in the three years following initial diagnosis were noted. Analysis included Chi-square and linear regression using $p<.05$ for significance. Results: 585 SC and 874 BP cases were identified. 21% of SC and 15% of BP cases were initially diagnosed as inpatients. Excluding admission associated with initial diagnosis, 42% of SC and 26% of BP cases were hospitalized during the first three years of treatment. For both SC and BP cases, likelihood of hospitalization (excluding admission associated with initial diagnosis) was significantly related to site of initial diagnosis (inpatient>outpatient), but was not related to residence or sex. In linear regression the total length of stay over the three years (TLOS3) was significantly related to site of diagnosis (inpatient>outpatient) for SC but not BP. TLOS3 was also longer for urban residence in both SC and BP, and longer for women with SC and for men with BP. Conclusion: The results highlight multiple factors influencing inpatient length of stay. As well, they support the concept that patients initially diagnosed with SC or BP as inpatients are at increased risk for re-hospitalization and, for SC, longer total inpatient stay. The data are, of course, limited by the inherent difficulties with administrative databases. Nonetheless the results suggest the need for specialized services for those SC and BP patients initially diagnosed as inpatients, with the goal of enhancing outcome and reducing service costs. (Supported by Dalhousie Psychiatry Research Fund).

IMPACT OF SCHIZOPHRENIA ON PULMONARY DISEASE AMONG INPATIENT DECEDENTS

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The primary objective of this study was to determine the risk associated with comorbid schizophrenia for common pulmonary illnesses, including pneumonia and chronic obstructive pulmonary disorder (COPD), during the last year of life. Veterans who died as inpatients in VA hospitals during 2002 (N=27,798) were identified from administrative data. Logistic regression models predicted a diagnosis of pulmonary illness in either the final year or last recorded admission as a function of schizophrenia, other mental illness, smoking history, substance abuse, age, race, gender, marital status, Charlson comorbidity score, and outpatient care during the last year of life. Among decedents, 943 (3%) had schizophrenia, 3% were women, most were white (76%) or African-American (18%), about half were married (46%), and average age at death was 72.4 years (SD 11.5). Three-fifths received VA outpatient care in the year prior to death. Among those with schizophrenia, only two-fifths had outpatient care. Over half the decedents had a pulmonary disorder in the last year of life. Indicators of smoking (nicotine dependence diagnosis and smoking cessation prescriptions) were nearly 60% more common among veterans with schizophrenia than other patients ($p<.001$). Pneumonia was also more common among schizophrenia patients (38% vs 31%) as was COPD (46% vs 38%). In the multivariable analyses controlling for history of smoking and other covariates, schizophrenia was a risk factor for pulmonary disease in the last year of life (OR=1.9, 95% CI 1.6-2.2); the effect size was smaller for pulmonary-related deaths, but also significant (OR=1.5, 95% CI 1.3-1.7). Lifestyle issues such as smoking and poor self-care put schizophrenia patients at increased risk for both pneumonia and COPD. These comorbidities are prevalent independent of smoking status. The common segmentation of mental health care and primary care systems may limit the extent to which these patients appropriately engage in their non-psychiatric medical care, as individuals with multiple disorders must often choose among numerous symptoms to identify their most urgent healthcare needs. Clinicians treating schizophrenia patients need to be especially alert to potential comorbid medical conditions and assist vulnerable patients to receive appropriate care.

HOME TREATMENT VERSUS HOSPITAL-BASED OUTPATIENT TREATMENT FOR FIRST EPISODE PSYCHOSIS: A RANDOMIZED CLINICAL TRIAL

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Specialized services for the treatment of first episode psychosis have been introduced in many countries with the aim of improving clinical outcomes. It is not known whether the service delivery model used impacts on the outcomes achieved. This study was undertaken in order to determine whether specialized first episode treatment offered in the home would lead to better clinical outcomes than treatment offered in a specialized hospital-based outpatient clinic. All subjects were referred for assessment to the First Episode Psychosis Program at the Centre for Addiction and Mental Health in Toronto, Canada. At the time of initial referral, patients were randomly assigned to be assessed and treated by one of two teams specializing in the treatment of first episode psychosis: 1) the Home Intervention for Psychosis (HIP) Team, a mobile team that carried out its initial and follow-up visits in the community, or 2) the First Episode Psychosis Clinic (FEPC), an outpatient treatment team based at a psychiatric hospital. Subjects provided informed consent for evaluations to be carried out at baseline, and at 3 month and 9 month follow-up visits. Outcome measures included the Brief Psychiatric Rating Scale (BPRS) and the Multnomah Community Ability Scale (MCAS). In total, 155 patients were randomized, of whom 40 met inclusion criteria and agreed to study participation (HIP=23; FEPC=17). The sample was predominantly male (M/F=26/4) and had a mean age of 23.2 (3.8) yrs. Of patients assigned to FEPC, 38% failed to attend their first assessment compared to 24% of those assigned to HIP ($\chi 2=3.79$, df =1, $p=0.05$). A total of 29 subjects had follow-up assessments at both 3 months and 9 months (HIP=17; FEPC=12). The two groups did not differ at base-

line on BPRS or MCAS scores. At 3 months, there were no significant differences between groups in the amount of change observed on either the BPRS or MCAS. At 9 months, MCAS-total scores had improved more in the FEPC group than in the HIP group. While interpretation of our results is limited by our small sample size, our findings suggest that a specialized home treatment team is more likely to be able to carry out initial assessments but that that once patients are entered into treatment, there appears to be no advantage to specialized home treatment relative to specialized clinic-based treatment. This study was supported by a grant from the Canadian Institutes of Health Research

19. Drug Side Effects & Tardive Dyskinesia

LOOKING BEYOND THE WEIGHT GAIN: PRECLINICAL EVIDENCE OF ANTIPSYCHOTIC-INDUCED ADIPOSITY AND PANCREATIC DYSFUNCTION

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A common side effect of atypical antipsychotic therapy is weight gain, with associated reports of increased risk of diabetes. Since weight gain often reduces insulin's ability to normalize blood glucose ("insulin resistance"), it has been suggested that effects on weight are the dominant metabolic disturbance caused by these agents. However, weight gain and resistance alone are insufficient to cause diabetes because of the feedback relationship between insulin sensitivity and insulin secretion, such that resistance is typically overcome by hypersecretion from pancreatic β-cells. Diabetes during antipsychotic use likely involves metabolic dysfunction beyond drug-induced weight gain, although direct study of these effects has been minimal. Preclinical placebo-controlled studies were performed to examine the effects of the atypical antipsychotics olanzapine (OLZ) and risperidone (RIS) on body weight, adiposity, insulin sensitivity, and pancreatic function in normal dogs treated for 6 weeks. At baseline and after treatment, we measured (1) adiposity (total, visceral, and subcutaneous) by abdominal MRI, (2) insulin sensitivity, and (3) pancreatic β-cell function using gold standard glucose clamp methods. OLZ caused weight gain similar to placebo, with no significant change with RIS. Body weight changes did not reflect striking differences between agents upon fat deposition. OLZ induced near-doubling of total adiposity, with 80-100% increases in visceral and subcutaneous fat mass. RIS effect on adiposity was modest and similar to placebo. OLZ also induced a severe decrement in insulin's ability to suppress glucose production ("hepatic insulin resistance") not evident in RIS- or placebo-treated dogs. Such resistance should engender enhanced pancreatic β-cell function. However, no β-cell upregulation was observed after OLZ treatment, indicating interference with the pancreatic response necessary to compensate for insulin resistance and obesity. Drug-induced metabolic abnormalities were independent of observed changes in body weight. In conclusion, effects of atypical antipsychotics on body weight do not reflect underlying metabolic effects on adiposity and insulin secretion. Further studies are required to determine the mechanisms by which observed defects may develop, and to quantify the effects of other agents on factors other than body weight which can increase diabetes risk in the psychiatric population.

IMPROVEMENT OF DAILY PHYSICAL ACTIVITY WITH A NON-PHARMACOLOGICAL INTERVENTION FOR PATIENTS WITH SEVERE MENTAL DISORDERS

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Inadequate feeding habits and sedentary life among schizophrenic patients are a major health concern because of risk of metabolic syndrome. Brazilian Wellness Program is a multicentric non-pharmacological group intervention for patients with severe mental disorders developed by a multi-disciplinary group. The 3-month intervention includes topics such as healthy feeding, self-esteem, motivational counseling and physical activity. The objective of the physical activity sessions was to increase awareness of patients and relatives of the importance of daily physical activity to avoid weight gain and improve quality of life. The intervention was performed in 15 mental health centers (4 academic, 8 publics and 3 privates) and included 3 one-hour physical activity sessions when patients and their families were taught the differences between exercise and physical activity, the benefits of improving the physical activity levels and the importance of regular exercising; they were also motivated to look for a physician to have an evaluation of their physical conditions. At the end of each session they were invited to participate of a 15 min of a warm up routine and relaxation session. The program included 191 patients, 141 (73.8%) of them completed the study. Initially, 65 patients (46%) were doing some physical activity routinely, and at the end of the study the number increased to 99 (70.2%; $p<.001$). Patients lost on average .4 kg ($p<.08$), and BMI remained stable. Routine physical activity is a fundamental measure for long-term weight management. Brazilian Wellness Program has achieved its goals such as physical education promotion and weight gain prevention.

REPLICATION OF GENETIC MARKERS ASSOCIATED WITH CLOZAPINE-INDUCED AGRANULOCYTOSIS

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Clozapine is a highly efficacious drug for the treatment of schizophrenia, but its use is limited, in part due to the side effect of agranulocytosis. In order to reduce the incidence of clozapine-induced agranulocytosis (CIA), patients are required to submit to a blood monitoring program. A genetic component to CIA is suggested by published associations in a number of genes. A genetic test assessing the risk of CIA might allow safer and more broad use of clozapine. We previously conducted a candidate gene-based case-control study to discover genes associated with CIA. Cases were patients with an ANC<500 during clozapine treatment, and controls were patients treated for at least one year without a significant reduction in WBC or ANC. For each case, we attempted to enroll 2 age-, gender- and ethnicity-matched controls. We collected blood, medical histories and informed consent from 33 CIA cases and 54 controls. Seventy-four candidate genes were sequenced in the exons, intron-exon boundaries, 5' untranslated region and promoter region for each of the cases and controls, and a haplotype analysis was conducted using logistic regression. A total of 20 haplotype markers in HLA-DQB1, 1 in HLA-C, 1 in NTSR1, 1 in DRD1 and 6 in CSF2RB were significant with permutation test adjusted p-values under 0.05. A replication analysis was performed on an independently collected cohort of 49 cases and 78 controls from Germany. Cases were patients who developed an ANC<500 during clozapine treatment, and controls were patients treated for at least two years without an adverse effect on the WBC or ANC. We attempted to replicate 28 haplotype markers from 4 of the 5 genes. We did not attempt to replicate the findings from HLA-C. Permutation tests were performed for markers within genes, and the Benjamini-Hochberg FDR method was applied to the best permutation p-values from the four genes. Markers with p-values less than 0.05 after these adjustments were considered replicated. One genetic marker in HLA-DQB1 replicated further implicating this as the strongest genetic association with

CIA.. Markers in CSF2RB were not statistically significant, but warrant further study. The strength of the findings is sufficient to develop a diagnostic test for CIA risk.

NON-PHARMACOLOGICAL MANAGEMENT OF WEIGHT GAIN: A BRAZILIAN NATIONAL MULTICENTRIC STUDY

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Weight gain and metabolic syndrome are serious health concerns for schizophrenia and other severe mental illness patients because they increase the risk of cardiovascular diseases. We have developed an educational intervention for weight gain management among patients with psychotic and affective disorders in Brazil (Brazilian Wellness Program). The program includes thirteen weekly 1-hour group sessions discussing topics, such as healthy diet, lifestyle, physical activity, psychoeducation and self-esteem with patients and their relatives. The objective of the study was to evaluate the effectiveness of the intervention in a national multicentric study. We have recruited 191 clinically stable patients with weight gain concerns from 15 outpatient clinics, mean age 39.1(SD 10.9) years, 103 (53.9%) female, 134 (71.3%) patients with schizophrenia or other psychotic disorders. Weight, body mass index (BMI), waist and hip circumferences and blood pressure were recorded before and after the intervention. Patients lost on average 0.4 kg and BMI remained stable (Table). Waist and hip measures and diastolic blood pressure levels presented small but significant decreases. The majority of the patients (57.7%) lost more than 2kg or remained stable (± 2kg). The intervention showed positive outcomes on weight gain, blood pressure, waist and hip circumferences in a short-term evaluation. A long-term weigh management program (9 months) has been developed and is expected to show even better results. Educational interventions, such as the Wellness Program, are effective to avoid weight gain and might be a standard of care for this population.

Clinical measures before and after the intervention

Variables	Baseline (mean,SD)	Endpoint (mean,SD)	Analysis	p
Weight (kg)	85.4 (20.4)	85.0 (20.3)	t= 1.76, 133 df	.08
BMI (kg/m2)	30.9 (5.6)	30.9 (5.7)	t=-.46, 132 df	.64
Waist (cm)	106.8 (14.6)	105.8 (14.6)	t= 2.4, 115 df	.01
Hip (cm)	111.3 (10.1)	110.5 (9.9)	t= 2.4, 116 df	.01
Sistolic BP (mmHg)	120 (14.5)	118 (16.3)	t= 1.49, 130 df	.13
Diastolic BP (mmHg)	81.4 (10.9)	78.2 (11.5)	t= 3.71, 130 df	<.001

BMI: body mass index; SD: standard deviation; BP: blood pressure; df: degrees of freedom

SCREENING FOR THE METABOLIC SYNDROME IN PEOPLE RECEIVING ANTIPSYCHOTIC MEDICATION IN ASSERTIVE OUTREACH TEAMS: RESULTS OF THE POMH-UK BASELINE AUDIT

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The metabolic syndrome is a collection of risk factors (hypertension, central obesity, glucose intolerance/insulin resistance, and dyslipidaemia) predictive of increased morbidity and mortality due to cardiovascular disease and type-2 diabetes. Schizophrenia has long been associated with elements of the metabolic syndrome, which may be partly explained by poor diet, lack of exercise, high prevalence of cigarette smoking, and stress/abnormalities of the hypothalamic-pituitary-adrenal axis. There is also increasing concern that antipsychotic drugs, particularly the second-generation (atypical) drugs, have metabolic consequences that contribute to the risk. Reviews of the association between psychotic disorder, the metabolic syndrome, diabetes and antipsychotic drugs have concluded that there is a need for active, routine physical health screening of all patients treated with antipsychotic drugs. We derived from published guidelines the audit standard that all patients prescribed any antipsychotic medication should have their blood pressure, body mass index (BMI) or other measure of obesity, blood glucose (or Hb1ac) and lipids measured at least once a year. Twenty-one specialist mental health Trusts within the UK participated in a baseline audit against this standard, providing data on 1,966 patients treated by 48 multidisciplinary, Assertive Outreach, clinical teams. Careful scrutiny of the clinical records of these patients over the previous year revealed a recorded test/measurement result for blood pressure in 26%, for BMI (or other obesity measure) in 17%, for blood glucose (or Hb1ac) in 28% and for lipids in 22%. Results for all four measures were documented for 11% of patients (range from 0 to 40% across the participating Trusts). In the total national sample, 6% had a documented diagnosis of diabetes, 6% hypertension and 6% dyslipidaemia. Extrapolating from the prevalence of these disorders in similar populations, it was estimated that for every patient with a known diagnosis of diabetes, another had not been recognised, for every known case of hypertension, four had been missed, and for every known case of dyslipidaemia, seven had been missed. Following the audit, POMH-UK will offer participating clinical teams a number of quality improvement interventions, including feedback of their screening data benchmarked against other teams and Trusts. A re-audit will be conducted after a year.

DISRUPTION OF SATIETY SIGNALING IN PATIENTS TAKING OLANZAPINE OR CLOZAPINE

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Weight gain has become an increasing concern for people treated with second generation antipsychotics (SGAs), particularly olanzapine and clozapine. Weight gain due to these antipsychotics is significant and has lead to an increase in other health problems including diabetes and cardiovascular disease. The mechanism by which these drugs cause weight gain is unknown. The present investigation set out to look at the effect of olanzapine and clozapine on satiety, compared with controls taking no antipsychotic medication, and patients (pts) taking a conventional antipsychotic. Participants arrived at 8:30am fasting and were asked to consume a standardized preload of 12 oz. vanilla Ensure or 12 oz. water. All participants received both conditions on separate days. Hunger ratings were taken at baseline, then every 30 min. until a test meal (TM) was given 1.5 hrs later. TM consumption and hunger ratings were measured as an indicator of satiety. Preliminary analyses reveal that the SGA pt groups (olan, n=10: M=234.03, SD=125.04; cloz, n=10: M=245.55, SD=206.75) tend to consume more TM than the controls (n=10: M=174.9, SD=164.12)

in the Ensure condition, and the water condition (olan: M=316.59, SD=135.93; cloz: M=330.59, SD=294.91; controls: M=178.05, SD=125.49). Though these results are not statistically significant, the magnitude of effect was moderate (Cohen's d=0.39) for the Ensure condition and large (Cohen's d=0.84) for the water condition. Comparisons between TM intake and hunger ratings reveal that olanzapine, but not clozapine, appears to disrupt hunger and satiety signaling. Olanzapine pts had a greater disconnect between their hunger ratings and TM intake (r=-0.05). In contrast, clozapine pts tended to consume less when they reported less hunger and vice versa (r=0.56). It is plausible that olanzapine pts gain weight due to aberrant hunger and satiety signaling causing increased consumption that is maintained throughout the day. Though clozapine pts consumed more than controls, they ate in accordance with their hunger ratings, suggesting that they do not tend to eat indiscriminately throughout the day, consistent with the theory that weight gain induced by clozapine may have a metabolic component. Data currently being collected from pts on conventional antipsychotics will aid in teasing apart the effects of the medication and other factors common in people with schizophrenia, such as poor nutrition and a sedentary lifestyle, on satiety signaling.

COMPARATIVE EFFECTS OF ARIPIPRAZOLE VERSUS OTHER ATYPICAL ANTIPSYCHOTICS ON GLUCOSE STIMULATED INSULIN SECRETION

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Treatment with certain atypical antipsychotics (APs) is associated with metabolic side effects such as weight gain, insulin resistance and type 2 diabetes. To better understand the potential mechanisms leading to such side effects, we compared the effect of aripiprazole (ARI) on insulin secretion to other APs. MIN6 cells (5 x 104 cells/well) were seeded in 96-well plates and cultured in low glucose medium for 2 days. Cells were challenged by 16.7 mM glucose and exposed to different concentrations (1/2 Cmax, Cmax and 10-fold Cmax of published plasma concentrations in humans) of the APs aripiprazole, olanzapine, quetiapine, risperidone, 9-OH risperidone, or Ziprasidone for 1 or 72 hrs. Insulin release was quantified as ng of insulin per µg of protein. Statistical comparisons were made using ANOVA with Dunnet's correction. After 1 hr of treatment at concentrations 1/2 Cmax (15 to 250 nM) and higher, glucose-stimulated insulin release from cultured pancreatic beta cells was inhibited significantly ($P<0.05$), and dose-dependently, by olanzapine and quetiapine, but not Ziprasidone, risperidone, 9-OH risperidone or aripiprazole. After 72 hrs of treatment, glucose-stimulated insulin release was significantly ($P<0.05$) inhibited by olanzapine and quetiapine at 1/2 Cmax or higher and by Ziprasidone at Cmax (0.5 µM) only. Treatment with aripiprazole, risperidone or 9-OH risperidone did not inhibit insulin release. Over all, glucose stimulated insulin release was inhibited 20 - 25% by olanzapine and quetiapine relative to control (vehicle control insulin release after 1 hr: 0.66 to 0.91 ng/µg protein). In conclusion, aripiprazole, risperidone, and 9-OH risperidone differed from Ziprasidone, olanzapine and quetiapine in exhibiting no significant inhibition of insulin secretion from pancreatic beta cells. Olanzapine and quetiapine exhibited a rapid (after 1 hr exposure) inhibition of insulin secretion at all 3 doses tested as well as chronic inhibition after 72 hrs exposure. The mechanisms for acute and chronic inhibition may be distinct, and are the subject of further investigation. The data are consistent with the current hypothesis that selective beta-cell inhibition of insulin secretion by some APs contributes to impairment of glucose homeostasis and development of type 2 diabetes, and may help to explain the neutral metabolic profile of aripiprazole in the clinic.

CATEGORICAL PREVALENCE OF HYPERPROLACTINAEMIA IN SCHIZOPHRENIA AND BIPOLAR OUTPATIENTS IN UK RECEIVING ANTIPSYCHOTICS

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Increasing attention has been paid to the importance of elevated prolactin levels. Sexual dysfunction and osteoporosis have been reported in patients with hyperprolactinaemia. Clinical significance of elevated prolactin levels is unknown for most patients. Most data derived from clinical trials presents results as mean change in a cohort rather than absolute patient numbers with abnormal values. There is little naturalistic data showing numerical prevalence and severity of raised prolactin levels in apparently asymptomatic patients. All outpatients in a community mental health team in Halifax receiving antipsychotics with a diagnosis of schizophrenia or bipolar disorder were asked to have prolactin measurements. Upper Limit of Normal (ULN) for prolactin 500mIU/L (males) and 700mIU/L (females). Prolactin levels were obtained in 226 patients providing 253 incident cases as antipsychotic changes were made over a 36-month period. No patient refused testing. In no patient had clinical symptomatology led to prolactin measurements previously. Abnormal values were found in 49% females and 29% males - 39% of the cohort. Levels >1000 mIU/L were seen in 23% (females 36%, males 10%). From the 61/125 females with abnormal levels, 74% of these had levels >1000 mIU/L and 16/125 (13%) > 2000 mIU/L. Only 13/128 males had levels > 1000 mIU/L. Prevalence of hyperprolactinaemia in those on antipsychotic monotherapy: olanzapine 7%, typicals 33%, amisulpride 92%, Clozapine 4%, risperidone oral 83%, and risperidone consta 65 %. Addition of typicals to risperidone did not further increase hyperprolactinaemia (74%). In Risperidone Consta patients, 15/23 (65%) had hyperprolactinaemia including 100% of females (10/10). Most females on oral risperidone (12/13) also had hyperprolactinaemia and had values >1000 mIU/L in11/12. Routine prolactin screening showed abnormal values in 39% and significantly abnormal levels (>1000 mIU/L) that could lead to drug/dosage alterations in 23%. Exceptionally high levels > 2000 mIU/L were found in 7%. In our cohort, males were relatively unaffected . Females on oral and consta risperidone had high rates of hyperprolactinaemia.

IMMEDIATE CHANGES IN INSULIN RESISTANCE AND SECRETION FOLLOWING OLANZAPINE ADMINISTRATION

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Second generation antipsychotics are increasingly linked with side effects in the metabolic domain, e.g. weight gain, dyslipidemia,

hyperglycemia, insulin resistance and type II diabetes. The mechanisms underlying this phenomenon are currently unclear, but some clinical observations suggest the possibility of an immediate effect of atypical antipsychotics on glucose metabolism. This study has endeavored to assess the acute affects of olanzapine administration on certain metabolic parameters. The euglycemic and hyperglycemic clamp procedures evaluate, in vivo, deficits in insulin resistance and secretion. Throughout the euglycemic clamp, a steady infusion of insulin inhibits endogenous glucose production. Exogenous glucose is infused at varying rates to maintain (clamp) plasma glucose at a predetermined concentration. The glucose infusion (GINF) rate is considered an index of insulin resistance. In the hyperglycemic clamp, subjects are given an initial glucose bolus and subsequent GINF infusion to maintain plasma glucose levels above 17mM (the hyperglycemia standard). Levels of insulin in the plasma are sampled to determine treatment effects on the beta cell's response to the glucose challenge. In our paradigm, male, Sprague-Dawley rats were implanted with arterial and jugular catheters to facilitate blood sampling and infusion and 3-4 days post-surgery, animals were clamped in one of the two procedures. Animals were treated subcutaneously with either, olanzapine (3.0 mg/kg) or vehicle (1% acetic acid) at 130 minutes prior to completion of the euglycemic clamp or 90 minutes prior to beginning the hyperglycemic clamp. Acute administration of olanzapine significantly lowered GINF rates in the euglycemic clamp, $p = 0.012$. Radioactive tracer analysis suggests olanzapine treatment induces hepatic glucose production ($p = 0.042$) and decreases glucose utilization in muscle cells ($p < 0.000$). Similar effects were observed in the hyperglycemic clamp, with olanzapine-treated animals requiring lower GINF rates than control animals, $p < 0.000$. In addition, deficits in insulin secretion have been confirmed through insulin assay analysis, with olanzapine-treated animals displaying a decrease in plasma insulin levels, $p = 0.0032$. These findings highlight olanzapine's immediate and potent effect on insulin resistance and insulin secretion in vivo.

CLOZAPINE-INDUCED TARDIVE DYSKINESIA

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Clozapine is known to cause less extrapyramidal symptoms and recommended as a treatment drug for severe tardive dyskinesia (TD). However, there are several case reports suggesting clozapine could cause also TD. To investigate whether clozapine really cause TD, we identified 101 patients in Yanbian Socio-Mental hospital and Yanbian Brain hospital in China to whom clozapine was administered as a primary antipsychotic drug since the first episode and evaluated the prevalence rate and the type and severity of TD using Extrapyramidal Symptoms Rating Scale (ESRS). The criteria for TD was ≥ 3 on 1 item or ≥ 2 on 2 items of ESRS. The mean age and duration of illness of the patients was 38.93±8.36 and 12.84±6.89 years, respectively. The mean duration of clozapine treatment was 12.10±6.26 years. The prevalence of TD was 3.96% (4/101). Compared to the patients without TD, patients with TD were found to have long duration of illness and clozapine treatment. They all showed oro-lingual type of TD. TD was relatively mild with the mean score of 4.7 and tended to accentuate with activation procedure like finger tapping test and rapid pronation and supination of hands. None of the patients with TD complained distressing symptoms related to TD. The results indicate clozapine does cause TD. However, the prevalence is low (4.7%) and severity is relatively mild with no self-reporting discomfort. Therefore, it is recommended that regular examination of TD with activation procedure should be performed in patients with long-term use of clozapine.

METABOLIC MONITORING FOR CLOZAPINE TREATED PATIENTS

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Patients treated on clozapine represent a particularly vulnerable group from a psychiatric and a metabolic perspective. While clozapine has superior efficacy in resistant psychosis, it is also associated with the greatest degree of weight gain and metabolic disturbance. In this paper we present baseline and 1 year follow up data on 107 clozapine treated patients entered into a monitoring protocol. Objective: To determine the efficacy and utility of a structured protocol for monitoring metabolic parameters in clozapine treated patients; to evaluate changes in insulin sensitivity over time; and to characterize metabolic disturbance in these patients. Methods: Initial screening includes fasting glucose, lipids and insulin followed by 3 mthly measures of HbA1c and random glucose. Patients have an annual assessment that includes a 2-hr glucose tolerance test. Results: 13% of the patients were already diagnosed with diabetes prior to screening. With systematic screening over 1 year the rate of diagnosed diabetes increased to 32%. Further data will be presented that indicate change in insulin sensitivity over time. Conclusions: A structured monitoring system can dramatically increase the number of patients identified with diabetes and promote appropriate treatment. Serial measures of A1C and random glucose can be a practical and effective way of identifying those in need of earlier diagnostic testing for diabetes.

ATYPICAL ANTIPSYCHOTIC-INDUCED CHANGES IN BODY COMPOSITION, LIPID METABOLISM AND INSULIN RESISTANCE IN ANTIPSYCHOTIC-NAïVE YOUTH

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Objective: Second-generation antipsychotics (SGAs) have been associated with significant weight gain, and abnormalities in lipid and glucose metabolism. This study aimed to assess the effect of SGAs on anthropometric and metabolic indices in youth independent of the confounder of previous antipsychotic treatment. Methods: 12-week, prospective, open-label study in antipsychotic-naïve subjects, age 4-19 years with psychotic, mood and/or disruptive behavior-spectrum disorders, treated with aripiprazole, olanzapine, quetiapine or risperidone. Comedications were not restricted. At baseline, 4, 8 and 12 weeks, height, weight, fat mass and percentage (via impedantiometry), waist circumference, fasting glucose, lipid profile, insulin, and leptin levels were measured. Insulin resistance was calculated using the homeostatic model (HOMA-IR). Results: In 256 antipsychotic-naïve youngsters (mean age: 13.7±3.6 years, 58.6% male, 48.2% Caucasian), treated with aripiprazole (n=40), olanzapine (n=45), quetiapine (n=35) or risperidone (n=136), for 10.8±3.0 weeks, signifi-

cant increases were observed for body weight (p<.0001), BMI z-score (p<.0001), fat mass (p<.0001), waist circumference (p<.0001), fasting glucose (p=.0094), insulin (p=.0036), HOMA-IR (p=.0029), triglycerides (p<.0001), total cholesterol (p<.0001), LDL-cholesterol (p=.013) and leptin (p<.0001). SGAs differed significantly regarding all body composition and lipid parameters, with olanzapine generally causing significantly greater increases than the other SGAs. However, SGAs did not differ in their effects on leptin (p=.66), fasting glucose (p=.61) and insulin (p=.58), or on absolute and relative HOMA-IR changes (aripiprazole: 0.12±2.1=36.0±104.1%; olanzapine: 0.54±1.9=62.2±137.3%; quetiapine: 0.65±1.9=21.5±52.1%; risperidone: 0.28±1.6=36.9±98.0%, p=.56 and p=.36, respectively). New-onset dyslipidemia (i.e., cholesterol >200 mg/dL and/or triglycerides >150 mg/dL) developed in 8.2% of youths on aripiprazole, 24.4% on olanzapine, 18.2% on quetiapine and 16.4% on risperidone (p=.29). Conclusions: In antipsychotic-naive children and adolescents, all examined atypical antipsychotics were associated with adverse effects in body composition and glucose and lipid metabolism parameters during the first 3 months of treatment. Careful selection of appropriate patients for SGA treatment and routine monitoring of weight and glucose and lipid measures are strongly recommended in this vulnerable population.

ADOLESCENTS GAIN LESS WEIGHT WITH ORALLY DISINTEGRATING OLANZAPINE THAN CONVENTIONAL OLANZAPINE TABLETS

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I) Methods. We measured the changes in weight (kg) and body mass index (BMI) (kg/m2) in hospitalized adolescents, at baseline, and during 12 weeks of treatment with either disintegrating olanzapine tablets (DisOlz) (N=11; 8 F, 3 M; 16.4 years ± 1.5 ; dose: 16.3 mg ± 4.5), or conventional olanzapine tablets (ConOlz) (N=10; 4 F, 6 M; 17.0 years ± 1.3; dose: 18.0 mg ± 4.22). Other adolescents treated with risperidone (N=20; 7 females, 13 males; mean age: 15.4 years ± 1.4 SD; dose: 2.8 mg ± 1.2 SD) were used as a supplementary comparison group. Three-fourths of the patients had no history of previous antipsychotic drug treatment. II) Results. After 12 weeks, ConOlz treatment was associated with significantly greater increases in weight and BMI than DisOlz treatment (8.95 kg ± 5.13 SD and 3.15 kg/m2 ± 1.87 SD with ConOlz, vs. 3.36 kg ± 2.14 and 1.22 kg/m2 ± 0.77 with DisOlz, respectively). Similarly, DisOlz treatment was associated with significantly greater increases in weight and BMI than risperidone (0.97 kg ± 1.89 and 0.36 kg/m2 ± 0.69) (all p<0.005, independent sample t-tests, two-tailed). The results were similar in boys and girls. III) Discussion. In this study, risperidone was used at comparatively low doses in patients who tended to be younger, which may limit the comparison with olanzapine. Another limitation is the open-label and non-randomized study design. The pharmacokinetic properties of these two forms of olanzapine might account for differing effects on weight. It has been suggested that the orally disintegrating form spends less time in the digestive tract, which would shorten the interaction with digestive serotonin (e.g., 5-HT3) receptors mediating satiety. Major implications for the treatment of adolescents would be expected if other studies confirmed that orally disintegrating olanzapine induces less weight gain than other forms.

INCREASED METABOLIC RISK IN ADOLESCENTS PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS: PRELIMINARY RESULTS

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Background: Atypical antipsychotics (AA) offer many advantages in the treatment of psychotic disorders but are associated with several metabolic side effects (weight gain, diabetes, dyslipidemia and metabolic syndrome) that may increase the cardiovascular morbimortality and the likelihood of medication non-compliance. The pathogenesis of weight gain is not well known and may include changes in resting energy expenditure (REE), food intake and physical activity. Objective: The aims of the study are to study the effects of the treatment with AA on REE and body composition in adolescent patients and the prevalence of metabolic syndrome. Methods: We studied 21 antipsychotic-naive adolescents (10F/11M), with a medium age 17 years (12-18), in their first psychotic episode at admission and 3 months after treatment with AA olanzapine (n=6), risperidone (n=10), quetiapine (n=5). Nutritional assessment included anthropometry and tetrapolar bioimpedance (Holtain BC). REE was measured by indirect calorimetry (IC) after an overnight fast (Deltatrac TM II MBM-200). ATP III criteria adapted for adolescents were used to diagnose metabolic syndrome. Values are expressed as median and range. Statistical analysis included non-parametric tests. Results: Weight gain was 5.3 kg (-0.5-17.2). There was an increase in fat mass (FM) and fat free mass (FFM). Waist circumference increased significantly (Table 1). REE decreased 3 months after treatment from 25.1 kcal/kg (20.4-35.2) to 23.5 (19.3-30.1), P= 0.019 and 35.6 kcal/kg FFM (31.1-48.9) to 33.9 (29.9-42.7), P= 0.073. Seven patients had 1 criterium, 4 patients had 2 criteria and 1 patient had 3 ATP III criteria. Two patients developed hypertension. Conclusions: 1) We observed an increase in body weight and abdominal fat in adolescent patients 3 months after treatment with AA. 2) A decrease in REE could be involved in the pathogenesis of weight gain. 3) These patients are in risk of developing metabolic syndrome.

Table 1.

	Body weight (kg)	Waist circumference (cm)	FM (kg)	FFM (kg)
Admission	57.6 (34.8-80.6)	73 (64-96.5)	17.1 (8-25.9)	41.2 (26.3-54.7)
3 months	64.2 (37.3-92.3)	79.5 (65-103)	18.8 (10.7-32.5)	44.5 (26.2-59.8)
p	0.000	0.000	0.003	0.000

PREVALENCE AND INCIDENCE RATES OF METABOLIC ABNORMALITIES AND DIABETES IN A PROSPECTIVE STUDY OF PATIENTS TREATED WITH SECOND-GENERATION ANTIPSYCHOTICS

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Background: Increased rates of medical comorbidity and mortality in the mentally ill population are a topic of growing concern, and metabolic side effects of psychotropic therapy are one factor that

may increase this risk. Methods: All consecutive patients with schizophrenia (n=238) started on antipsychotic medication at our university psychiatric hospital and affiliate services were entered in an extensive prospective metabolic study including an oral glucose tolerance test and followed for 3 months. Results: The overall incidence rate of new onset diabetes within 3 months of antipsychotic initiation was 4% (95%CI: 2%-7.5%, n=226). Incidence rates by specific agent were 8.7% (1.3-%-28%) for clozapine (n=23), 6.8% (2.2%-16.6%) for olanzapine (n=59), 6.7% (2%-23%) for quetiapine (n=30), 1.8% (0.1%-10.1.%) for risperidone (n=57), and 0% (0%-16.9%) for amisulpride (n=23) and 0% (0%-12.1%) for aripiprazole (n=34). The overall incidence of pre-diabetes was 20.4% (15.6%-26.1%). New onset diabetes was reversed in 11 patients following switch to amisulpride (n=4), aripiprazole (n=7) or risperidone (n=1) and not reversible in 1 patient switched to quetiapine. The incidence rate of ATP-A metabolic syndrome was 20%, with significant differences between antipsychotic agents. 19.7% of patients developed severe dyslipidaemia requiring an intervention with a statin. Conclusion: Metabolic abnormalities are frequently observed and can occur fast after the initiation of antipsychotic medication. The liability to induce metabolic abnormalities differs significantly between antipsychotics. The data underscore the need for screening for metabolic abnormalities in patients diagnosed with severe mental illness treated with antipsychotics.

TREATMENT WITH ROSUVASTATIN FOR SEVERE DYSLIPIDAEMIA IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Background: Mortality rates in patients with schizophrenia are double compared to the general population, with cardiovascular disease causing 50% of the excess. Lowering LDL cholesterol is recognized as a primary target for the prevention of cardiovascular mortality according to National Cholesterol Education Program (NCEP; Adult Treatment Protocol, ATP III). Use of lipid-lowering drugs as statins is recommended when life style changes aren't sufficient enough to reach LDL goal. The efficacy and safety of rosuvastatin treatment were evaluated in schizophrenic patients. Methods: One-hundred schizophrenic patients with severe dyslipidaemia were identified (27.5% of patients on long-term treatment with antipsychotics and 15.7% of patients recently started on antipsychotics). All were treated with antipsychotics. Fifty-two patients were treated with rosuvastatin and compared to forty-eight who did not receive statin treatment. All patients were screened for cardiovascular risk factors and examined at baseline. The effects of lipid lowering medication on lipid profile, glucose homeostasis and components of metabolic syndrome were evaluated at 3 months follow-up. Results: After 3 months of statin therapy, a significant decrease in triglycerides, total cholesterol, LDL cholesterol, non-HDL cholesterol and in associated ratios (LDL/HDL, CHOL/HDL) was observed. The difference is highly significant compared to patients not receiving statin treatment. No significant changes occurred in HDL cholesterol, body mass index and waist circumference or glucose homeostasis. The only component of metabolic syndrome affected by statin therapy was the serum triglyceride level. Conclusion: Rosuvastatin proved effective in the management of dyslipidaemia in patients with schizophrenia treated with antipsychotics. More complex treatment may be required for associated metabolic disturbances.

CHANGES IN PROTEOMIC PROFILE OF HUMAN CAUDATE NUCLEUS IN ANTIPSYCHOTIC DRUG-TREATED SCHIZOPHRENIA

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Antipsychotic drugs (APD)-induced extrapyramidal side effects (EPS) are frequently observed side effects in the treatment of psychosis including schizophrenia. These unpleasant effects significantly affect drug compliance, which leads to a high risk of relapse. Mechanisms of chronic, irreversible APD-induced EPS, such as Parkinsonism and tardive dyskinesia are largely unknown, and no effective treatments are available. Current knowledge on the mechanisms behind the EPS mostly comes from the animal studies, where the main APD-induced changes are observed in the striatum. These include neuron size enlargements, decreased neuronal density, altered synaptic structure and discrete changes in the expression of presynaptic proteins. In humans APD have also been shown to produce structural changes in the striatum, such as large swollen neurons, gliosis, glial satellitosis and changes in striatal volumes. However, the precise molecular mechanisms of APD effects (both therapeutic and toxic) on the striatum remain unclear. Using proteomic approach this study aimed to characterize changes in the protein expression profile of caudate nucleus obtained form postmortem brains of APD-treated schizophrenia patients with and without EPS. Protein extracts from the caudate nucleus of 10 well-characterized schizophrenia cases and 10 matched controls were separated using 2D gel electrophoresis. Over 1000 protein spots were visualized in each gel and over 500 matched spots identified. Differentially expressed proteins were classified into several functional categories including metabolism, signaling and cytoskeleton. EPS-related changes were extracted by cross-correlating findings observed in the EPS-positive and negative groups. Further, we compared the proteomic changes identified in the human caudate nucleus with those observed in the striatum of APD-treated animal models in order to pinpoint specific APD-unrelated (schizophrenia-causative) alterations.

FEASIBILITY OF QUANTIFYING ACTIVITY ENERGY EXPENDITURE AND CALORIC INTAKE BY DOUBLY-LABELED WATER IN TREATED PATIENTS WITH SCHIZOPHRENIA

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Schizophrenia is associated with an average loss of 25-30 years of life vs. population norms. The major factor explaining this dramatic increase in mortality is an increased prevalence of cardiovascular disease in comparison to the general population. Overweight/obesity, a major risk factor for cardiovascular disease, occurs at a high prevalence among schizophrenia patients. Antipsychotic medications used in the treatment of schizophrenia can induce significant increases in weight and adiposity, with different medications associated with

well-characterized differences in weight change. Less well characterized are the differential effects of specific antipsychotic medications on changes in regional adiposity, or on mechanisms underlying changes in adiposity. There are currently no in vivo experimental data from humans that quantify the degree to which antipsychotic medications alter caloric intake, physical activity level, or some combination of both. The doubly-labeled water (DLW) method has been recognized as the gold-standard measure of total energy expenditure, energy intake, and activity energy expenditure in humans. However, this method has never been applied to the evaluation of antipsychotic-induced increases in adiposity in treated patients. This ongoing project uses DLW to quantify treatment-induced changes in Activity Energy Expenditure (AEE) and Energy Intake (EI) in schizophrenia patients during twelve weeks of prospective, randomized treatment with either olanzapine or ziprasidone. For this pilot study, chronically treated patients with schizophrenia undergo single DLW assessments to confirm the feasibility of engaging patients in the required procedures. Details on the procedure and calculations of AEE and EI will be presented. Preliminary data support the feasibility of using the gold-standard DLW method to assess the effects of antipsychotic treatment on caloric intake and energy expenditure. This information will be relevant to the interpretation of observed changes in adiposity during antipsychotic treatment, and critical for planning appropriate interventions to address this problem.

CLOZAPINE AND CARDIOTOXICITY: ECHOCARDIOGRAPHY FINDINGS FROM BARWON HEALTH

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Clozapine continues to have a unique efficacy profile that to date has not been matched or enhanced by other second-generation antipsychotics. However, the risk of life threatening adverse effects associated with clozapine treatment remains. While agranulocytosis is a well-documented vulnerability for these patients, other serious risks are less well recognised and are yet to be investigated as rigorously. Myocarditis and dilated cardiomyopathy are acknowledged adverse effects associated with clozapine treatment and pose a serious risk to patients, yet there remains a dearth of examination in this area. The current study aims to investigate changes in cardiac functioning in a group of patients treated for the first time with clozapine. Transthoracic echocardiograms were conducted on seventy-seven clozapine naïve patients, prior to commencing clozapine treatment (Time 1) and were repeated after 6 to 12 months (Time 2), as part of routine cardiac monitoring. Patient psychiatric and medication history were documented, as were full white blood count, troponin 1 and creatinine kinase results. The rate of clozapine titration was also recorded. Preliminary analyses of the data set indicate a decrease in left ventricular shortening, a measure of ventricular contractility, from Time 1 (pre clozapine) to Time 2. Further analyses will be presented. While there appears to be a trend towards a worsening of cardiac function with clozapine treatment, further investigations need to be carried out taking into account confounding factors that are known to be implicated in cardiac dysfunction to such as age, BMI, smoking, medical history, familial history, amongst others. Establishing a clearer understanding of the link between the two will help patients and clinicians balance the risk of cardiac problems and improved psychopathology and help to institute cardiac monitoring guidelines for patients treated with clozapine.

RELATIONSHIP OF PLASMA CORTISOL TO ADIPOSITY AND METABOLIC INDICES IN SCHIZOPHRENIA PATIENTS

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Recent reports have postulated that stress-related increases in circulating cortisol levels could account for increases in adiposity as well as insulin resistance and related dyslipidemia observed in patients with schizophrenia. This hypothesis has been suggested for unmedicated, drug-naïve patients and extended to treated patients. To test this hypothesis in a group of treated schizophrenia patients, we analyzed the association between fasting early morning plasma cortisol levels and direct measures of adiposity, gold-standard measures of insulin sensitivity, and fasting lipid levels, using a sample size (n=77) with good power to detect moderate or larger effects. Magnetic Resonance Imaging (MRI) was used to quantify adipose tissue, and the hyperinsulinemic, euglycemic clamp technique with stable isotopomer tracers was used to determine whole body and tissue-specific insulin sensitivity. No significant association was detected between plasma cortisol and MRI-measured visceral adipose tissue area ($F[1,46]=0.37$, $p=0.55$), subcutaneous adipose tissue area ($F[1,46]=0.36$, $p=0.55$), or combined visceral and subcutaneous adipose tissue ($F[1,46]=0.003$, $p=0.95$). Similarly, there was no significant association between plasma cortisol and clamp-derived measures of whole body insulin sensitivity (glucose disposal rate, $F[1,42]=0.63$, $p=0.43$), or tissue-related insulin sensitivity (hepatic: glucose rate of appearance, $F[1,66]=0.033$, $p=0.86$; skeletal muscle: glucose rate of disappearance, $F[1,66]=0.33$,$p=0.57$; adipose tissue: glycerol rate of appearance, $F[1,67]=1.71$, $p=0.20$). Finally, no significant relationship was detected between plasma cortisol and other metabolic indices, including fasting glucose level ($F[1,75]=1.41$, $p=0.24$), fasting insulin level ($F[1,75]=0.75$, $p=0.39$), fasting triglyceride level ($F[1,73]=2.11$, $p=0.15$), fasting total cholesterol level ($F[1,73]=0.025$, $p=0.87$) fasting LDL level ($F[1,72]=0.09$, $p=0.76$), or fasting HDL level ($F[1,73]=2.98$, $p=0.09$). These results do not support the hypothesis that increased adiposity or impairments in glucose and lipid metabolism are related to plasma cortisol levels in chronically treated schizophrenia patients. Support Contributed By: MH63985, Washington University General Clinical Research Center USPHS MO1 RR00036, Washington University Clinical Nutrition Research Center Grant P30 DK56341 and P60-DK20579.

MICE LACKING THE IMMEDIATE EARLY GENE EGR3 REVEAL SEPARABLE SEDATING AND THERAPEUTIC EFFECTS OF CLOZAPINE

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Although both genetic and environmental factors contribute to the risk to develop schizophrenia, the mechanisms by which these factors interact to elicit illness remains elusive. We have focused our studies on a family of immediate early genes (IEGs) that are activated in the brain in response to environmental stimuli such as stress and, in turn, regulate processes such as learning and memory. Purpose: To test the hypothesis that defects in the function of the IEG early growth response gene 3 (Egr3) in mice will result in behavioral abnormalities associated with schizophrenia which are reversible

with clozapine treatment. Experimental Methods: We have studied the behavior of mice lacking Egr3. We performed the Resident-Intruder test in which individually-housed adult male Egr3-/- and wildtype (WT) littermate control mice are confronted with the social stressor of a foreign intruder being placed in their cage for a 10 minute test period. Mice were then chronically administered either clozapine (3.5 mg/kg/d x 1 week followed by 7 mg/kg/d x 1 week) or vehicle and re-tested. The locomotor activity of Egr3-/- and control mice in a novel environment was also tested following acute treatment with 3.5 mg/kg clozapine or vehicle for assessment of sedation. Results: We found that Egr3-/- mice display increased aggression and a decreased latency to attack an unfamiliar mouse in the resident-intruder test. These results, together with our findings of persistent and intrusive social investigation of familiar mice, suggest that Egr3-/- mice are more impulsive that WT controls. We also found that chronic administration of the antipsychotic medication clozapine significantly reduces the aggression of Egr3-/- mice. Notably, despite their sensitivity to this therapeutic effect of this medication, Egr3-/- mice show marked resistance to the sedating effects of clozapine compared to controls. Conclusions: These results show that the anti-aggressive action of clozapine is separable from its sedating activity. This parallels the observation that schizophrenia patients tolerate many fold greater doses of antipsychotic medications without severe side effects than do healthy controls. Thus Egr3-/- mice may be a tool for elucidating the mechanism of action of clozapine, and may provide insight into the neurobiological abnormalities that give rise to schizophrenia.

LIFESTYLE AND CORONARY HEART DISEASE (CHD) IN PSYCHOTIC PATIENT WITH AND WITHOUT METABOLIC SYNDROME (MS): THE CLAMORS STUDY

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Purpose: To compare the lifestyle and the coronary heart disease (CHD) risk in schizophrenic patients treated with antipsychotics with and without metabolic syndrome (MS). Methods: Retrospective, cross-sectional, multicenter study where 117 Spanish Psychiatrists (The CLAMORS Collaborative Group) recruited consecutive outpatients meeting DSM-IV criteria for Schizophrenia, Schizophreniform or Schizoaffective Disorder, under antipsychotic treatment for at least 12 weeks. Coronary Heart Disease (CHD) risk was assessed by SCORE (10-year CV death) and Framingham (10-year all CV events) functions. Metabolic Syndrome (MS) was defined by at least 3 of the following components: waist circumference >102cm(men)/>88cm(women); tryglicerides >=150mg/dL; HDL-cholesterol <40mg/dL (men) / <50mg/dL (women); blood pressure >=130/85mmHg; fasting glucose >=110mg/dL. Results: 1452 evaluable patients (863 men, 60.9%), 40.7±12.2 years (mean±SD) were included. MS was presented in 357 patients (24.6%) [23.6%(men), 27.2%(women); p=0.130)]. Patients with MS were older [m=44.1(DT=11.8) vs 39.5(DT=12.1) years], more frequently married (26.3% vs 21.4%) and with allowance (61.6% vs 42.9%)(p<0.05), with longer evolution of illness [m=18.0(DT=10.2) vs 14.7(DT=10.9) years], more previous hospitalisations [m=3.1(DT=3.2) vs 2.5(DT=2.9)] and more frequent diagnosis of residual schizophrenia (20.2% vs 10.5%)(p<0.05). Differences were not found in smoking, alcohol, caffeine consumption habits, caloric consumption and high fiber diet, but less patients with MS followed some diet (79.8% vs 84.7%), controlled sale consumption (78.7% vs 88.0%) and avoided saturated fat/cholesterol (70.8 % vs 77.9%) (p<0.05). The overall 10-year risks were 0.9±1.9 (mean±SD) and 7.2±7.6 for SCORE and Framingham. 8%(95%CI:6.5-9.5) and 22.1%(95%CI:20.0-24.3) of patients showed high/very high risk according to SCORE (>=3%) and Framingham (>=10%) functions. More patients with MS showed high/very high risk according to SCORE (>=3%) [12.9%(95% CI:9.8-16.8) vs 6.2%(95%CI=4.8-8.0)] and Framingham functions (>=10%) [44.2%(95%CI:39.1-49.4) vs 12.9%(95%CI=11.5-15.0)] (p<0.05). Conclusions: Schizophrenic patients treated with antipsychotics with MS were older and showed longer evolution of illness, worst eating habits and higher CHD risk. More prevention actions could be taken on patients treated with antipsychotics with MS in order to prevent more increase of their CHD risk. *On behalf of the CLAMORS Collaborative Group.

RECOMMENDATIONS FOR MONITORING AND MANAGING METABOLIC DISTURBANCES DURING ANTIPSYCHOTIC TREATMENT

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Individuals with schizophrenia have elevated rates of mortality and medical comorbidity, related to increased rates of conditions such as type 2 diabetes mellitus and cardiovascular disease. While it is likely that lifestyle issues (e.g., reduced activity, poor nutrition) play a key role, a range of evidence suggests that treatment with antipsychotic medications is associated with an increased risk for insulin resistance, hyperglycemia, and dyslipidemia. An American Diabetes Association (ADA) Consensus Development Conference, co-sponsored by the American Psychiatric Association (APA) and other organizations, recently addressed this topic. Other international organizations have also published recommendations. The APA Committee on Research on Psychiatric Treatments convened a workgroup to address outstanding questions and to provide additional guidance to the field. Experts in endocrinology, cardiology, psychiatry and services research reviewed relevant literature in their respective areas of interest. Over 60 contributors submitted subsections for review that are incorporated into the report, and over 80 participants reviewed and edited the final report. Literature references were identified primarily via Medline searches. The reports identified can be broadly divided into 1) uncontrolled observational studies, 2) large, controlled, observational database analyses using prescription, administrative or – less commonly – population-based databases, and 3) controlled experimental studies, including randomized clinical trials. On the specific topic of antipsychotics and diabetes or dyslipidemia risk, over 1000 papers are currently in the literature, with a more limited literature of well-controlled experimental studies. The Workgroup identified areas of consensus and discrepant results and/or discrepant interpretations that will be incorporated into the final report. Similar to the ADA's ongoing use of Consensus Development Conferences, the APA Workgroup offers an opportunity to address controversial areas of research with comprehensive expertise in order to identify areas of consensus, discrepant results and directions for future research. The APA workgroup identified opportunities for managing metabolic risk during antipsychotic treatment and improving health outcomes.

CHANGES IN DIRECT MEASURES OF ADIPOSITY IN SCHIZOPHRENIA PATIENTS DURING DIVALPROEX AUGMENTATION OF ANTIPSYCHOTIC TREATMENT

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Schizophrenia and its treatment are commonly associated with obesity and increases in adiposity. Studies are underway to compare effects of monotherapy with various antipsychotics on direct measures of adiposity, but schizophrenia patients are commonly treated with polypharmacy in the community. Few studies have described the effects of commonly used polypharmacy strategies on changes in adiposity. Increased adiposity can disturb glucose and lipid metabolism via disturbances in insulin sensitivity, and schizophrenia patients experience an increased prevalence of diabetes mellitus in comparison to the general population. Increased adiposity, plasma glucose and lipids are independent risk factors for cardiovascular disease, and schizophrenia patients experience increased cardiovascular (CV) mortality in comparison to the general population. Adiposity can be directly measured using whole body dual energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging (MRI). Subjects included patients with schizophrenia chronically treated with antipsychotic medications that were randomized to three months of augmentation with divalproex or placebo. Preliminary analyses indicate that divalproex augmentation can result in significant increases in direct and indirect measures of adiposity. Covarying the baseline value of the dependent variable, time X treatment group (placebo or divalproex) effects were observed with BMI ($F[1,14]=10.23$, $p=.006$), DEXA total fat ($F[1,13]=7.32$, $p=.018$), and MRI subcutaneous fat ($F[1,9]=7.98$, $p=.020$). Sensitive techniques such as these can be used to carefully assess effects of polypharmacy that may contribute to disturbances in glucose and lipid metabolism and cardiovascular risk in schizophrenia, allowing patients and clinicians to make informed decisions about the risks and benefits of a given polypharmacy strategy. Support: NARSAD (Stephen and Connie Lieber Young Investigator Award), NIMH K23 MH 067795, Abbott Laboratories (medication only), NIH R01 63985, USPHS, #MOIRR00036, GCRC, CNRU P30 DK56341 and P60-DK20579.

CHANGES IN METABOLIC PARAMETERS IN ADOLESCENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER I DURING TREATMENT WITH OLANZAPINE: A POOLED ANALYSIS OF 4 STUDIES

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Introduction: Changes in weight and other metabolic parameters have been reported in adults treated with olanzapine during acute and long-term studies. Methods: Data from 454 adolescents (13–18 years; mean age=15.9 years) with schizophrenia or bipolar disorder I were pooled from 4 studies (4–32 weeks; 2 double-blind, placebo-controlled studies with open-label extension phases, 2 open-label studies) of olanzapine (2.5–20.0 mg/day). Changes in metabolic parameters in adolescents were compared with adults with schizophrenia or bipolar disorder pooled from 84 olanzapine clinical trials, and changes in height, weight, and BMI were compared with US age- and sex-adjusted standardized growth curves. LOCF mean changes from baseline to endpoint were analyzed using a one-sample t-test, and were compared with adult data using an ANCOVA model, with terms for baseline and population. The incidence of abnormal metabolic parameters was compared with adult data using Fisher's exact test. Results: Olanzapine-treated adolescents had significant increases from baseline to endpoint in fasting glucose ($p=.021$); total cholesterol, LDL cholesterol, and triglycerides ($p<.001$); and significant decreases in HDL cholesterol ($p<.001$). Compared with adults, significantly more adolescents gained ≥7% of weight from baseline (65.1 vs 35.6%, $p<.001$); mean change from baseline to endpoint in weight was also significantly greater in adolescents (7.0 vs 3.3 kg, $p<.001$). Compared with adults, adolescents had significantly lower mean changes from baseline to endpoint in fasting glucose (0.3 vs 0.1 mmol/L, $p=.002$) and triglycerides (0.3 vs 0.2 mmol/L, $p=.007$). Significantly more adults experienced treatment-emergent normal-to-high changes at anytime in fasting glucose (4.8% vs 1.2%, $p=.033$), total cholesterol (6.9% vs 1.1%, $p=.001$), LDL cholesterol (5.8% vs 1.5%, $p=.014$), and fasting triglycerides (25.7% vs 17.4%, $p=.030$). Compared with standardized growth curves, olanzapine-treated adolescents had greater increases from baseline to endpoint in weight (0.95 vs 7.1 kg, $p<.001$), height (0.5 vs 0.7 cm, $p<.001$), and BMI (0.2 vs 2.2 kg/m2, $p<.001$). Conclusion: During treatment with olanzapine, adolescents may gain significantly more weight compared with adults, but may have lower (and less frequent) changes in metabolic parameters. Clinicians should consider both efficacy and potential changes in weight and metabolic parameters when selecting treatment options for this patient population.

SEXUAL FUNCTIONING IN MALE SCHIZOPHRENIC PATIENTS: A CASE-CONTROL STUDY

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Objectives: To evaluate the sexual function in male schizophrenic patients and to compare the frequency of sexual dysfunction between patients and a healthy control group. Methods: This is a case-control study with 120 participants: 60 male schizophrenic outpatients from the Schizophrenia Program (PROESQ) of Federal University of São Paulo (UNIFESP), and 60 healthy controls were interviewed. The Dickson and Glazer Inventory assessed sexual function in the patients and controls. Psychopathology, extrapiramidal symptoms, depressive symptoms, antipsychotics and tobacco use were also evalueted. Results: Patients had less stable sexual relation than controls ($p<.001$), less sexual thoughts ($p=.001$), higher comfortable time without sex or masturbation ($p<.05$), and less frequency of sexual relations ($p=.05$). It was found no differences between groups regarding masturbation frequency. Patients had more erectile dysfunction both in sexual relations (<.001) and in last masturbation (p.001), and they were less satisfied with masturbation (<.001). Twenty-nine (48.3%) patients complained about adverse effects of drugs. Sexual adverse effects were related for 19 (65.5%) patients taking first generation

antipsychotics and associated drugs, and 10 (32.3%) patients taking second generation antipsychotics (p<.05). Conclusions: Schizophrenic male patients taking antipsychotics had more sexual dysfunction compared to control group. Active questioning about those symptoms and adequate clinical management of them might help them to deal with these problems and this could improve their quality of life.

SERTINDOLE: A NEWLY AVAILABLE ATYPICAL ANTIPSYCHOTIC WITH PLACEBO LEVEL EPS

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Sertindole is an antipsychotic agent that shows affinity for D2, 5-HT2A, 5-HT2C, and a1-adrenoceptors. Preclinical research suggests that sertindole has a preferential effect on the activity of limbic and cortical dopaminergic neurons, and clinical trials have confirmed that sertindole is efficacious at a low D2 receptor occupancy, comparable to that produced by clozapine, which may confer a lower risk of EPS. PubMED was searched for all randomised controlled trials of sertindole where EPS ratings were performed and published in English language in peer-reviewed medical journals. All of these published studies were reviewed regarding the occurrence of EPS in patients. Five clinical trials of sertindole fulfilled these criteria. Comparators were placebo, haloperidol and risperidone. Rating scales used were: Simpson –Angus Scale (SAS), Barnes Akathisia Scale (BAS), and Abnormal Involuntary Movement Scale (AIMS). Furthermore, the need for anti EPS medication, and the incidence of EPS-related events (presented as percentage of patients), if registered, was recorded. If significant differences were reported, NNT (number needed to treat) values were calculated and presented with point estimates and 95 % CI. In three studies significant differences between sertindole and haloperidol were observed. In the two remaining studies, no significant differences were noted between sertindole vs placebo and risperidone, respectively. In summary sertindole has been shown to have an exceptionally low propensity for EPS, and abnormal movement side effects.

THE EFFECTS OF OLANZAPINE ON WEIGHT GAIN AND LOCOMOTOR ACTIVITY: AN ANIMAL MODEL

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The newer 'atypical' antipsychotic medications have, as a class, been associated with an increased risk of weight gain and metabolic abnormalities. As of yet, though, the mechanisms responsible for these side effects remain poorly understood. Using an animal model, we have been evaluating weight gain in rats exposed to atypical antipsychotics, in this case olanzapine, to determine whether this increase in weight is associated with food intake, diet, and/or locomotion. In 2 experiments, female Sprague-Dawley rats were chronically treated with olanzapine (7.5 mg/kg), which results in D2 occupancy levels in Sprague-Dawley rats that would be in keeping with clinically therapeutic doses in humans i.e., >65%, or vehicle for 28 days via Alzet® osmotic pump. In Experiment 1, rats were fed standard rat chow (LabDiet 5001) and water ad libitum. In Experiment 2, rats were fed a 60% fat diet (Dyets Inc.) and water ad libitum. In both experiments, body weight, food intake, and locomotor activity were measured weekly. Chronic treatment with olanzapine in rats fed the high fat diet, but not standard rat chow, significantly increased body weight after 28 days compared to vehicle treated rats. A nonsignificant trend towards increased food intake was observed in both experiments. Olanzapine treatment produced a significant decrease in locomotor activity compared to vehicle treated rats when fed both standard rat chow and a high fat diet. These data confirm that chronic treatment with olanzapine induces weight gain in female rats when offered a high fat diet ad libitum. It would appear that both diet and activity are involved, as olanzapine administration was also associated with decreased locomotor activity. Whether this same pattern occurs with all atypicals remains to be established.

PSYCHOPHARMACA PRESCRIBED DURING MOTHERS' PREGNANCIES AND OFFSPRING MENTAL DISORDER IN ADULTHOOD: A PROSPECTIVE INVESTIGATION OF GENETIC HIGH-RISK OFFSPRING

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The goal of the study was to determine whether psychopharmaca prescribed during pregnancies of women with a psychosis history is associated with offspring adult mental disorders and, more specifically, with schizophrenia-spectrum and affective disorders, respectively, in offspring at genetic risk for these particular disorders. High-risk (HR) offspring born to women with a history of schizophrenia-spectrum (n=38) or affective-spectrum (n=36) psychoses were studied prospectively from before birth to 22 years. According to the mothers' psychiatric records, some psychopharmaca (neuroleptics, hypnotics-sedatives, anti-Parkinson drugs, lithium and/or anti-depressives) was prescribed for some period during the pregnancies of 8/38 (21%) of the women with schizophrenia-spectrum disorders (neuroleptics in all 8, plus other drugs in 6; 7 had drugs in multiple trimesters) and 8/36 (22%) of the women with affective-spectrum disorders (both neuroleptics and other drugs in 5; 5 had drugs in multiple trimesters). Among the offspring with HR for schizophrenia, prescription for any drug(s) was not significantly related to adult axis I, axis II, schizophrenia-spectrum or affective disorders. Among the offspring with HR for affective disorder, prescription for any drug(s) was significantly related to adult axis I and/or II (p=.019, OR 12.36), axis I (p=.002, OR 20.00), and affective (p=.006, OR 11.50) disorders, but not to axis II (p=.215, OR 2.93) or schizophrenia-spectrum (p=1.00, OR 0.56) disorders. This relationship between pregnancy drug(s) and offspring adult affective disorder remained significant (p=.026, OR 18.5) with pregnancy stress, active maternal mental disturbance during pregnancy, notable smoking and unwanted pregnancy controlled for. Neuroleptics and other drugs prescribed in pregnancy may have different associations with offspring adult mental health depending on the offspring's genetic background, and these drugs' relationship to offspring schizophrenia remains uncertain.

TREATMENT-EMERGENT TARDIVE DYSKINESIA IN PATIENTS RECEIVING ARIPIPRAZOLE OR HALOPERIDOL FOR THE TREATMENT OF SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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Tardive dyskinesia (TD) is a debilitating and often persistent movement disorder associated with long-term antipsychotic treatment. Clinical trials suggest that treatment with atypical antipsychotic medications may lower the risk of developing movement disorders compared to treatment with conventional agents. We assessed the incidence of treatment-emergent TD during the long-term treatment of schizophrenia or schizoaffective disorder with aripiprazole, a dopamine D2 and serotonin 5-HT1A receptor partial agonist and serotonin 5-HT2A receptor antagonist, or the conventional antipsychotic haloperidol. We conducted a post hoc analysis of pooled data collected from two 52-week double-blind trials involving 1294 patients treated either with aripiprazole 20-30mg/d (N=861) or haloperidol 5-10mg/d (N=433). Treatment-emergent TD was identified based on Research Diagnostic Criteria (RDC) extracted from the Abnormal Involuntary Movement Scale (AIMS) (Schooler-Kane criteria), defined as a score of 1 (mild) in two or more body regions (AIMS items 1-7), OR a score of 2 (moderate) or higher in one. Severity of RDC-defined treatment-emergent TD was extracted from the AIMS severity item. In patients without baseline TD (N = 1177), the rate of new-onset TD at any time point following randomization was 5.09% for aripiprazole-treated patients, compared with a rate of 11.76% for haloperidol-treated patients (P <0.0001). Using a stricter definition of RDC-defined TD on the last two study visits, the rates of new-onset TD were 0.25% in aripiprazole-treated patients versus 4.09% in haloperidol-treated patients (P <0.0001). In the stricter analysis, the severity of new-onset TD was mild in 100% of aripiprazole-treated patients and 68.75% mild and 31.25% moderate or severe in haloperidol-treated patients. The mean baseline to endpoint increase in AIMS score was significantly greater in haloperidol- versus aripiprazole-treated patients in both LOCF (N=1177, P =0.0001) and OC (N=427, P <0.0001) analyses. Our findings indicate that treatment with aripiprazole is associated with a significantly reduced risk of new-onset tardive dyskinesia compared with haloperidol in patients with schizophrenia or schizoaffective disorder treated for up to 52 weeks. Aripiprazole's dopamine D2 partial agonist and/or serotonin 5HT2A antagonist receptor binding profile may contribute to its favorable safety profile with respect to treatment-emergent TD.

ACUTE AND LONG-TERM EFFECTS OF ATYPICAL ANTIPSYCHOTICS ON PROLACTIN LEVELS AND SEXUAL FUNCTIONING IN CHILDREN AND ADOLESCENTS

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Background: Atypical antipsychotics (AAs) have heterogeneous effects on prolactin and sexual functioning. Little is known about these effects during development and in response to a partial dopamine agonist. Methods: As part of an ongoing, observational study in youths (4-19 years) started on AAs, fasting AM prolactin and sexual side effects were measured within 7 days of AA initiation and at month 1, 2, 3, 6, 9, and 12. Results: Of 478 enrolled youth, 378 (age: 13.4±3.6 years, 63.2% postpubertal, 60.3% male, 47.5% Caucasian) with mood disorders (44.6%), disruptive behavior disorders (29.2) and schizophrenia spectrum disorders (26.3%) had >/=1 post-baseline assessment. Data from 511 AA trials included aripiprazole (ARI, n=116), olanzapine (OLA, n=81), quetiapine (QUE, n=104), risperidone (RIS, n=176) and ziprasidone (ZIP, n=34). Table 1 shows the observed cases prevalence of hyperprolactinemia (>25.7 ng/mL), hypoprolactinemia (<3.4 ng/mL), and incidences of sexual side effects at 1-3, 6, 9 and 12 months. In multivariate analyses, hyperprolactinemia was associated with RIS, OLA, ZIP, female sex and older age [r 2: 0.36, p<0.0001]. Hypoprolactinemia was associated with prepubertal status and ARI [r 2: 0.62, p<0.0001]. Conclusions: In youth, prolactin abnormalities are common and often sustained with AAs. RIS has the greatest risk for hyperprolactinemia, but in youth this also occurs with OLA and ZIP to a relevant degree. QUE and ARI cause hyperprolactinemia the least. Particularly in prepubertal youth, ARI is associated with hypoprolactinemia, confirming its dopamine agonist activity. Although rates are consistently lower, sexual side effect rates roughly follow the prolactin elevating properties of AAs. Further research needs to assess potential consequences of abnormally elevated or decreased prolactin levels.

Variable	ARI	OLA	QUE	RIS	ZIP	P-Value
PRL >25.7 ng/mL at 1-3 months	9.5%	48.1%	14.4%	84.1%	52.9%	<0.0001
PRL >25.7 ng/mL at 6 months	7.0%	38.2%	7.0%	71.9%	33.3%	<0.0001
PRL >25.7 ng/mL at 9 months	5.0%	55.6%	10.0%	69.2%	16.7%	<0.0001
PRL >25.7 ng/mL at 12 months	6.1%	36.8%	3.9%	47.6%	20.0%	<0.0001
PRL <3.4 ng/mL at 1-3 months	45.7%	0.0%	1.0%	0.0%	0.0%	<0.0001
PRL <3.4 ng/mL at 6 months	57.9%	0.0%	2.3%	0.0%	0.0%	<0.0001
PRL <3.4 ng/mL at 9 months	62.5%	0.0%	6.7%	0.0%	0.0%	<0.0001
PRL <3.4 ng/mL at 12 months	63.6%	0.0%	0.0%	0.0%	0.0%	<0.0001
New sexual side effects at 1-3 months	7.3%	15.8%	9.0%	19.9%	10.5%	0.013
New sexual side effects at 6 months	6.0%	23.5%	14.6%	10.2%	22.2%	0.152
New sexual side effects at 9 months	5.3%	36.4%	6.9%	10.3%	0.0%	0.0031
New sexual side effects at 12 months	3.2%	33.3%	9.1%	14.3%	0.0%	0.046

A MULTIDISCIPLINARY, SOLUTION-FOCUSED DIABETES EDUCATION GROUP FOR PATIENTS WITH MENTAL ILLNESS

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There is mounting evidence that major mental illnesses are associated with weight gain and increased rates of diabetes. The prevalence of diabetes type 2 in patients with schizophrenia is 2-4 times higher than that of the general population. Multiple factors contribute to increasing the risk of diabetes such as antipsychotic medications, obesity, cardiovascular disease, and nicotine use. Cognitive impairment, social withdrawal, poor access to healthy food, neglect of self-care and sedentary lifestyle may play a part in poorer outcomes for these patients. They are less likely to receive specialized care for medical illnesses and preventative services in part due to difficulty coordinating and attending appointments, especially at different sites. Insufficient time for the presentation of information in an understandable format may also pose an educational barrier. In light of the prevalence rates of diabetes and other

medical illnesses and the challenges in meeting the needs of patients with major mental illness, a multidisciplinary team of the Schizophrenia Program of the Royal Ottawa Hospital has developed an integrated treatment option. The clinical group intervention for patients who are interested in adopting a healthier lifestyle is available to all Royal Ottawa Hospital patients from the hospital's on-site endocrinology clinic. The educational group uses a solution-focused approach and is held over a 12-week period. A team of nurses and other disciplines educate and support patients as they attempt to work towards their individual healthy lifestyle goals. The poster will detail the development, structure and evaluation of the group.

CHANGE IN ADIPOSITY DURING RANDOMIZED ANTIPSYCHOTIC TREATMENT IN SCHIZOPHRENIA

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Increased adiposity can disturb glucose and lipid metabolism via disturbances in insulin sensitivity, leading to increases in cardiovascular risk. Schizophrenia patients have an increased prevalence of overweight and obesity, with associated increases in cardiovascular risk, in comparison to the general population. Recent data indicate that antipsychotic medications, particularly some commonly-used second generation agents, may contribute to significant increases in weight. However, limited information concerning treatment effects on body composition is currently available. In this ongoing NIMH-funded study, schizophrenia patients undergo prospective randomized assignment to 12 weeks of treatment with olanzapine, quetiapine, risperidone, or ziprasidone, with no other medication changes allowed. Dual Energy X-ray Absorptiometry (DEXA) is used to quantify whole-body adiposity and lean tissue mass. This preliminary analysis indicates that treatment with different medications is associated with significantly different changes in adiposity. A significant time X treatment condition effect was detected on DEXA-measured total body fat mass ($F[3,32]=4.18$, $p=.01$), whereas there was no significant time x treatment condition effect on DEXA-measured total lean body mass. In summary, direct measures of adiposity can be used to quantify treatment-induced changes in fat mass, relevant to risk for diabetes and cardiovascular disease. Support Contributed By: MH63985, Washington University General Clinical Research Center USPHS MO1 RR00036, Washington University Clinical Nutrition Research Center Grant P30 DK56341 and P60-DK20579.

ANTIPSYCHOTIC DRUGS EFFECTS ON THE PROTEOMIC PROFILES OF RAT STRIATUM

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Antipsychotic drug (APD)-induced extrapyramidal symptoms (EPS) represent one of the largest determinants of poor compliance to medication by schizophrenia patients. EPS take place when the occupancy of DA2 receptors in the striatum by APD exceeds 80%. The precise molecular basis for EPS remains unclear, in particular for chronic type of EPS. Using animal models, this study aimed to characterize specific changes occurring in the brain proteome (striatum) due to the chronic administration of typical (haloperidol) or atypical (risperidone) APD. Using subcutaneous minipumps adult male SD rats were treated with supratherapeutic doses of haloperidol (n=12) and risperidone (n=12) for four weeks. During treatment animals underwent behavioural testing, including assessment of EPS-like symptoms. Using two-dimensional gel electrophoresis (2D-PAGE), we resolved total protein extracts from the striatum, and analyzed protein expression with Phoretix 2D Expression and Image Beta V4.02 software followed by the identification using MALDI-TOF. Behavioral testing revealed significant EPS caused by both drugs and changes in motor activity and exploration. 2D gels of striatum resolved up to 600 different protein spots (pI 3-10), presumably different proteins and/or their isoforms. Comparison between the protein spot densities of the APD- and vehicle-treated groups revealed statistically significant changes in the expression of 35 and 40 protein spots in the striatal extracts from haloperidol and risperidone-treated groups, respectively. Altered protein spots were identified and classified according to their known functions. The majority of altered proteins belong to the metabolic and signal transduction groups, suggesting important roles of these pathways in the behavioural effects produced by both drugs. Other functional groups included cytoskeletal, intracellular transport and molecular chaperones. Proteomic changes are possibly the result of an overlap between the altered biochemical pathways responsible for both the therapeutic (anti-psychotic) and toxic (EPS-inducing) drug effects. These changes should be taken into account when investigating proteomic profiles of human post-mortem brain in schizophrenia as the majority of patients would have been treated with APD during their lives.

CHANGES IN METABOLIC PARAMETERS IN FIRST EPISODE SCHIZOPHRENIA FOLLOWING TREATMENT WITH ATYPICAL ANTIPSYCHOTICS FOR 52 WEEKS: SUBSET ANALYSIS FROM THE CAFE STUDY

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Weight gain and metabolic syndrome associated with the treatment of schizophrenia is a health concern, especially in young patients and during the first episode. In The Comparison of Atypicals for First Episode (CAFE) study, efficacy and tolerability of olanzapine, quetiapine and risperidone in treatment of First-Episode Psychosis until dropout up to 52 weeks was assessed using a randomized, double-blind, flexible dose, multicenter design. Patients met DSM-IV criteria for schizophrenia, schizophreniform or schizoaffective disorder. For continuous longitudinal measures, a mixed random coefficients model was used: outcome being change from baseline, and fixed effects for time, treatment group, random effects for intercept and time and baseline as a covariate. For categorical responses, we used a logistic regression model containing treatment and baseline if appropriate. Results of this metabolic analysis are presented, however the study was not designed to test metabolic parameters and fasting status of subjects was not confirmed. 400 first episode psychosis subjects at 26 centers were randomized to quetiapine (n=134), risperidone (n=133) and olanzapine (n=133) treatment and followed for 52 weeks. Mean age of the subjects was 24.5 (range: 16.4 - 44.4) years. The mean modal daily doses were 11.7 mg for olanzapine, 506 mg for quetiapine and 2.4 mg for risperidone. At baseline,

50.94% had a normal BMI, 30.73% were overweight and 18% subjects were obese. Weight gain of >7% at 12 and 52 weeks for quetiapine was 29.2% and 50%, for olanzapine 59.8% and 80% and risperidone was 32.5% and 57.6%, respectively. In women, weight gain and increase in BMI associated with risperidone was greater than that associated with quetiapine (P<0.01). At weeks 12 and 52, BMI increase of >1 unit was significantly more in subjects treated with olanzapine compared to quetiapine (p=0.0003 & p=0.01) and risperidone (p=0.0086 & p=0.019). At baseline, 17 (4.25%) subjects met NCEP diagnostic criteria for metabolic syndrome which increased to 57 (14.36%) during the study with 15, 8 and 17 new cases on quetiapine, risperidone and olanzapine, respectively. Treatment with risperidone resulted in least elevations in triglycerides and total cholesterol levels along with smallest decreases in HDL cholesterol. Only 50% of the young first episode subjects recruited for the study had normal BMI at baseline. Weight gain occurred more commonly and with a larger magnitude in olanzapine-treated subjects.

ONE YEAR RANDOMIZED CLINICAL TRIAL OF HALOPERIDOL, OLANZAPINE OR RISPERIDONE TO DETERMINE WEIGHT GAIN PATTERN IN A DRUG-NAïVE POPULATION OF FIRST EPISODE PSYCHOTIC PATIENTS

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Weight gain induced by antipsychotic drugs is one of the main concerns of antipsychotic therapy. In spite of the growing scientific literature focus on this issue, the independent effect of antipsychotic treatment on weight gain has not been established yet. Factors related with non-random design, previous exposure to antipsychotics and chronic schizophrenic study population are likely source of variability in results. The aim of this study is to assess the weight gain secondary to antipsychotic treatment in a cohort of drug-naïve subjects. 164 drug-naïve first episode psychotic patients were included in a randomized, open label, prospective clinical trial. Patients were randomly assigned to haloperidol, olanzapine or risperidone. The main outcome was the weight gain and BMI change at 3 months and at 1 year follow-up. The analysis were performed on a per protocol (PP) basis as well as according to the intention to treat (ITT) basis. ANCOVA analysis was conducted using sex, age and BMI at baseline as covariates. After 1 year follow-up 146 patients were evaluated (drop-out rate: 11%). Of them, 65.8% completed the protocol and 34.2% needed treatment change. Groups differed significantly in anticholinergic concomitant medication. Statistical significant differences in weight gain between treatments were found at 3 months. In an ITT analysis the mean weight gain was 4.1kg for haloperidol, 5.8kg for risperidone and 7.3kg for olanzapine group (F = 7.0; p=0.001). In a PP analysis the mean weight gain was 3.7kg for haloperidol, 5,8kg for risperidone and 8.4kg for olanzapine (F =6.7; p=0.002). After 1 year follow-up the difference in weight gain had disappeared. In an ITT analysis mean weight gain was 10.8kg for haloperidol, 9.5kg for risperidone and 11.3kg for olanzapine group (F = 0.8; p=0.444). In a PP analysis the mean weight gain was 9.7kg for haloperidol, 8.9kg for risperidone and 10.9kg for olanzapine (F =0.8; p=0.445). The distribution of weight gain in the study population was similar with the three treatments. In summary, drug-naïve patients experience an extraordinary weight gain after 1 year of treatment with haloperidol, olanzapine or risperidone. There is no difference in weight gain between treatments after 12 months. Nevertheless, at 3 months the variation in weight gain was very pronounced, which means the main difference among these antipsychotic treatments is the pattern of weight gain but not the final amount of weight gain.

ATYPICAL ANTIPSYCHOTICS ASSOCIATED WITH INSULIN RESISTANCE IN NEW ZEALAND MAORI

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Aims/hypothesis: Antipsychotic treatment is associated with new onset Type 2 diabetes. In New Zealand the prevalence of Type 2 diabetes in Maori is 21.1% compared to only 2.1-7.5% in non-Maori. The aim of this study was to determine whether antipsychotic treatment was associated with an increased prevalence of insulin resistance in New Zealand Maori as this ethnic group may be particularly vulnerable to antipsychotic induced impaired glucose metabolism. Method: We analysed fasting plasma glucose, insulin, HbA1c, triglycerides, total cholesterol, IGF-1 and cortisol in 30 Maori patients treated with antipsychotics (olanzapine, clozapine, risperidone, quetiapine or depixol) and 30 Maori controls. Data on weight, age, gender, personal and family history of diabetes was also recorded. Insulin resistance was determined using the homa model assessment (HOMA). Results: Antipsychotic-treated patients had significantly higher plasma insulin levels, 84 pmol/L (46-186) compared to the control group, 38.5 pmol/L (30-75), p=0.0005. Patients treated with antipsychotics were significantly more insulin resistant than the controls (p=0.001) increasing the risk for insulin resistance in this group 2-3 fold. Plasma triglycerides were significantly higher in the patient group 1.7 mmol/l (1.3-2.5) compared to the control group 1.25 mmol/l (0.9-1.8), p=0.03. Free cortisol was significantly higher in the patient group 54.4 nmol/L (43.7-73.) than in the control group 33.6 nmol/L (22.1-46.1), (p = 0.0005). Fasting plasma glucose levels were higher in the control group compared to the treatment group however were not clinically significant. There was no significant difference in body mass index (BMI), plasma glucose, HbA1c or cholesterol plasma levels between antipsychotic-treated Maori and control Maori. Conclusion: Maori treated with antipsychotic medication were significantly more insulin resistant than control subjects but had similar BMI to control Maori. Therefore, ethnicity is likely to be an important factor in susceptibility to antipsychotic induced impaired glucose metabolism and needs to be taken into account in prescribing practice and general care of this ethnic group.

ASSOCIATION BETWEEN ANTIPSYCHOTIC INDUCED HYPERLEPTINEMIA AND BONE MINERAL DENSITY AND BONE METABOLISM IN MEN AND PREMENOPAUSAL WOMEN WITH SCHIZOPHRENIA

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Background: Studies in individuals with schizophrenia have demonstrated low bone mineral density (BMD), high prevalence of pathological fractures and osteoporosis. Although antipsychotic induced hypeprolactenemia has been implicated in bone loss in schizophrenia, however, studies have failed to show a consistent correlation

between the two. Leptin, the protein product of the obesity gene (ob) is synthesized and secreted by adipocytes and its serum concentrations are highly correlated with adipose tissue mass. Animal studies have linked leptin as a potent inhibitor of bone formation. Human studies have shown BMD to be inversely related to leptin and carboxy terminal propeptide of type 1 procollagen, a marker of bone formation. There is current evidence that treatment with the atypical antipsychotics in schizophrenia can cause an increase in serum leptin levels. It is thus plausible that the leptin elevations in patients with schizophrenia treated with antipsychotics might contribute negatively to BMD and increase the risk for osteoporosis. Methods: This study utilized a cross sectional design consisting of 2 visits. 29 patients were screened with 25 patients enrolled in the trial. Diagnosis of Schizophrenia/Schizoaffective was confirmed using SCID-I. Subjects on olanzapine or clozapine monotherapy for the past 2 years were enrolled in the study. Overnight fasting serum levels of leptin, serum 25 hydroxyvitamin D, bone specific alkaline phosphatase, urinary Type 1 N-terminal telopeptide (NTx) were obtained. Patients were also given a food diary to complete to assess daily calcium intake. Bone density was determined in the lumbar vertebrae, L1 to L4 and in the left hip for each subject using a dual-energy X-ray absorptiometry (DEXA) scan. Results: Descriptive statistics will be used to report the number of subjects with Z scores outside the established norms. Correlations statistics will investigate whether reduced BMD correlates with leptin levels and other peripheral makers of bone metabolism. The calculations will be adjusted for BMI. Conclusions: The study results will be analyzed and interpreted to determine the association between antipsychotic induced hyperleptinemia and bone mineral density.

PILOT JOINT PSYCHIATRY/ENDOCRINOLOGY CLINIC AT A TERTIARY CARE PSYCHIATRIC HOSPITAL

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Schizophrenia, schizoaffective disorder, bipolar affective disorder, and major depressive disorder are associated with increased medical co-morbidity and mortality. Atypical and typical antipsychotics, mood stabilizers and some antidepressants have been associated with weight gain, dyslipidemia, derangements of glucose metabolism, and type 2 diabetes. Thyroid and prolactin abnormalities are known side-effects of lithium and certain anti-psychotics respectively. Psychiatric patients have an intrinsic vulnerability to overweight/obesity, abnormal glucose metabolism, dyslipidemia and type 2 diabetes independent of medication effects. Life expectancy and quality of life are reduced due to the interaction between higher rates of vulnerability to medical co-morbidity and the metabolic effects of psychiatric medication. Patients with mental illness often have cognitive impairments that limit their ability to recognize symptoms and follow through with medical treatment. Some authors report that treatment for medical co-morbidity offered within the psychiatric setting results in improved quality and outcomes of medical care. This is a naturalistic study of a pilot joint psychiatry/endocrinology clinic at the Royal Ottawa Hospital (ROH). Patients of the ROH with suspected endocrine pathology were referred by their treating psychiatrists. Data from 77 clinic referrals for the period May 2004 to February 2005 are reported on. The age range of referees was 14-87 years. There were equal numbers of males and females and slightly more non-smokers than smokers. Twenty-five percent of referrals did not have a family physician. Psychiatric diagnoses were: 50 schizophrenia spectrum, 11 bipolar, 13 major depression, 6 anxiety, 2 dementia. Twenty-nine percent of referrals were in their first 5 years of psychiatric illness. The most common endocrine diagnoses were: obesity, dyslipidemia and impaired fasting glucose/type 2 diabetes. The main intervention was diet and lifestyle monitoring/adjustment in 74%. Numbers of patients started on lipid or glucose lowering medication or insulin were 6, 2, 1, respectively. Referring physicians found that the referral process was straightforward, that the clinic belonged in a psychiatric hospital, and supported its continuance.

CHANGES IN PROLACTIN IN ADOLESCENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER I DURING TREATMENT WITH OLANZAPINE: A POOLED ANALYSIS OF 4 STUDIES

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Introduction: Previous research suggests increases in prolactin (PRL) may occur in adolescents during antipsychotic treatment. PRL data from adolescents treated with olanzapine are presented. Methods: Data from 454 adolescents (13–18 yrs; mean =15.9 yrs) with schizophrenia or bipolar disorder were pooled from 4 studies (4–32 weeks; 2 double-blind, placebo-controlled studies [combined to analyze the acute phase endpoint PRL levels] with open-label extensions and 2 open-label studies) of olanzapine (2.5–20.0 mg/day). Age-specific Covance reference ranges defined abnormal PRL; categorical increases were based on multiples of the upper limit of normal (ULN). Baseline to endpoint PRL changes in adolescents were compared with data pooled from 84 olanzapine clinical trials in adults with schizophrenia or bipolar disorder. LOCF mean changes were analyzed using a one-sample t-test, and were compared with adult data using an ANCOVA model, with terms for baseline and population. The incidence of abnormal PRL values at anytime during treatment was compared with adult data using Fisher's exact test. Results: Olanzapine-treated adolescents had PRL increases at both the acute (11.4µg/L) and open-label endpoints (4.7 µg/L, p<.001). Of those patients with normal PRL levels at baseline (N=311), treatment-emergent high PRL occurred in 54.7% of patients at anytime during treatment; 32.2% at endpoint. The percentage of patients shifting from baseline normal to abnormally high levels during treatment was consistently smaller at endpoint than at anytime during treatment; 26.7% shifted to a higher category. Among patients with normal PRL at baseline (≤1 ULN; N=311), 32.7% remained within ≤1 times ULN; 32.3% increased to 1–¬≤2; 6.0%, >2-≤3 times; and 1.2%, >3 times at anytime during treatment. No adverse event related to PRL occurred in >10% of patients; 4.6% had at least one treatment-emergent adverse event potentially related to PRL levels. Compared with adults, adolescents had significantly larger endpoint ULNs (–4.2 vs 23.0; p=.004); significantly more adolescents had treatment-emergent high PRL levels at anytime during treatment,(29.0% vs 55.5%, p<.001). Conclusion: Incidence of high and mean increases in PRL were significantly higher in adolescents compared with adults. Mean increases in and the incidence of high PRL was lower at the open-label than at the acute endpoint.

INCIDENCE OF TARDIVE DYSKINESIA IN FIRST AND SECOND GENERATION ANTIPSYCHOTIC MEDICATIONS

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Tardive dyskinesia (TD) is a serious complication related to antipsychotic therapy. Tardive dyskinesia is manifested by repetitive, involuntary muscle movements including chorea, athetosis, and dystonia. Unfortunately, there is no known cure for TD. It has been widely assumed that the incidence rate of TD is lower in second generation antipsychotic medications than in first generation medications. Thus, is was surprising when the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a large head to head comparison of second generation antipsychotics and a first generation comparator, found that there was no significant difference in TD between first and second generation antipsychotics (Lieberman et al., 2005). Based on the questions raised by the results of the CATIE study, the purpose of this poster is to provide an overview of the current literature regarding risk factors associated with the development of TD and a review of annual incidence rates of both first and second generation antipsychotic medications. Primary risk factors associated with an increased risk of developing TD are exposure to an antipsychotic medication (particularly first generation), increased length of exposure, advanced age, substance abuse, and extrapyramidal symptoms. A review of the available literature on first generation antipsychotics found five studies of an adult population reporting annualized TD incidence rates ranging from 2.7%-7.5% (M=5.4). Four studies of first generation antipsychotics in a geriatric sample found that the annualized incidence rate of TD ranged from 2.5%-26% (M=19.0). In contrast, annualized TD incidence rates associated with second generation antipsychotics given to an adult population were as follows: injectable risperidone (1 study) 1.2%; risperidone (2 studies) 0.6%-0.3% (M=0.5); olanzapine (2 studies) 0.0%-0.5% (M=0.3); and quetiapine (1 study) 0.7%. Second generation antipsychotics given to a geriatric population found the following annual TD incidence rates: risperidone (2 studies) 2.6%-4.3% (M=3.5); and quetiapine 2.7%. Review of TD incidence rates reveal that the risk of developing TD is greater in first generation antipsychotics than in second generation antipsychotics, particularly in older adults. The results from the CATIE study may have been influenced by methodology and should not be interpreted to conclude that first and second generation antipsychotics pose equivalent risks for TD.

A BRAIN-DERIVED NEUROTROPHIC FACTOR POLYMORPHISM IN CAUCASIANS WITH TARDIVE DYSKINESIA AND PARKINSON'S DISEASE

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This study aimed to investigate the association between the Val66Met brain-derived neurotrophic factor (*BDNF*) gene polymorphism (rs6265) and tardive dyskinesia (TD) and Parkinson's Disease (PD) in Caucasians. Our samples comprised 72 patients with TD, 72 patients with PD, and 78 controls with no history or family history of psychiatric illness or PD. There was no significant difference in the Val66Met genotypic distribution on chi-squared test between TD and controls ($p = 0.671$), PD and controls ($p = 0.683$), or PD and TD grouped together versus controls ($p = 0.781$). Our data replicates previous reports indicating that the *BDNF* Val66Met polymorphism is not associated with TD or PD.

SCREENING FOR DIABETES AND OTHER METABOLIC ABNORMALITIES IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: EVALUATION OF INCIDENCE AND SCREENING

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Objective: Guidelines to screen and monitor schizophrenic patients for diabetes were recently proposed by the American Psychiatric Association. Preliminary evidence however suggests that the use of these guidelines may result in a large underdiagnosis of glucose abnormalities. The aim of the current study was to investigate the adequacy of the current screening guidelines for the detection of diabetes in patients with schizophrenia, and to assess potential improvements of these guidelines. Methods: Over a two-year period, 415 patients with schizophrenia were screened with a full laboratory screening and a 75 g Oral Glucose Tolerance Test (OGTT). Patients were not known with diabetes prior to the baseline screening.The sensitivity of two screening strategies was compared to the 'Gold Standard': the OGTT. The two strategies were: 1) assessing fasting glucose in all patients, as suggested by the APA/ADA and 2) a screening strategy derived from the guidelines of the World Health Organization (WHO) of assessing fasting glucose in all patients (step one), and subsequently performing an OGTT in patients with impaired fasting glucose (step two). Results: In the total sample, 6.3% (n=26) met criteria for diabetes. Another 23.4% (n=97) showed prediabetic abnormalities. A screening based on the APA/ADA guidelines detected diabetes in 12 patients (2.9%). However, these 12 diabetes cases only represented 46.2% of the 26 cases identified by means of an OGTT. The WHO derived two-step strategy of performing an OGTT in patients presenting with IFG would have detected 96.2% of diabetes cases (25 out of 26 cases). Conclusion: These data confirm that metabolic abnormalities are highly prevalent in schizophrenic patients treated with antipsychotics, certainly when taking into account that all patients that were screened were not diagnosed with diabetes prior to the baseline screening, so that the diagnosed cases are newly detected or incidence cases. As the screening was performed over the period of two years, the current data suggest a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years). The guidelines as proposed by the ADA, did not sufficiently detect diabetes in this specific high risk group. The alternative two-step strategy was able to detect the vast majority of diabetes cases and should therefore be considered in the clinical routine of screening and monitoring patients with schizophrenia.

INCIDENCE OF TARDIVE DYSKINESIA WITH ATYPICAL AND CONVENTIONAL ANTIPSYCHOTICS

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In several studies, the risk of tardive dyskinesia (TD) has been reported to be substantially lower in patients treated with atypical antipsychotics than with conventional antipsychotics. Most of those studies, however, were not specifically designed to identify incident

cases of TD, raising the possibility of bias in effect estimation. The aim of the present study was compare the incidence of TD with atypical vs. conventional antipsychotics. Methods: A prospective cohort study of TD was conducted among 352 initially TD-free psychiatric outpatients. All subjects were maintained on antipsychotics and were examined for TD every 6 months for up to 4 years in the setting of a community mental health center, 2000-2005. At baseline, 23% of subjects were receiving conventional antipsychotics only, 64% atypicals only, and 14% both types. The main outcome measure was a new diagnosis of persistent TD, using the Abnormal Involuntary Movement Scale and Glazer-Morgenstern criteria. Proportional hazards analysis was used to estimate the relative rate of TD for atypical vs. conventional antipsychotic use, controlling for potential confounders and treating type of antipsychotic as a time-dependent covariate. Results: At baseline, the median duration of previous conventional antipsychotic use was 6.0 years. Fifty-two new cases of TD were identified during 783 person-years of follow-up, yielding an estimated incidence rate of 0.066/year. Compared with subjects who were treated with conventional antipsychotics alone since the previous visit, the adjusted incidence rate ratio for subjects treated with atypical antipsychotics alone was 0.68 (95% confidence interval 0.29-1.64). Only 26 subjects had never received conventional antipsychotics. Conclusions: Although we found the TD rate to be lower among users of atypical than conventional antipsychotics, this association was weaker than estimates reported in most previous studies. We cannot generalize our results to new users of atypicals because most of our subjects had been treated with conventionals for several years at baseline. Supported by US Public Health Service grant R01 MH61008 (SWW). The VA New England Mental Illness Research Education and Clinical Center provided some assistance with data management. ClinicalTrials.gov identifier: NCT00237835.

ASSOCIATION OF A POLYMORPHISM UPSTREAM OF DOPAMINE RECEPTOR DRD3 GENE WITH TARDIVE DYSKINESIA

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Tardive dyskinesia (TD) is a potential side effect of chronic antipsychotic exposure, particularly with first generation agents. Its etiology is unknown, but dopamine neurotransmission system changes have been suggested to be involved. Genetically, while there have been repeated positive findings between the Ser9Gly polymorphism of DRD3 and TD, there have also been negative results. Thus, the role of DRD3 in TD still remains complex. In the present study, we investigated 10 polymorphisms, spanning the DRD3 gene, and their association with TD in our European Caucasian (N=196) sample. The rs905568 polymorphism upstream of the DRD3 gene was significantly associated with TD (p=0.004) and quantitative AIMS scores (p=0.003), while the other polymorphisms across DRD3 were negative. Since DRD3 has been reported to be regulated by BDNF in rodents, we next tested if BDNF polymorphisms were associated with TD. Preliminary results did not reveal significant association with five BDNF markers tested. When Ser9Gly and BDNF Val66Met were treated as a haplotype and analyzed in combination for association with TD, the results were not significant. The present study suggests that DRD3 contributes to TD development, but may involve different marker combinations in different populations. Further studies investigating the role of BDNF and DRD3 as well as their interaction in TD are warranted.

20. Cognitive Neuroscience

ASSOCIATIVE RECOGNITION MEMORY IN SCHIZOPHRENIA: A META-ANALYSIS ON THE IMPACT OF INCLUDING NEW ITEMS IN THE RECOGNITION TEST

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Recognition memory deficits have been repeatedly reported in schizophrenia, especially when the task involves associative retrieval. Associative recognition tasks however differ on several variables, including the type of association (pair or source) and the response alternatives available to the subject (whether "new" is among the response alternatives). The current meta-analysis aimed to examine the effect of these two variables on the recognition memory deficit of people with schizophrenia relative to healthy controls. A literature search led to the identification of 15 associative recognition studies meeting our inclusion criteria, from which 16 independent measures of associative recognition could be extracted. A greater deficit ($z=2.58$, $p=0.005$) was observed for pair recognition ($n = 4$, mean effect size $d=1.20$) relative to source recognition ($n = 12$, effect size $d=0.70$). Although none of the pair recognition tests included new items among the response alternatives, 8 out of 12 source recognition tests did and showed a smaller effect size ($d=0.54$) than the 4 studies that did not ($d=1.03$; $z=2.69$, $p=0.004$). A direct comparison between pair ($d=1.20$) and source recognition tests without new items ($d=1.03$) revealed no significant difference ($z=0.73$, $p=0.23$). These results suggest that both the type of association and the presence or absence of new items in the response alternatives have an impact on the magnitude of the recognition deficit in schizophrenia. Moreover, it suggests that the possibility for the subject to give a "new" response should be taken into account when comparing pair and source recognition tests.

CORRELATION BETWEEN SERUM ANDROGEN LEVELS AND NEUROPSYCHOLOGICAL FUNCTIONS IN SCHIZOPHRENIA

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Decades ago, studies had linked 'body types' with psychological parameters including those of schizophrenia. Rees (1957) wrote, "The work of [several authors] suggests that schizophrenics with an asthenic body build tend to have [an early onset], apathy and scattered thinking." In contrast, Manfred Blueler et al (1954) observed that women with signs of virilism had a poor prognosis leading to severe deterioration. There have so far been three published studies of 92 male schizophrenics, from India, Iran and Japan, all showing a negative correlation between testosterone (T) levels and negative symptoms. We present the findings of the first 28 (18 male and 10 female) schizophrenics from an ongoing study to correlate T, dihydrotestosterone (DHT) and dehydroepiandrosterone (DHEA) levels with PANSS scores and a battery of neuropsychological tests. Patients fulfilled DSM-IV TR criteria for schizophrenia. The local ethical committee approved the study. Twenty-eight patients, 18 men and 10 women, between ages 25 and 67 (mean=34.8), were selected. Serum levels of T, DHT and DHEA were estimated by radioimmunoassay. Neuropsychological tests for Attention, verbal fluency, abstraction ability and working memory were administered for each patient. Pearson correlation test, linear regression analysis and independent 't' test were used for statistical analysis. Mean PANSS score for all 28 patients was 82.3; 18 patients had predominantly positive symptoms and 10 had predominantly negative symptoms. Independent 't' test did not show any significant difference for any of the serum hormone levels between the groups of patients based on PANSS scores. However, when women were excluded, the mean T level was significantly lower in negative symptom dominant group ($p=0.05$). The correlation between serum T levels and the total scores on all neuropsychological test results was significant ($p=0.017$). Among different neuropsychological functions, verbal fluency showed the greatest correlation followed by working memory. This significance disappeared when women were excluded. No significant correlations were found between neuropsychological test scores and serum DHEA or DHT. Negative symptoms correlate negatively with T levels, but only in men.

TIME AND FORCE INTEGRATION IN PATIENTS WITH SCHIZOPHRENIA

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People diagnosed with schizophrenia have been shown to be impaired in the fluent execution of action sequences (Manschrek 1982; Sullivan et al. 2001; Delevoye-Turrell et al. 2003). These deficits might be due to a problem in the control of time for motor execution, or rather in the more complex problem of integrating information from multiple sources. The dopamine circuits play an important role in time control (Rammsayer, 1990, Penney et al., 2006). Our principle hypothesis was that schizophrenic patients would be impaired especially in the more complex task where both time and force were alternating, and that the patients' impaired performance would be correlated with the dopamine-level in their medication. 30 patients with schizophrenia and 30 healthy controls had to squeeze a load cell in its center in order to produce 4 different rhythms lasting each 48 s, with [1] equal time intervals (500 ms) and equal force-levels (12N); [2] equal time intervals (500 ms) and alternating force-levels (8N/16N); [3] alternating time intervals (300/700 ms) and equal force-levels (12N); [4] alternating time intervals (300/700 ms) and alternating force-levels (8/16N). Three trials for each rhythm were performed with each hand. To assess the influence on performance of self versus external pacing, each trial was constituted of a 24s period of synchronization followed by a 24s period of continuation. The patients' performance patterns were close to normal during synchronization. In continuation, the patients revealed normal performance levels for equal time intervals only. Patients were the most impaired in continuation when time intervals were alternated ($p<0.5$). Finally, we observed a significant correlation between the patients' levels of chlorpromazine equivalent dose of drugs and their ability to perform the task. And ages represent the most significant correlation we have found. These results suggest that schizophrenia is characterized by a specific problem in force-time integration and this, specifically in absence of external cue. These results suggest that the dopamine circuits play an important role in time control especially when subjects are to act upon an internal representation of the rhythm to produce. Ages might play a role by the long time exposure to neuroleptic and antipsychotic drugs. On therapeutic standpoint, we suggest that our simple tapping task could be used to adapt objectively the patients' doses of antipsychotic drugs.

THEORY OF MIND IN SCHIZOPHRENIA: A POSITRON EMISSION STUDY

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The capacity to have a "theory of mind" is an important component of social cognition. The concept of "theory of mind" (TOM) refers to the ability to infer and attribute mental states to one's self and to others and to recognize that behaviors are guided by these mental states. This capacity, which is related to the capacity to have empathy, is an important component of social interactions. It appears to be impaired in many individuals with schizophrenia. We undertook a study of TOM in a group of healthy volunteers and patients with schizophrenia, using PET to identify the neural circuits used during a language task that required subjects to attribute a mental state to another person. In normal individuals this task activated a distributed group of nodes that included anterior cingulate and paracingulate regions, L anterior frontal regions, L anterior temporal lobe, and R cerebellum. Many of these regions are implicated in the identification of goals and associative memories. The patients with schizophrenia had decreased flow in multiple regions (lateral cerebellum and vermis, visual association cortex, and the thalamus) and increases in others (R inferior frontal, R dorsolateral frontal, R parietal, and R putamen). The areas of decreased flow are consistent with many previous studies indicating problems in recruiting cortical-cerebellar circuits in schizophrenia. The areas of increase may reflect a need to draw on right hemisphere regions to perform the task, in order to compensate for deficits in left frontal and cingulate regions.

PREDICTORS OF CAPACITY AMONG IN-PATIENTS: A UK PERSPECTIVE

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Making judgments on the capacity to make treatment decisions in the face of major psychiatric disorder is a major challenge to clinical teams. Currently, legislation in England and Wales enables involuntary treatment based on the 'status' of the individual concerns, namely that s/he is suffering from a mental illness of a particular nature and sufficient degree of seriousness. This is being overhauled in favor of capacity-based legislation. In order to examine the implications of such a change, we carried out a survey of consecutive in-patients, both voluntary and involuntarily committed by employing standardized assessments of capacity using the MacArthur Competence Assessment Tool for Treatment (MacCAT-T). Participants included over 250 psychiatric or acute mixed medical inpatients. Interrater reliability, established by two interviewers who independently administered the MacCAT-T was high (kappa=0.82; the two interviewers agreed on binary capacity judgments in 91.0% of the cases). We found that approximately 40% of the patients were being treated outside any legislative framework despite lacking capacity. However, only a small minority of involuntary patients were deemed to lack capacity. Predictors of incapacity included lack of insight, which was also assessed using a standard schedule, and is a construct which appears to be implicit in decisions about the need for involuntary treatment and capacity. Insight is a familiar clinical concept in psychiatry and is generally considered to be multidimensional. A small but consistent proportion of the variance in insight has been demonstrated to be due to cognitive impairment, particularly executive dysfunction. The interrelationships between insight, cognitive impairment, and capacity deserve further study.

FRONTAL LOBE FUNCTIONS NOT ASSOCIATED WITH THE CATECHOL-O-METHYLTRANSFERASE (COMT) GENE IN SCHIZOPHRENIA

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Both schizophrenia and bipolar affective disorder patients have been found to exhibit fluency deficits that implicate frontal lobe dysfunction in the disorders. Relatives of schizophrenia patients have also been found to exhibit verbal and nonverbal fluency deficits suggesting that the cognitive deficits may reflect a heritable frontal lobe anomaly possibly related to the genetic diathesis of schizophrenia. The current research investigated whether verbal and nonverbal fluency measures may be specific endophenotypes for schizophrenia by examining fluency deficits in first-degree biological relatives of schizophrenia patients in contrast to relatives of bipolar disorder patients and nonpsychiatric control subjects. In addition, we tested for associations between fluency and a genes purported to affect frontal lobe cognitive functions (catechol-O-methyltransferase [COMT]). Verbal fluency tasks included the Controlled Oral Word Association Task (COWAT [letter fluency]) and the category fluency task (semantic fluency). Subjects were also assessed using nonverbal fluency (figural fluency) tasks. As predicted, schizophrenia patients showed letter and figural fluency deficits compared to controls. The schizophrenia patients also demonstrated impaired letter fluency compared with bipolar patients. Relatives of schizophrenia patients tended to show similar deficits. The val allele of the COMT gene failed to be consistently associated with verbal and nonverbal fluency measures in patient groups and first-degree relatives of patients. Results suggest some association between thought disturbance and lower semantic fluency in individuals with genetic liability for schizophrenia. A verbal fluency deficit may mark an aspect of genetic liability for schizophrenia, but the dysfunction likely reflects frontal lobe abnormalities that are not determined by the COMT gene.

HOW DO PATIENTS WITH SCHIZOPHRENIA KNOW THAT THEY KNOW? RETRIEVAL OF PARTIAL AND COMPLETE INFORMATION AND ITS RELATIONSHIP WITH METAMEMORY AWARENESS

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The aim of the study was to see if patients with schizophrenia, as well as healthy people, rely on the products of retrieval in order to monitor their awareness about what they know and what they don' know. Indeed, even when people fail to recall a particular target, they can provide feeling of knowing judgments (FOK) about its availability in memory. Feeling of Knowing is a metamemory judgment that reflects the ability to judge one's own memory capacity. According to Koriat (1993, 1995), the computation of FOK evaluations relies on the accessibility of partial and/or contextual information.

Cognitive deficits and insight problems are now considered core symptoms of schizophrenia, and there is some evidence that the FOKs expressed by patients with schizophrenia differ from those of controls whereas their predictive accuracy as regards future recognition (the gamma coefficient) is preserved (Bacon & al., 2001). The accessibility of total and partial recall of recently learned material, the relationship between the retrieved partial information and FOK ratings, and the predicitive accuracy of FOKs were investigated in 21 patients with schizophrenia and 21 healthy matched volunteers. The material to be learned consisted of 4-letter nonsense tetragrams, where each letter provided partial information with regard to the four-letter target (Koriat, 1993). Following each presentation, there was a short retention interval, after which participants were asked to recall the letters (they could choose to produce from 0 to 4 letters). They then estimated the probability of recognizing the correct tetragram (FOK) from among 8 possibilities. Lastly, they had to recognize the correct tetragram. The number of letters reported by patients was lower. The mean global FOK magnitude was lower for patients than controls. However, the relationship between partial information retrieval and FOK ratings, and the predictive value of FOK for recognition were preserved in patients. The accessibility hypothesis as a basis for the construction of FOK seems to be relatively preserved in patients with schizophrenia. Patients were as capable as the healthy participants of relying on the products of retrieval to monitor their awareness of what they did or did not know.

PARIETAL AND PREFRONTAL CONTRIBUTIONS TO WORKING MEMORY DYSFUNCTION IN SCHIZOPHRENIA: DORSAL VERSUS VENTRAL DISSOCIATIONS AND ABNORMAL CONNECTIVITY

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Although it is clear that individuals with schizophrenia have working memory dysfunction, there is still controversy as to whether this reflects a deficit in central executive processing or domain specific storage buffers. Numerous studies have documented abnormal dorsolateral prefrontal cortex activation during working memory in schizophrenia. However, abnormal parietal activation has also been observed. In healthy individuals, there are at least two functionally dissociable subregions of parietal cortex, which likely support different subcomponents of working memory (central executive versus storage buffers). The goals of this study were to examine in schizophrenia: 1) which of these parietal subregions has abnormal working memory related activation; and 2) the relationship between prefrontal and parietal cortex activity during working memory task performance. Participants were 57 individuals with schizophrenia and 120 demographically similar healthy controls. FMRI was used to scan participants during the performance of verbal and non-verbal working memory tasks. Individuals with schizophrenia compared to controls showed deficits in activation of bilateral dorsal parietal regions during both verbal and non-verbal working memory tasks. There were no significant group differences in left ventral parietal cortex activation and the individuals with schizophrenia demonstrated the typical pattern of greater activity in verbal compared to non-verbal working memory in this region. Further, these same individuals with schizophrenia showed clear deficits in activation of bilateral regions of dorsolateral prefrontal cortex that was equal in magnitude across verbal and non-verbal working memory. In contrast, individuals with schizophrenia showed an intact pattern of greater verbal than non-verbal working memory related activation in ventrolateral prefrontal regions. In addition, functional connectivity analyses indicated that individuals with schizophrenia demonstrated abnormal connectivity between prefrontal and parietal regions during performance of both verbal and non-verbal working memory tasks. These results support the hypothesis that working memory deficits in schizophrenia reflect disturbances in the coordinated activity of multiple regions that support specific different components of central executive function.

A NEW VIDEO-BASED TASK (LIS) FOR THE ASSESSMENT OF THE ATTRIBUTION OF INTENTIONS TO OTHERS IN SCHIZOPHRENIA, DEPRESSION, AND MANIA

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Several aspects of social cognition are known to be impaired in schizophrenia. Patients suffering from this illness exhibit a complex pattern of cognitive impairments associated with disturbances of theory-of-mind, attribution of intentions and emotion perception. This view is supported by numerous experiments using behavioral tests and/or neurofunctional methods. Usually, the tasks are based on impoverished social stimuli (simple pictures, drawings, short stories, etc.). They are poorly ecological and do not test the patients' capabilities to integrate complex social cues, based on visual and verbal modalities, into an integrated representation of the social situation. We propose here a new task ("Lecture Intentionnelle en Situation" meaning "situation-based intention reading") based on six short video-excepts of movies that depict complex real life scenes involving social interactions between two characters. Those realistic social situations involve intentional and emotional aspects. Subjects are required to rate on a four-level scale the probabilities of five independent affirmations concerning the intentions of one of the characters. The score of a single subject was defined as the Manhattan distance between his/her ratings and the mean ratings of the healthy subjects. The task was proposed to several groups of subjects: 15 schizophrenic patients, 15 depressed patients, 15 manic patients and 15 healthy controls. All patients were receiving medications. Schizophrenic patients had significantly higher mean scores than healthy ($p<.05$) and depressed subjects ($p<.05$). Manic patients' scores differed from normals at a .06 p-level. The manic group displayed significantly higher scores than normal subjects ($p<.05$). The schizophrenic patients' LIS scores were significantly correlated with their scores in another attribution of intentions task using comic strips ($r=.64$, $p=.01$). Tasks based on ecological stimuli, which require integration of multiple social cues (human actions, facial emotions, speech, prosody) in realistic human interactions are able to measure theory-of-mind abnormalities in pathological populations such as schizophrenic patients and manic patients. The main results confirm that schizophrenic patients have impaired theory-of-mind in comparison to normal subjects and mood-disordered patients. Recent experience using this task shows that such material is easy-to-use and may be applied on larger patients groups leading to comparable results.

VISUAL PROCESSING RESPONSE TO RED LIGHT: A USEFUL ENDOPHENOTYPE FOR SCHIZOPHRENIA?

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A previous study reported a novel finding in first-degree relatives of persons with schizophrenia, which involved a differential change in visual backward masking accuracy with a red background, compared to controls (Bedwell et al, 2003). This differential change to red light was also reported in cortical area V5 (MT+) of the first-degree relatives using fMRI (Bedwell et al, 2006). These findings may relate to the established ability of red light to suppress the magnocellular visual system. The present study aimed to examine this effect in persons with schizophrenia for the first time, using an updated backward masking paradigm. An initial sample of 10 inpatients diagnosed with schizophrenia (mean age = 35.47, SD = 9.68, range = 19 to 52; 90% male; 60% Caucasian) were compared to 10 community controls (mean age = 42.20, SD = 10.34, range = 21 to 54; 90% male; 70% Caucasian). As part of a larger battery of neurocognitive tasks, participants completed a visual backward masking paradigm. This paradigm required the participant to state the location of a square target out of four possible locations, followed by a visual pattern mask. The stimulus onset asynchrony (SOA – onset of target to onset of mask) was varied at random from a set of nine speeds ranging from 0 to 81 ms. Participants completed the task on both a green and red background (counterbalanced order). The groups did not differ in backward masking accuracy with the neutral (green) background, suggesting no substantial group differences in attention during the task, $F(1,18) = 1.03$, $p = .32$. However, as hypothesized, there was a statistically significant group x background color interaction, $F(1,18) = 6.51$, $p = .02$, $\eta 2 = .27$; large effect size. Participants with schizophrenia tended to make more errors with the red background across all SOAs, while the controls showed the opposite effect at some SOAs. Post hoc analyses revealed that this group difference in change in accuracy to the red background was most evident at the 25 ms SOA. This finding extends earlier reports with nonpsychotic first-degree relatives, to include individuals diagnosed with schizophrenia. Findings suggest that a specific unique visual processing reaction to red light may represent a novel and useful endophenotype for schizophrenia. Ongoing research will address relative sensitivity compared to several existing endophenotypes.

COGNITIVE PHENOMICS: INFORMATICS STRATEGIES FOR SCHIZOPHRENIA RESEARCH

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Informatics approaches are revolutionizing knowledge discovery in other aspects of biomedical science, but so far the representation of neuropsychiatric and cognitive phenotypes in knowledge repositories is rudimentary. With support from the NIH Roadmap Initiative we have established a Center for Cognitive Phenomics that has developed new informatics strategies for the representation, modeling, and testing of competing hypotheses about complex neuropsychiatric syndromes. This presentation describes: (1) the extension of controlled vocabularies for literature mining (with more than 2000 new lexical entries representing cognition, and overall increase over existing resources such as the "NIH Specialist" lexicon by ~100,000 terms important to neuropsychiatry); (2) new web applications including PubBrain (an interactive query engine that displays concept/keyword searches as three-dimensional maps on a probabilistic human brain atlas, see www.pubbrain.org) and PubGraph (an interactive engine that plots PubMed terms or concepts as nodes, and the edges as Jaccard coefficients, covariances, or correlations reflecting literature-mined associations between these concepts, see www.pubgraph.org), and a new web-based interactive ("wiki"-style) database for cognitive phenotype annotation, currently populated with heritability and validity statistics for selected cognitive phenotypes, see www.phenomics.ucla.edu). Examples will be shown, including graphical models of hypotheses: (1) linking genetic variation in DISC1 to neural system and cognitive phenotypes relevant to schizophrenia and bipolar disorder; and (2) linking dopamine signaling genes to cognitive processes of response inhibition and syndromes including schizophrenia, bipolar disorder, attention deficit/hyperactivity disorder and stimulant abuse. Brain maps of the relevant concepts will be shown and compared to data mining from existing empirical databases. The interactive "cognitive pheno-wiki" will be demonstrated, including its role as a portal for entering new data, and for automated meta-analysis of existing data on heritable cognitive phenotypes important to schizophrenia. This work opens several novel avenues for knowledge representation and discovery in schizophrenia research, and is particularly designed for cognitive phenotype representation, modeling and analysis. (Supported by NIH Roadmap Grant P20 RR020750)

DIRECT COMPARISON OF TWO ENCODING STRATEGIES IN SCHIZOPHRENIA: BEHAVIORAL AND NEUROBIOLOGICAL FINDINGS

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Episodic memory deficits are a well-established finding in schizophrenia. Such deficits are thought to be related to ineffective stimulus processing, particularly at the encoding stage. Functional neuroimaging studies of individuals with schizophrenia have consistently demonstrated abnormal patterns of encoding-related brain activity in regions associated with semantic processing and successful subsequent memory. However, recent work in this area has suggested that use of beneficial encoding strategies can improve memory performance and encoding-related brain activity in individuals with schizophrenia. The current study compared the influence of two types of verbal encoding (Incidental and Intentional) on brain activity and subsequent memory performance in 18 participants with schizophrenia (SCZ) and 15 control participants. In support of previous findings, SCZ recognized significantly more words seen during Incidental than during Intentional encoding. Furthermore, Incidental (compared to Intentional) encoding in SCZ activated bilateral inferior frontal gyrus (BA 45/47) and left inferior parietal lobe (BA 40), among other regions, while Intentional (compared to Incidental) encoding was not associated with any regions of significant activity in SCZ. SCZ also showed normal subsequent memory effects (greater encoding-related activity for subsequently-remem-

bered items compared to missed items) in left medial frontal gyrus (BA 6) and left inferior parietal lobe (BA 40), among other regions. The results of this study demonstrate a significant role of encoding orientation, both behaviorally and neurobiologically, during memory processing in individuals with schizophrenia. Furthermore, it provides additional evidence that faulty encoding processes underlie memory deficits in schizophrenia and that such impairments can be modulated via orientation to beneficial encoding strategies.

THE IMPACT OF FRAGMENTING VISUAL STIMULI ON THE RECOGNITION PERFORMANCE OF PEOPLE WITH SCHIZOPHRENIA

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It is well established that episodic memory in people with schizophrenia is significantly impaired. However, the precise cause of this impairment has yet to be determined, since the formation of episodic memories is dependent on other processes, among which some also show impairment. For instance, people with schizophrenia often present with difficulty in binding the separate parts of an object into a unified representation, which may affect their ability to properly encode the object into memory. This possibility was tested in the present study by evaluating subjects' ability to recall 120 abstract forms with varying degrees of contour fragmentation. The experiment was divided into six blocks, each of which involved both an encoding and a recognition phase. During the recognition phase, 20 forms were presented sequentially and subjects had to determine whether each was symmetric or asymmetric. These forms were either complete, slightly fragmented, intermediately fragmented or very fragmented. In the recognition phase, 40 abstract forms were presented, among which, 20 were new and 20 were old. All forms were complete in this phase. Twenty-seven people with schizophrenia and 16 healthy comparison subjects matched on sociodemographical variables participated in this study. Results demonstrated that fragmentation of the encoded forms lowered the recognition performance for both schizophrenic and control subjects. This confirms that the visual quality of a stimulus during encoding can significantly affect recognition memory performance. Interestingly, schizophrenic subjects seemed more affected by fragmentation, since their performance accuracy was decreased, diverging to chance levels for forms that were both intermediately and very fragmented. This episodic memory deficit in patients with schizophrenia thus may be partly explained by increased difficulty in building unified representations of some types of stimuli.

DEVELOPMENTAL VITAMIN D DEFICIENCY, POSTNATAL DEVELOPMENT AND ADULT BEHAVIOUR IN SPRAGUE-DAWLEY RATS

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It is now recognized that vitamin D is active in the brain and plays an important role in brain development. Guided by certain features of the epidemiology of schizophrenia [1], we have explored the role of vitamin D in brain development and behaviour in Sprague-Dawley rats. Prenatal vitamin D deficiency results in subtle alterations in pup ultrasonic vocalization and maternal behaviour, as well as long lasting effects on the adult offspring. The behavioural phenotype of developmental vitamin D (DVD) deficient rats include a developmental onset in response to the non-competitive NMDA antagonist MK-801 [2], which shows a delayed onset in females. In addition, the DVD model has enhanced locomotion in response to novelty, enhanced amphetamine induced locomotion and altered latent inhibition. By contrast the DVD model has no effect on PPI or on tests of social interaction, anxiety and depression [3]. The behavioural phenotype suggests specific disruption in dopamine and glutamate signaling, rather than a general disruption in brain development, as suggested by normal vitamin D levels during postnatal life and normal functioning of the hypothalamic-pituitary axis [4]. These affects are specific to transient prenatal (gestational) vitamin D depletion as adult vitamin D depletion, combined prenatal and chronic postnatal vitamin D depletion [3], or ablation of the vitamin D receptor in mice, lead to markedly different outcomes [5]. In summary, low prenatal levels of vitamin D can influence critical components of orderly brain development which have long lasting effects on behaviour. 1. McGrath, J., Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schiz. Res., 1999:40, 173-7. 2. Kesby, J.P., et al., Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: An animal model of schizophrenia. Biol. Psych., in press. 3. Burne, T.H.J., et al., Transient prenatal vitamin D deficiency is associated with hyperlocomotion in adult rats. Behav. Brain. Res., 2004:154, 549-555. 4. Eyles, D.W., et al., Developmental vitamin D (DVD) deficiency in the rat alters adult behaviour independently of HPA function. Psychoneuroendocrinology, 2006:31, 958-964. 5. Burne, T.H.J., et al., Behavioural characterization of vitamin D receptor knockout mice. Behav. Brain. Res., 2005:157, 299-308.

BEHAVIORAL AND PHYSIOLOGIC INDICATORS OF DEFICITS IN CONTEXTUAL ENCODING AND EPISODIC MEMORY IN THE PRODROMAL AND PSYCHOTIC PHASES OF SCHIZOPHRENIA

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Deficits in learning and memory are robust correlates of schizophrenia and are thought to contribute to poor social and work functioning in these patients. It is unclear whether these deficits reflect a differential disruption of the neural systems mediating episodic encoding and/or retrieval processes and whether they precede onset and deteriorate during the development of psychotic illness. We administered the Remember-Know (R-K) task, drawn from basic research on the cognitive neuroscience of episodic memory, in prodromal, first-episode schizophrenia and matched healthy control samples during functional MRI. Compared with controls, both prodromal and schizophrenia patients had significantly lower recognition accuracy on the R-K paradigm. In both patient groups, successful recognition of a target was more likely to be based on an impression of familiarity than on an explicit memory of the moment of learning, and both groups recalled fewer contextual details of the learning episode compared with controls. These behavioral findings

were paralleled by a pattern of higher activation in the hippocampus, parahippocampal gyrus, and prefrontal cortex in the patients compared with controls during encoding of stimuli for which they demonstrated subsequent episodic memory relative to trials in which they failed to show episodic memory. In other words, greater activation of the circuitry mediating encoding was required in the patient groups for later successful episodic retrieval. This pattern of physiologic inefficiency was also associated with increasing symptom severity and poorer functional outcome in the patients. Both behavioral and physiological indicators of episodic encoding and memory deficits were significantly more pronounced in the first-episode compared with prodromal patients. The memory impairments in schizophrenia thus appear to be based at least in part on a failure to encode contextual information during the study phase. Such impairments are present, though to a lesser degree, in the prodromal phase of psychosis, suggesting that behavioral and/or physiological indicators of encoding and retrieval processes in long-term memory may predict conversion to schizophrenia among prodromal subjects and may deteriorate in association with symptom onset and poor functional outcome, hypotheses that are being pursued in longitudinal studies of these same subject groups.

YOU KNOW WHAT I THINK! AN EXPLORATORY STUDY OF THE SUSPICIOUS THOUGHTS IN A NON-CLINICAL SAMPLE USING AN ERP PARADIGM

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Background: Previous studies of paranoid ideation and suspicious thoughts have primarily focused on rating scales and self-reported questionnaires. Very little is known about the neural basis of this psychopathological mechanism. Aims: To explore the validity of an experiment-based paradigm for assessing the suspicious thoughts in healthy volunteers and its corresponding neural process. Methods: Twenty four pairs of healthy college students participated in this study and were randomly assigned to two experimental conditions: the known (12 pairs) and the unknown (12 pairs) conditions. Participant A in each pair would be required to input one-single digit randomly, whereas participant B would press the 'guess' digit into the other connected computer in another cubicle. Participant A would be notified the "guess" digit on the computer and would be subject to the EEG recording. In the unknown condition, participant A was not known to this manipulation and was told that this study was about friendship and brain activity, whereas participant A in the known condition was given the details of the study before the running of the experiment. Three conditions were also set to manipulate the frequency of being guessed correctly, i.e., high frequency (about 70%), moderate frequency (about 50%), and low frequency (about 30%). After finishing the recording procedure, all participants were asked to fill in self-reported paranoid checklist. Results: (1) A prominent positive deflection of the difference wave (the 'correct guess wave' subtracted 'incorrect guess wave') within the time window 200ms-400ms after the stimuli presentation (0ms) in the unknown group; (2) LORETA analysis showed that more brain areas were activated when the unknown group observed the 'correct' feedback; (3) The difference between 'correct' and 'incorrect' feedback might reduce from anterior area to posterior area; (4) The ERP amplitude of frontal and central scalp sites were significantly different between high and low paranoia rating scores, particularly in high and mid frequency conditions. Conclusions: These findings provide preliminary evidence on the use of an ERP paradigm to detect paranoid ideation or suspicious thoughts in non-clinical sample. This paradigm may also serve as a potential tool to examine psychopathology of paranoid ideation in the clinical group.

IMPAIRED STRATEGIC DECISION MAKING IN SCHIZOPHRENIA

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Background: Adaptive decision making in dynamic social settings requires frequent re-evaluation of choice outcomes and revision of strategies. This requires an array of multiple cognitive abilities, such as working memory and response inhibition. Thus, the disruption of such abilities can have significant implications for social dysfunctions in schizophrenia. Methods: Twenty schizophrenia patients and 20 control subjects completed two binary decision-making tasks. In the first task, the computer simulated the behavior of an opponent in a competitive zero-sum game with a biased payoff matrix, in which the optimal strategy was to choose the two targets randomly with 20 and 80% probabilities. In the second task, the expected payoffs of the two targets were fixed, so the optimal strategy was to choose the target with the higher expected payoff exclusively. Results: The schizophrenia patients earned significantly less money in the competitive decision-making task, even though their overall choice probabilities were not significantly different from the control subjects. This was due to the fact that the choices of the patients were more strongly influenced by previous choices and their outcomes, which was disadvantageous during the competitive task. During the non-competitive decision-making task, the choices of patients and control subjects displayed more similar patterns. Conclusions: This study elucidated the specific components in decision making that are impaired in schizophrenia, and such deficits may have implications for the schizophrenia patients' poor social adjustment.

TRANSITIVE INFERENCE: DISAMBIGUATING REINFORCEMENT SENSITIVITY AND TASK DIFFICULTY FROM RELATIONAL MEMORY DEFICITS IN SCHIZOPHRENIA PATIENTS

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Abnormalities involving structure and function of the hippocampus (HP) are among the most consistently replicated findings in schizophrenia (SZ). The HP plays a critical role in relational memory organization. The capacity for transitive inference (TI) — if A>B and B>C, then A>C — is a fundamental component of relational memory. We previously reported that 40% of schizophrenia patients are impaired in making a TI. In order to disambiguate task difficulty from ability to make a TI, we developed a new TI paradigm that allows trials requiring a TI to be compared with trials matched for difficulty but involving non-TI relational judgments. The TI series consisted of four hierarchically ordered sequential pairs (A>B, B>C, C>D, D>E). Subjects were required to make a TI to high-difficulty (no endpoint stimulus) and low-difficulty (endpoint stimulus) novel pairs. The non-TI series consisted of four non-sequential pairs

(F>G, H>I, J>K, L>M). These non-sequential stimulus pairs also included low-difficulty and high-difficulty pairs. The two low-difficulty pairs had perfectly predictable reinforcement contingencies during training (100% reinforcement probability). In contrast, the two high-difficulty pairs had moderately predictable reinforcement contingencies (75% reinforcement probability). Subjects were tested on low-difficulty and high-difficulty novel non-TI pairs. Normal control (NC) subjects performed the high-difficulty non-TI and TI tasks with equivalent accuracy, indicating that the two tasks were well matched for difficulty. SZ and NC showed equivalent performance on both the high-difficulty non-TI novel pairs and on non-sequential previously learned difficult pairs, indicating that SZ subjects perform as well as controls on a difficult task that does not tap relational memory organization. However, SZ subjects performed the TI task (novel high-difficulty sequential pairs) substantially worse than NC: 71% vs. 90% accuracy (effect size: 1.0). SZ also showed reduced accuracy, 76% vs. 89%, on previously learned difficult pairs from the sequential series (effect size: 0.8). Thus, impaired performance in SZ occurs only when inference from a hierarchy (making a TI) is required and it occurs independent of novelty. This selective deficit provides empirical evidence that it is possible to distinguish between difficulty effects and transitive inference impairments in schizophrenia.

ARE THERE SYMPTOMS OR DEFICITS SPECIFIC RISK FOR SCHIZOPHRENIA?

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Background: Previous studies led to the hypothesis that poor cognitive abilities in adolescence, depression, anxiety poor or social adjustment are associated with increased risk for the later appearance of schizophrenia. Methods: We utilized the cognitive and psychiatric assessments performed by the Israeli military on all adolescents in the country, and ascertained hospitalization for schizophrenia using a National Psychiatric Hospitalization Registry. In addition we examined consecutive referrals to military mental health professionals and later hospitalizations for schizophrenia. Results: Future schizophrenia patients had cognitive test scores that were 0.4-0.5 SDs below population means. Their un-affected siblings had cognitive test score that were below population norms, but less impaired then their siblings later affected with schizophrenia. However, analysis of cognitive data on adolescents with non-psychotic disorders (depression, anxiety and personality disorders) found that they also had decreased cognitive test scores, and that their un-affected siblings also had cognitive test score that were below population norms, but less impaired then their un-affected siblings. These same cognitive deficits that were associated with increased risk for schizophrenia were associated with risk for imprisonment during military service, which we consider to be an adverse life event. Finally, none of the symptoms reported by recruits to military mental health professional was specific for impending schizophrenia. Discussion: Although cognitive deficits and other symptoms in adolescence are associated with later schizophrenia and some are genetically medicated, it appears that these same symptoms and cognitive deficits are associated with having a non-psychotic disorder, and for adverse life events. Generalized cognitive deficits might be non-specific risk factors for adverse life events, and are probably not specific for schizophrenia.

SEMANTIC MEMORY IMPAIRMENTS IN SCHIZOPHRENIA ARE BETTER EXPLAINED BY A FRONTAL-STRIATAL DEFICIT THAN BY TEMPORAL LOBE DYSFUNCTION

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Reviews of neuroimaging studies in schizophrenia report loss of tissue in the temporal lobes to be a consistent finding, an area traditionally thought to be central in explaining schizophrenic phenomenology and cognition. Nevertheless, neurological conditions featuring prominent damage to the temporal lobes have not provided adequate models for some of the cognitive impairments seen in schizophrenia. One area of cognition which is primarily impaired in schizophrenia is semantic memory. A neuroimaging review (Cabeza & Nyberg 1997) stated that semantic memory is processed mainly in the temporal lobes and areas of the prefrontal cortex. People with damage to the temporal lobes as the result of neurodegenerative illnesses such as Alzheimer's dementia (AD) and fronto-temporal dementia often have severe semantic memory problems with evidence that semantic memory representations become degraded. 26 people with schizophrenia were matched on IQ with 22 people with mild-moderate AD and then compared on an extensive battery of semantic memory tests. A degree of semantic memory impairment was evident in both groups although was far more severe in AD. Certain qualitative differences emerged between the two groups e.g. people with AD suffered from anomia (an inability to name objects) and their performance was consistent with an explanation of a degraded semantic memory attributable to temporal lobe damage. In the schizophrenia group tasks requiring discovery of semantic relations were impaired and executive dysfunction influenced task performance to some extent. A better model for the semantic memory impairments in schizophrenia might be Huntington's Dementia (HD). Unlike AD, neurological damage in HD is defined by a frontal-striatal dysfunction. Direct comparisons between HD and AD on tests of semantic and episodic memory have resulted in qualitatively different deficits. Similar to our schizophrenia group, people with HD display a less severe semantic memory deficit which is related more to difficulties retrieving knowledge (i.e. an executive dysfunction) than degraded knowledge. Following imaging studies which report a dysfunctional frontal-striatal system in schizophrenia, we speculate that as with HD, the semantic memory impairment in schizophrenia results more from a dysfunctional frontal-striatal system and less from the temporal pathology. But this dysfunction is not a straightforward executive dysfunction associated with frontal lobe injury per se.

OVERINCLUSIVE THOUGHT IS AS COMMON IN ALZHEIMER'S DEMENTIA AS IT IS IN SCHIZOPHRENIA

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Overinclusive thinking is where two or more unrelated concepts are linked together, a concept synonymous to Bleuler's "loosening of associations" which define psychotic thought. Overinclusive thought was traditionally seen as fundamental to psychosis and although interest has died down recently, this claim has never been refuted. One way of measuring overinclusion cognitively is to use a semantic categorisation task in which the use of conventional, as opposed

to idiosyncratic, semantic categories is clearly the preferred strategy. Studies have found that true to their overinclusive thinking, people with psychosis 'overinclude' i.e. combine items from different semantic categories, forming bizarre groupings. A card sorting, categorisation task was used in our studies (referred to as the Category Generation Test or CGT). Previously, Lawrence et al (2006) found that overinclusion was not explainable by an executive dysfunction as a group with severe executive dysfunction arising from acquired brain injury (ABI) were unimpaired on the CGT. As overinclusion involves forming unusual connections between objects and concepts both in thought, speech and on card sorting tasks, it was important to assess the role a deficit in semantic memory plays in overinclusion in schizophrenia. It is well known that people with schizophrenia have a certain degree of impairment on tasks assessing semantic memory. In addition, people with a probable diagnosis of Alzheimer's dementia (AD) have a well known semantic memory impairment resulting in difficulties naming and identifying objects. We compared a group of 45 people with schizophrenia to 45 people with AD on the CGT to see if overinclusion is related to poor semantic memory. We found that overinclusion is as common in AD as it is in schizophrenia and were surprised at the "psychotic-like" nature of the card sorts made in the AD group. It is possible that this formation of abnormal connections between words is related to a loss of semantic memory representations (which is known to occur in AD) but we found no connection between overinclusion and other semantic memory impairments in either group. In fact many people who overincluded could name, identify and answer detailed semantic probes about the objects they missorted. To conclude, overinclusion is not specific to psychosis and frequently occurs in people with AD. Explanations of disturbed attentional salience or a disorganised semantic memory network are proposed.

A NEUROPSYCHOLOGICAL AND FMRI STUDY OF SCHIZOPHRENIA

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The purpose of this study is to identify cognitive deficits, and length of illness and symptom severity correlates, using neuropsychological testing and fMRI in patients with schizophrenia. Twenty-four clinically stable outpatients with chronic schizophrenia (20M:4F) and 18 healthy controls (16M:2F), matched on age, gender and parental education, were administered a neuropsychological battery consisting of measures of executive function, working memory, verbal comprehension, semantic processing, speed of processing and intelligence. Ten of these patients (7M:3F) and 10 matched controls also performed a fMRI task called the Category Judgement and Substitution Task (CJAST), an analogue of the the Hayling Sentence Completion Test (HSCT). The CJAST is a novel task that differentiates activity associated with verbal response initiation and verbal response inhibition. In comparison to controls, patients showed significant deficits on all of the neuropsychological tasks. Longer illness duration was associated with poor performance on WAIS-III block design. Poor performance on WMS-III letter number sequencing was associated with greater positive symptoms, negative symptoms and general psychopathology. Poor performance on Digit Symbol and the National Adult Reading Test (NART) was also associated with negative symptoms. fMRI showed differential activation of the right middle frontal gyrus, right putamen, and left precentral and postcentral gyri for response inhibition relative to response initiation, in patients versus controls. These regions have been implicated in response inhibition in previous functional imaging studies. Compared to controls, patients showed deficits on neuropsychological measures of executive functioning, intelligence, working memory, verbal comprehension, semantic processing and speed of processing. Correlations suggest that impairment in executive functioning is associated with length of illness, while impairment in working memory, speed of processing and premorbid intelligence is associated with symptom severity. Functional activation maps of CJAST performance in schizophrenia revealed regions that are classically involved in response inhibition, a component of executive function. Patients are utilising the same neural networks as control subjects while performing the CJAST, but are having more difficulty in doing so.

INSIGHT IN SCHIZOPHRENIA CORRELATES WITH COGNITIVE REDUCTION AND INDICES OF FRONTAL LOBE DYSFUNCTION. NEGATIVE IMPACT ON THE REHABILITATION OF SCHIZOPHRENIC PATIENTS

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Lack of disease insight and negative attitude to medication affects the course of disease in schizophrenia. 166 patients were followed yearly over 5 years. At study end-point 101 patients were evaluated. 88 patients were included in a prospective 5-year longitudinal follow-up study of cognitive functioning in schizophrenia, of whom 69 were subjected to repeated neuropsychological testing. Patients were rated for symptoms, side effects, functioning and QoL with PANSS, AIMS, ESRS, UKU, CGI, GAF and Strauss-carpenter. SCID-PERS was performed at baseline. Medication and self-ratings of CGI and GAF was registered every year. DAI was rated at study end point. Results: Expert GAF last month had 33% shared variance with all three PANSS sum-scores (r appr.= 0.57). Patient GAF did not correlate with any PANSS sum score. Negative drug attitudes were associated with pronounced positive symptoms (threshold effect) whereas the association with 'lack of judgement and insight' was linear over the whole range. All PANSS-factors were significantly related to expert GAF ratings but not to patient ratings, which indicates that the patients have difficulties in assessing their symptom load. Lack of judgement & insight (PANSS item G12) correlated more strongly with poor overall cognitive performance (executive, IQ, memory, attention, speed factors and a compound index of frontal dysfunction), than with any other variable, including PANSS Negative symptoms. A strong correlation was also seen between cognitive performance (particularly failure to inhibit responses in a complex reaction time test), and a failure to identify ones performance and strategies in the neuropsychological tests. An index of such insight-related indices for instance discrepancy scores was computed as the sum of the absolute differences between expert and patient ratings formed one factor in a factor analysis, which correlated with the "Judgement and insight" item (G12) and the Cognitive factor but not with the other two symptom factors. No differences between antipsychotic drugs were seen in modulating effects on insight. Conclusion: Expert-rated cognitive symptoms and lack of insight was linked to self-monitoring problems. The findings suggest that lack of judgement and insight is primarily a cognitive symptom reflecting subcortical (loss of mental speed) and frontal (executive) cognitive func-

tions. Linking poor insight to the cognitive domain might help us to cope better with the problem.

TRANSLATIONAL GENETICS AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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Purpose: Genetic studies have implicated specific molecular mechanisms in cognitive impairment associated with schizophrenia. Several of these appear to be tractable targets for drug development. Method: Genetic studies have found that single nucleotide polymorphisms (SNPs) in a variety of genes impact risk for schizophrenia and/or performance on cognitive tests. Follow up studies using brain imaging and molecular techniques have provided convergent evidence implicating these genes and related molecular mechanisms. Results: Evidence for a role in schizophrenia and/or cognition is strongest for NRG1, dysbindin, COMT, and DISC1. Additional studies to confirm these and clarify risk alleles and transcripts are needed. Nevertheless, these findings implicate several molecular pathways and targets for drug development. Perhaps the most straightforward is COMT, which appears to modulate cognition via its effects on prefrontal dopamine. Of available COMT inhibitors, tolcapone does cross the blood brain barrier and has been reported to improve cognition. Toxicity and uncertain degree of central COMT inhibition suggest new COMT inhibitors are needed. The discovery of a highly penetrant gene, DISC1, where a translocation produces a dominant, truncated protein, provides a second avenue for drug development. DISC1 exerts myriad effects in neural processes, and it is unclear where or when DISC1 produces its deleterious effects. The recent finding that a DISC1 binding partner PDE4B also impacts risk for schizophrenia points to a specific DISC1 related pathway for drug targeting. Emerging work on molecular networks is beginning to provide network models that could further constrain DISC1 related targets. Recent reports that dysbindin-related BLOC 1 genes and the NRG1 receptor ERBB4 are associated with schizophrenia may constrain the candidate pathways for these genes, which have myriad effects. Conclusions: Molecular genetics provides a new path forward for developing novel therapeutic agents to enhance cognition in schizophrenia. While additional molecular studies are need to validate these mechanisms, they suggest a new model for schizophrenia drug discovery based on specific molecular and cellular phenotypes. The remaining challenge, inherent to all complex genetic disorders, is to understand in greater detail how genes and disordered pathways work together to impair cognition and what mechanisms are most tractable for normalizing them.

DO PATIENTS WITH SCHIZOPHRENIA HAVE A SMALLER VISUAL SPAN?

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Previous research has shown that, compared to healthy controls, persons with schizophrenia (SCZ) are slower and less efficient on visual search tasks. However, the attentional mechanism underlying this deficit is unknown. We propose that SCZ-related visual search impairment is mediated, in part, by a smaller visual span. "Visual span" is the region of the visual field from which one can extract information during an eye fixation. Research on healthy participants has shown that perceptual discriminability (i.e. the dissimilarity between a target and neighboring distractors) can influence visual span. For example, decreasing the distinctiveness of a target letter from distracter letters causes one's visual span to become smaller. Importantly, visual span also becomes smaller under conditions of divided attention and decreased visual span has been linked to less efficient visual search performance. These findings suggest that increasing attentional processing demands results in a narrowing of one's visual span with resultant decreases in visual search efficiency. Because patients with SCZ are believed to have less attentional resource, it is plausible that they employ a smaller visual span during search tasks. Such a constraint would decrease search efficiency – that is, to acquire the same amount of visual information a greater number of eye movements would be needed. To test this hypothesis a group of patients with SCZ and a group of healthy controls completed a same-different judgment task where two letters were briefly presented on the right and left of the screen at an equal distance from the centre. The distance of the two letters was manipulated over 5 possible distances. Reaction times and error rates were measured as indices of performance on this task. Our preliminary results from 10 patients with SCZ and 5 healthy controls demonstrate that in both groups there is an increase in reaction time as the distance increases. However the inflection in this function (i.e., an accelerating function toward greater response times) starts at a narrower distance for the patient group (i.e., 5 degrees visual angle) as compared with the control group (i.e., 7 degrees visual angle). These data suggest that patients with SCZ do indeed have a smaller visual span, which, in turn, leads to less efficient visual search.

RELATIONSHIP BETWEEN NEUROLOGICAL SOFT SIGNS AND COGNITION IN FIRST EPISODE PSYCHOSIS

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Neurological Soft Signs (NSS) are minor neurological abnormalities present in excess in psychosis. NSS have been suggested to predict poor cognitive performance, specifically executive function, mostly in patients with chronic psychosis. Unfortunately, it remains unclear whether this is already true for patients at the first illness episode. We examined an epidemiological sample of 248 first episode psychosis patients from the AESOP study (mean age 30 SD 10.81; 146 males; 48% Schizophrenia, 33% Affective Psychosis, 19% Other Psychosis. Mean current IQ 90.79 SD 17). Data relating to NSS were obtained using the Neurological Evaluation Scale (NES). IQ was obtained from the WAIS-R, executive function was measured using Trail Making Tests A and B and a Verbal Fluency task. NSS scores were divided into age quartiles (16-22, 23-35, over 35). Neurocognitive data were divided into four groups on the basis of performance. Multinomial logistic regression analysis revealed that individuals with more NSS were more likely to have a low IQ (p=0.005), while individuals with less NSS were more likely to have a high IQ (p=0.014). Similarly, individuals with more NSS were more likely to perform worse on Trails A (p=0.004) and B (p=0.001) and the Verbal Fluency Task (p=0.001).Likewise, individuals with less NSS were more likely to perform well on the Verbal Fluency Task (p=0.007). These results suggest that neurological impairment predicts a worse general cognitive performance. Further investigation is needed from tests evaluating specific cognitive domains, such as short term and working memory, to clarify this issue. This study is funded by the UK Medical Research Council. We would like to thank the Stanley Medical Research Foundation and The Wellcome Trust for their support.

PUPILLARY RESPONSES AND THE NATURE OF ATTENTIONAL IMPAIRMENT ON THE BACKWARD MASKING TASK IN CHRONIC SCHIZOPHRENIA

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The nature of impairment in early visual processing on backward masking in patients with schizophrenia was investigated. Task-evoked pupillary responses were recorded during a visual backward masking task to index attentional allocation in patients (n = 51) and age-matched nonpsychiatric controls (n = 51). Increased pupillary dilation indicates increased allocation of processing resources. Patients detected significantly fewer targets than controls only when the stimulus onset asynchrony (SOA) between targets and masks reached 717 ms, but not at shorter SOA intervals. Pupillary responses were larger in the 717 ms SOA condition relative to a no-mask condition for both groups, suggesting that the processing load of this condition was greater than the no-mask condition. Additionally, a principal components analysis of pupillary response waveforms identified time-related factors that appeared to differentially index attentional allocation to targets (middle factor) versus masks (late factor). Patients showed greater attention to masks than to targets, whereas, controls demonstrated the opposite pattern. These results replicate our previous findings with a larger sample and suggest that masking impairments in schizophrenia at SOA intervals greater than 100 ms may be due to abnormalities in attentional allocation mechanisms. To examine relationships between resource allocation and performance, patients were divided into high and low pupillary response subgroups based on a median split of their average pupillary responses across conditions. The low pupillary response subgroup demonstrated impaired detection accuracy, smaller overall pupil responses relative to controls, and equal allocation of resources between target and mask factors. These findings suggest reduced resource allocation contributed to performance deficits in the higher processing load 717 ms SOA condition. In contrast, the high pupillary response subgroup showed impaired detection accuracy, despite normal pupillary responses, suggesting reduced resource allocation may not account for the visual information processing deficit in this subgroup. This subgroup showed greater allocation of resources on the mask relative to target factors, suggesting impairment in early visual processing may be due to misallocation of resources to task irrelevant stimuli. Pupillary responses showed that the nature of cognitive impairments associated with resource limitations in schizophrenia can vary across subgroups.

TOP-DOWN ATTENTIONAL CONTROL OF AN IRRELEVANT SINGLETON IN SCHIZOPHRENIA: THE ROLE OF THE MAGNOCELLULAR PATHWAY

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An item with a distinctive feature within an otherwise homogeneous array attracts attention, even if this "singleton" is task-irrelevant, and top-down control is necessary to avoid being distracted by the singleton. We used two different types of irrelevant singletons to explore the top-down control of attention in schizophrenia (SC). In both experiments, subjects searched for a single diamond shape among 8 circles (or vice versa), and reported the orientation of a line at the center of the diamond by making a speeded button press. On half of the trials all of the stimuli in the search array were the same color and brightness, and on half the trials one of the distracters was a different color (Exp1) or was black (Exp 2), making it a highly salient irrelevant singleton. The color or luminance singleton was never the target, so any capture of attention by the singleton would delay the allocation of attention to the target and slow RTs. We tested 35 SC and 32 healthy controls (HC) in Experiment 1. Both groups showed significant slowing in the face of the irrelevant distractor. Surprisingly, this effect did not differ across groups ($p>.1$), suggesting that patients are unimpaired at using top-down control processes to resist processing irrelevant but salient distractors. Experiment 2 used luminance singletons that are preferentially processed in the magnocelluar pathway, which plays a role in the initial processing and orientation to salient stimuli. The other distractors and the target were isoluminant with the background, as determined by heterochromatic flicker-fusion photometry, making the luminance singleton the only item that could strongly activate the magnocellular pathway. A total of 35 SC and 24 HC subjects were tested. In contrast to the results obtained with color singletons, the luminance singletons produced greater slowing in SC subjects than in HC subjects ($p<.05$). A combined analysis of the data from Experiments 1 and 2 revealed a significant interaction of Group x Experiment x Singleton ($p=.05$), confirming that SC patients show deficient attentional control primarily when trying to resist distraction from singletons that activate the magnocellular pathway. This finding is consistent with evidence that patients have difficulty resisting the impact of sudden onset stimuli that also preferentially involve the magno system as in antisaccade paradigms, as well as evidence for enhanced backward masking deficits under magno masking conditions.

MAZE TASKS AND FUNCTIONAL IMAGING IN THE INVESTIGATION OF COGNITIVE DEFICITS IN SCHIZOPHRENIA

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Maze tasks have been used to investigate cognitive dysfunction in schizophrenia for a long time. While most maze tasks are used to investigate processing of learning, Porteus mazes can also be used to identify executive dysfunction. Since the latter is thought to be central in schizophrenia, Porteus mazes are especially suitable for the investigation of such cognitive processes. On a behavioural level, schizophrenic patients show prolonged processing times and increased error rates when solving mazes. In an fMRI study, we have recently demonstrated that solving mental Porteus mazes is accompanied with the activation of regions known to be involved in executive functions, such as dorsolateral and ventrolateral prefrontal and inferior parietal cortex. In the present experiment, we investigated whether the same maze tasks are suitable to study the neurobiological origins of cognitive deficits in schizophrenia. The expectation was to reveal altered brain activation patterns in the structures linked to executive function. Using fMRI, we investigated 21 schizophrenic inpatients and 21 matched healthy controls while they were performing mental maze tasks presented to them on a screen. Direct comparison between healthy subjects and schizophrenic patients exhibited no difference between groups regarding hypo- or hyper-

frontality during maze task solution,although patients were significantly slower to solve maze tasks and they were less exact, too. However, there was a marked difference in the time-course of activation during the experiment between the two groups: during the experiment, right frontal and left inferior parietal activation increased in the control group and it decreased in the schizophrenic group. In the case of frontal activation this could in part be attributed to learning processes in controls and possibly to upcoming fatigue in patients. We conclude that maze tasks are an appropriate experimental tool for the investigation of cognitive dysfunction in schizophrenia. Brain regions activated during the latter tasks are prefrontal and parietal areas known to be involved in executive functioning. It is important to notice that cognitive deficits in maze solution in schizophrenia cannot merely be attributed to hypo- or hyperactivation of these brain areas, but they are more likely originate in dynamic processes of the brain influenced by attention, learning and performance capacity.

USING IMPLEMENTATION INTENTIONS TO IMPROVE NEUROPSYCHOLOGICAL FUNCTION IN SCHIZOTYPY

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Introduction: Schizophrenia sufferers with negative signs and disorganisation have well documented problems with voluntary, self-initiated action and effortful control. This makes it difficult for them to pursue important interpersonal and social goals. Implementation intentions, an intervention from the health and social psychology literature (based on inculcating 'if…then' plans), can make goal pursuit automatic, bypassing the need for effortful control. This gives them great promise as the basis for cognitive remediation in schizophrenia sufferers. Since schizotypy is part of the broad schizophrenia phenotype we examined the interaction of implementation intentions and severity of schizotypy on neuropsychological performance in a student sample. We hypothesised that higher scores on the introvertive anhedonia subfactor (IA; negative symptom analogue) and cognitive disorganisation subfactor would be associated with greater benefit from implementation intentions. Method: 90 participants were allocated to perform a distracted verbal fluency and paired-associate learning (PAL) task with: simple instructions; reinforcement of the goal; an added strategy; or implementation intentions. Schizotypy was measured with the O-LIFE. Results: Mean score on IA in this sample was lower than previously found in normative studies or similar samples. IA was not associated with significant differences between conditions. The most cognitively disorganised participants benefited significantly (2-tailed, post-hoc) from strategy suggestion, significantly more than from implementation intentions. Discussion: Our sample's few symptoms and high function may have accounted for our results. Schizophrenia sufferers, with worse executive function, may still benefit specifically from implementation intentions.

PRESERVED GROUPING BUT IMPAIRED BUILDING OF AN EMBEDDED REPRESENTATION IN PATIENTS WITH SCHIZOPHRENIA

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Processing visual information involves automatic grouping and top-down attentional processes that help to reorganize information. The present results provide new insights on how reorganization of information leads to an embedded representation and allow to explore the building of such a representation in schizophrenia. We used a paradigm derived from Beck and Palmer (JEP, 2002) in 30 patients with schizophrenia and 30 matched controls. Subjects decided whether series of stimuli with geometrical features included, or not, two consecutive identical stimuli. The manipulation of proximity defined groups of two figures. Patients, like controls, benefited from grouping by proximity: they were faster and more accurate when the two identical stimuli belonged to the same group than to different groups of figures. However patients had difficulties reorganizing information. Reorganization of information was explored by manipulating the percent of target-present trials where the targets belonged to the same group (within-group trials) or to different groups (between-group trials). Between-group targets were processed faster and looked at longer as the percent of between-group trials increased, and conversely. Recordings of ocular movements showed that healthy volunteers control the exploration of between-group regions independently from within-group regions. Hence healthy volunteers were able to prioritize selectively objects that were part of different groups. Patients were able to prioritize groups of objects defined by proximity when targets belonged more frequently to the same pair, showing that top-down processes are partly preserved. However, they were unable to prioritize objects that were part of different groups independently of groups defined by proximity. Better performance in patients than in controls in some conditions allows to eliminate an explanation in terms of a generalized deficit. The results suggest that healthy volunteers create a representation involving two sub-representations, one with groups defined by proximity and one with pairs of figures that belong to different groups. Such representations help to focus on group parts without fragmenting information. Patients with schizophrenia appear to be impaired in the building of embedded representations, which might impact on the way they explore and adapt to the environment. It may reveal a more general deficit in building complex representations in other domains like motor control or memory.

DYSFUNCTION OF ADAPTIVE NEURAL GAIN CONTROL IN SCHIZOPHRENIA

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Auditory cortex response to sensory input normally increases in amplitude as the density of information presented increases. Increasing the density of information presented to schizophrenia patients, however, results in a paradoxical decrease in auditory evoked responses at rates of stimulation above about 20 Hz, as well as an inability to sustain gamma band oscillatory responses. These phenomena may be related to low excitatory drive on supragranular pyramidal cells in schizophrenia. As a result, schizophrenia patients' brains attempt to compensate for this low excitatory drive by increasing the gain in the thalamocortical system. The possible consequences of this increased gain control (higher background brain activity, compromised information integration ability, longer post-stimulus neural recovery time) were tested in the present study by driving the thalamocortical system using steady-state stimulation. This study evaluated schizophrenia patients' ability to integrate and recover from presentation of temporally dense auditory information. Dense-array (256 channel) EEG was recorded while 16 schizophrenia patients and 16 normal subjects were binaurally presented 1500

ms duration noise bursts amplitude modulated at frequencies from 16 – 44 Hz, in 2 Hz steps. Spectral power across time was compared between the schizophrenia and normal subjects. Results showed that 1) both groups entrained to the driving frequency of the stimulus at frequencies above 16 Hz, 2) steady-state responses (SSRs) in both groups were stable at frequencies above 32 Hz, 3) patients had stronger SSR than normals, but patients' SSRs were less focal, 4) even with stronger SSR, patients' N1 was decreased, 5) patients' SSR took longer to return to baseline following the offset of steady-state stimulation, 6) background brain state differed between groups (patients had higher power around 4 Hz, normals at 10Hz). These results demonstrated the increased thalamocortical gain control in schizophrenia and its maladaptive consequences. While signal is increased, indexed by the stronger SSR in schizophrenia across steady-state frequencies, so is noise, as shown by the less focal SSR and smaller cortical N1 response. Abnormally high gain control also increased the time for patients' auditory system to return to baseline following stimulation offset. The consequences of this inefficient compensatory activity by schizophrenia patients' auditory system may be related to hallucinatory phenomena.

THE NEUROCOGNITIVE SIGNATURE OF PSYCHOTIC BIPOLAR DISORDER

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Objective: Psychotic bipolar disorder may represent a neurobiologically distinct subgroup of bipolar illness. We sought to ascertain the profile of cognitive impairment in patients with bipolar disorder and determine whether a distinct profile of cognitive deficits characterizes bipolar patients with a history of psychosis. Methods: 69 outpatients with bipolar I disorder (34 with a history of psychotic symptoms and 35 with no history of psychosis) and 35 demographically matched healthy comparison subjects underwent a comprehensive neurocognitive battery. Results: Despite preserved general intellectual function, bipolar patients overall showed moderate impairments on tests of episodic memory and specific executive measures (effect size=0.58), and moderate to severe deficits on attentional and processing speed tasks (effect size=0.88). Patients with history of psychosis were impaired on measures of executive functioning and spatial working memory compared to bipolar patients without history of psychosis. Conclusions: The impact of history of psychosis on neuropsychological performance was limited to tasks requiring frontal/executive processing, suggesting that psychotic symptoms may have neural correlates that are at least partially independent of those associated with bipolar disorder more generally. However, deficits in attention, psychomotor speed and memory, appear to be part of the broader disease phenotype in patients with bipolar disorder.

IMPAIRED USE OF TASK REPRESENTATIONS MAY UNDERLIE WORKING MEMORY DEFICITS IN SCHIZOPHRENIA

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Patients with schizophrenia demonstrate working memory (WM) deficits, but the origins of the impairment remain unclear. One plausible hypothesis is that patients have difficulty maintaining a precise representation of task demands in WM and are therefore prone to errors. To test this idea, we developed a paradigm based on the computational modeling of O'Reilly and colleagues called the 12-AX-CPT which adds another dimension of control to the context CPT developed by Cohen et al. Specifically, each trial begins with a task cue (a 1 or a 2), which signals which of two target sequences is active on that trial. A task cue of 1 indicates that AX is the target; a task cue of 2 indicates that BY is the target. On each trial, the task cue is followed by two letter pairs. Each letter pair consists of an A, B, or C followed by an X, Y, or Z. Subjects press a button with one hand if the target sequence is detected, pressing a button with the other hand for any other stimulus. Pairs containing a C or a Z are never targets, providing a performance baseline. In this paradigm, WM is challenged by the need to remember the task, context, and target cues. Impairments in the use of task representations should lead to omission errors (e.g., missing 1-A-X because the task cue was misrecalled as "2") and false alarms to the sequence that is sometimes the target (e.g., responding to 2-A-X because the task cue was misrecalled as "1"). A total of 27 medicated outpatients and 21 healthy controls were tested. A d' score was calculated based on correct target detections and misremembered task cue false alarms. Patients showed dramatic impairment on this overall measure ($d' = 2.5$ vs.3.3, $p<.01$) with target omission and false alarm rates >10%. Error rates on baseline trials were <3% supporting the specificity of the deficit. We will also report the results of an-ongoing follow-up experiment using 3 letter pairs following the cue to address the role of delay effects. These results suggest that patients with schizophrenia have difficulty updating and using task representations to control WM performance. Such a deficit in representing task demands may be a critical underlying determinant of WM deficits, and compromise the use of WM representations in the service of other complex cognitive operations.

COGNITIVE NEUROSCIENCE OF ATTENTION IN SCHIZOPHRENIA

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Disturbances of attention have long been considered a critical feature of schizophrenia. Because attention does not directly control behavior but instead operates by modulating the performance of other cognitive systems (perception, working memory etc.), it is difficult to distinguish impairments of attention from deficits in other cognitive systems using clinical neuropsychological measures. In order to isolate the operation and control of attention, we have adopted methods and models developed in the basic cognitive neuroscience literature. In a series of experiments, we have examined two different questions: 1) Does schizophrenia impact the ability of selective attention to modulate visual perception and visual working memory?; and 2) Does schizophrenia impact the control of attention by salient "bottom-up" cues or the ability to use "top-down" goals to guide performance? This approach has yielded converging evidence of surprisingly preserved islands of performance as well as evidence of deficits that span cognitive systems. Specifically, patients demonstrate fully normal ability to make rapid shifts of visual attention that bolster perceptual performance when guided by strong bottom-up cues; 2) patients show fully normal ability to bind multi-feature objects into integrated working memory representations, a process thought to demand the operation of perceptual-level attention; 3) patients are surprisingly able to use selective attention to guide working mem-

ory encoding. In each of these cases, strong bottom-up cues serve to support attentional control. In contrast, patients demonstrate non-linear deficits in visual search suggesting a failure in top-down control. Impairment is also evident when representations of task rules must be updated and applied to working memory representations in order to guide response selection. Thus, across perceptual and working memory systems, patients demonstrate intact performance when strong bottom-up cues are available to guide attention. In contrast, deficits emerge across perceptual and working memory systems when top-down attentional control is stressed by competition from salient bottom-up cues. These data illustrate the potential of bringing the models and tools of modern cognitive neuroscience for parsing the cognitive deficits of schizophrenia and developing more precise targets for treatment intervention.

NEUROBEHAVIORAL HETEROGENEITY IN CHRONIC SCHIZOPHRENIA

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To examine possible neuromolecular mechanisms for cognitve deficits in schizophrenia, we studied 25 cognitively intact and 21 cognitively impaired schizophrenia subjects compared to 16 control subjects. 31P-1H magnetic resonance spectroscopic imaging (MRSI) examined membrane phospholipids [PME(s-τc), PDE(s-τc)] and phosphate metabolism (PCr), synaptic/transport vesicles [PDE(i-τc)], phosphorylated proteins [PME(i-τc)], lipid/protein glycosylation [(α-γ)ATP], and neuronal integrity (NAA/Crt). Compared to controls, cognitively intact schizophrenia subjects have decreased utilization of high-energy phosphate in right prefrontal cortex and increased membrane phospholipid precursors in right basal ganglia suggesting synaptic hypoactivity in right prefrontal cortex and ongoing membrane phosopholipid repair in right basal ganglia. Cognitively impaired schizophrenia subjects have decreased utilization of high-energy phosphates in prefrontal cortex bilaterally and left basal ganglia and decreased neuronal integrity in left temporal cortex. Compared to cognitively intact subjects, cognitively impaired schizophrenia subjects have decreased utilization of high-energy phosphate in left prefrontal cortex, left basal ganglia, and left superior temporal cortex, decreased precursors of membrane phospholipids in right basal ganglia and right temporal cortex and decreased measures of neuronal integrity in lefttemporal cortex. These findings suggest that cognitive impairment is associated with widespread synaptic hypoactivity, failed membrane repair attempts in multipleregions, and diminished regional neuronal integrity in left superior temporal cortex. Correlational analysis of all 46 schizophrenia subjects were obtained between MRSI variables and neuropsychological test scores. General measures of cognitive performance correlated with NAA/Crt and PME(s-τc) MRSI variables; memory correlated with PME(s-τc) PDE(i-τc), and PME(i-τc); abstract and spatial abilities correlated with PME(s-τc) and (α-γ)ATP; attention correlated with PDE(i-τc); and language correlated with PME(i-τc) and PCr. In summary, metabolic measures determined by 31P–1H MRSI are associated with cognitive impairment in chronic schizophrenia subjects and correlate with specific measures of cognitive performance. These findings suggest molecular and metabolic mechanisms underlying the cognitive impairment and suggest new therapeutic approaches to prevention of cognitive impairment.

SOCIAL COGNITION IN SCHIZOPHRENIA ACROSS PHASES OF ILLNESS

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Mounting evidence suggests that schizophrenia patients have deficits in social cognition, which refers to mental operations underlying social interactions, including the capacity to perceive the intentions of others. The goal of this project is to collaborate with basic behavioral scientists to newly apply more informative social cognitive measures to the study of schizophrenia. Paralleling other Center studies, this project assessed three clinical samples (prodromal, first episode and chronic) and demographically-comparable controls to examine the magnitude of the social cognitive deficit at each stage. The project also examined the relationships between social cognition and functional outcome. For this study, we applied two existing measures of social cognition: a measure of emotion processing (MSCEIT) and one of theory of mind (TASIT). These domains are considered examples of "person" perception. No previous studies in schizophrenia examined "relationship" perception (perception of relationships between people), due to the absence of a performance measure in this area. We worked with an expert in relationship perception (Dr. A. P. Fiske) to develop a new measure for this purpose. This measure (Relationships Across Domains Test) demonstrated good range and internal consistency in samples of college students and schizophrenia patients. The results indicate that all three social cognitive measures distinguish between patient groups and their respective matched controls (effect sizes from medium to large). At this point, we see no evidence of increased impairment with increased chronicity. We examined relationships to functional status for the first-episode and chronic samples, and all three measures showed significant relationships (.3 - .5 range). These relationships between social cognition measures and functioning were significant even after controlling for reading ability. Relationships between the social cognitive measures and positive symptoms were very low; they were higher for negative symptoms (.2-.4 range). Overall, it appears that patients at all three phases of illness show impairment in person perception (emotion processing, theory of mind) and relationship perception. These abilities are considered prerequisites for community functioning. As hypothesized, these measures are related to functional status in the patient groups.

EFFECTIVE NETWORK CONNECTIVITY DURING WORD AND LETTER STRING PROCESSING IN PERSONS WITH SCHIZOPHRENIA

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Functional neural network connectivity is thought to be aberrant in persons with schizophrenia (SZ). Functional coupling patterns between brain regions during processing often differ in strength and kind from those observed in healthy volunteers (HV), with the mostly commonly reported differences involving frontal-posterior cortical disconnectivity. We examined basic word processing networks during an fMRI task by characterizing effective connectivity using Structural Equation Modeling (SEM). During a scan session participants viewed four-letter words, four-letter consonant strings, and

simple geometric shapes presented one-per-second, 200ms stimulus duration. Behavioral performance did not differ between the SZ (n = 10) and HV (n = 8). Volumes were obtained every 2.1s of 6mm axial plane slices. Volumes of interest for the modeled brain regions were extracted from the time series separately for word and string stimuli. Covariance computed between regions of interest (ROIs) was fit to effective connectivity models. Modeled ROIs were: lateral geniculate nucleus (LGN), primary visual cortex (V1/V2), secondary visual cortex (V4), inferior temporal cortex (IT), dorsolateral prefrontal cortex (DPF) and ventral frontal region (VFR) and the hippocampal cortex (HC). For the HV group, modeled interactions revealed the expected stronger interactions for the left (i.e., language) compared to the right hemisphere and weaker feedback interaction compared to feedforward interaction between ROIs. The SZ group displayed a weaker degree of laterality and anterior-posterior disconnection between regions, especially in the right hemisphere, and reduced feedback interactions between regions compared to the HV group. Strong left hemisphere DPF and VFR interactions in SZ indicate processing focused on internally generated network input compared to external stimuli. Disconnections between the V4 and IT object processing path and frontal regions were also possibly compensated for by top-down feedback from the hippocampus, most likely through attention modulation via thalamic connections (not modeled). Stronger top-down functional influence in SZ was further supported by group differences in network coupling during consonant string processing. These modeling results extend previous findings of disconnections and reorganization in SZ by showing that beyond disconnectivity there appears to be some reversals in the direction of influence in functional networks.

MODULATION OF THETA POWER DURING VISUAL STIMULUS PROCESSING IN CROSS-MODAL SELECTIVE ATTENTION IN SCHIZOPHRENIA

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ABSTRACT Introduction: Schizophrenia is associated with abnormalities in selective attention and visual processing. Time/frequency analyses of EEG data provides us with a tool to detect when these deviations may emerge. Based on evidence suggesting theta power as a mechanism in selective attention, we investigated theta power and phase synchrony during a cross-modal selective attention task in subjects with schizophrenia and healthy controls. Methods: Subjects with schizophrenia (n=13) and healthy controls (n=13) participated in a task in which they were presented with four equiprobable stimuli: two auditory (soft and loud phoneme) and two visual (dim and bright checkerboard). Subjects pressed a button to dim checkerboards during visual and to soft phonemes during auditory condition. We calculated individual trial based event-related spectral perturbation (iERSP) and inter-trial coherence (ITC) values of EEG to the dim checkerboard (non-target) onset during both conditions. Results: For theta power, there was an attention (visual vs auditory)* time* group (patients vs controls) interaction (p=0.03) after the first 200 msec in the epoch at Cz. We also found a significant attention* time * group interaction (p=0.02) for theta ITC. The three-way interaction in theta power was attributable to greater values in healthy controls than in subjects with schizophrenia during the visual attention condition between 200-350 msec. These findings were paralleled for delta range power and synchrony values, but not for those in gamma range. Conclusion: In spite of normal task performance, patients with schizophrenia fail to achieve adequate power and synchrony in theta and delta bands during visual processing in cross modal selective attention.

USING TEXT ANALYSIS SOFTWARE IN SCHIZOPHRENIA RESEARCH

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In order to detect and quantify speech abnormality in schizophrenia, we designed and tested three text analysis software applications using cutting-edge natural language processing (NLP) technologies, which perform accurate, objective and speedy analysis of language without requiring substantial linguistic expertise or tremendous time from the researchers. The NLP applications tested in our schizophrenia experiment are: the Vocabulary Analyzer analyzing vocabulary rarity at the lexical level, the D-Level Rater rating syntactic complexity at the syntactic level, and the Idea Density Rater computing idea density at the semantic level. They were designed to target some of the often reported linguistic deviances in schizophrenia and other psychiatric diseases (Andreasen 1979, Covington et al. 2005), such as neologism and stilted speech, lowered syntactic complexity, and lowered idea density. The applications were implemented with the widely used computational linguistic tools, such as the OpenNLP package (Baldridge & Morton 2004), WordNet (Miller et al. 2003), and the frequency tables from the British National Corpus (Burnard 2000). Twelve controls and eleven schizophrenia patients matched for age, IQ, and parental socioeconomic status were recruited for the experiment at the University of British Columbia. The subjects were recorded describing pictures from the Thematic Apperception Test (Murray 1971) using the administration procedure outlined in Liddle et al. (2002). These recordings were transcribed by typists unaware of each subject's psychiatric status. The transcripts were input into the software applications for automatic text analysis at different linguistic levels. Contrary to reports in literature, statistical results from the Vocabulary Analyzer show that the patients used significantly fewer rare words than the normal controls. Results from the D-Level Rater conform to the common belief that syntactic complexity is compromised in schizophrenia speech: the patients used significantly more simple sentences and fewer complicated structures than the normal controls. Results from the Idea Density Rater showed no difference between the idea density of the patients' speech and that of the normal speech. Our experiment shows that high-precision automatic speech analysis is feasible with current NLP technologies. Software computing sophisticated psycholinguistic measures will facilitate data analysis for large-scale experiments in schizophrenia research.

DIFFERENTIAL EFFECTS OF SECOND GENERATION ANTIPSYCHOTICS ON THREE DOMAINS OF COGNITIVE FUNCTIONS IN SCHIZOPHRENIA PATIENTS

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Objective: Previously the authors have investigated cognitive functioning of schizophrenia and their healthy siblings in comparison

with the normal controls. We could identify three characteristic cognitive domains, i.e., CD1) possible endophenotype markers: impaired both in the patients and siblings groups, CD2) possible state-dependent markers: impaired only in the patients group, CD3) cognitive functions for which impairment was not observed in the patients or siblings groups. The aim of this study was to assess the differential effects of second generation antipsychotics on those cognitive domains in schizophrenia patients. Method: The subjects were twenty schizophrenia patients with active psychotic symptoms. All the subjects were treated with one of the second generation antipsychotics for 8 weeks. Positive and Negative Syndrome Scale(PANSS), Clinical Global Impression(CGI), and a battery of neurocognitive tests were administered at baseline and after 8 weeks of treatment. Paired t-test was used to compare the clinical and cognitive status of the patients before and after the treatment. Results: Significant improvement of the clinical symptoms was observed both on PANSS and CGI scores. For all the tests reflecting CD1(Immediate recall of Rey-Auditory Verbal Learning Test(RAVLT), Backward digit span, and Letter and Category fluency tests) and CD3 (copy of Rey-complex figure test(RCFT), N(0)-back, Forward digit span, False rate of Continuous Performance Test(CPT), Span of apprehension test, Trail A test, Number of error, Finger tapping test), we could not find any difference between the pre- and post-treatment scores. Significant improvement of the functioning was observed in Immediate recall(p=0.002) and Delayed recall(p=0.035) of RCFT, and Hit rates of CPT(p=0.006) after treatment. Conclusion: These results suggest that impairments in verbal learning and memory, verbal fluency and working memory are independent of the clinical state and might be associated with vulnerability of schizophrenia. Second generation antipsychotics showed a significant positive effect on the continuous attention and visual learning and memory.

REDUCED IMPACT OF POSITIVE EMOTION ON MEMORY IN SCHIZOPHRENIA

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Many people with schizophrenia have abnormalities in emotion, such as anhedonia, or decreased motivation. These emotional deficits, or negative symptoms, are strongly related to long-term outcome. Interestingly, many studies have also shown that individuals with schizophrenia report normal responses to emotional pictures, tastes, and movies at the time they are presented. However, individuals with schizophrenia often report fewer positive experiences when asked about events occurring in the past — suggesting that memory for positive experiences may be impaired. The current study used a well-established emotional memory model from the neuroscience literature to assess the facilitative impact of emotional valence of information on long-term memory consolidation in schizophrenia. Schizophrenia participants (n = 33) and healthy participants (n = 28) matched on demographic characteristics and intellectual functioning participated in the study. At the encoding state, schizophrenia participants reported higher levels of emotional intensity in response to positive, negative, and neutral IAPS images than did healthy participants. However, when recognition memory was tested 24 hours later, schizophrenia participants did not show enhancement of memory for positive images as was found in healthy participants. Further, correlations between self-reported physical and social anhedonia were significantly inversely correlated with intensity ratings of positive stimuli during the encoding phase for healthy subjects, but were negligible for schizophrenia participants. These results suggest a failure to adequately integrate positive emotional experience in memory consolidation processes in schizophrenia participants, despite appropriate initial response to positive stimuli. This failure of enhancement of memory by positive emotion may contribute to symptoms such as anhedonia by reducing the long-term impact of positive experiences in motivating hedonic behavior in day to day life.

EMOTION IN VOICES NOT RECOGNIZED IN SCHIZOPHRENIA

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Deficits in affect perception may be one of the most pervasive disturbances in schizophrenia patients, possibly leading to social isolation and stigma. In meta-analyses emotion processing deficits in schizophrenia have been neglected. In this report the focus will be on the perception of vocal affect perception, as this is an important aspect of social cognition which is thought to be impaired in schizophrenia. We used meta-analysis to integrate findings of published studies on emotional prosody in schizophrenia. From 344 studies published from 1980, 13 studies provided enough valid information to be included in the analysis. After calculation of the effect sizes, a mean weighted effect size was computed in the random effects model and the publication bias was tested using funnel plots and fail-safe number of studies. The magnitude of the overall effect size was large: 1.24 (range 0,42 to 2,46). All effect sizes, including confidence intervals were below zero. In this analysis all 13 studies were included, with a total group size of 501 (range 15 to 100). The effect can be considered as stable, it is also found in the early stages of the illness. When looking at moderator variables, patient status had a significant effect on the magnitude of the impairment. Inpatients show larger impairments in this aspect of emotion processing than outpatients. Age, duration of illness, valence or number of emotions and other task variables did not affect the magnitude of the effect size. Results of this study indicate that individuals with schizophrenia experience substantial problems with the perception of emotional prosody. These problems are even more severe in inpatients than in outpatients. However, our results do not include elaborate information on potential influence of clinical and study variables. Further research is needed to elucidate the relative contribution of variables like severity of psychopathology and duration of illness.

INFORMATIVE FEEDBACK ENHANCES ACCURACY THROUGH ALTERNATIVE PATHWAYS IN SCHIZOPHRENIC VOLUNTEERS

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Background. Feedback is a crucial component of learning. Behavioral and physiological changes that follow an informed incorrect trial should reveal some of the characteristics of successful skill acquisition. This study examines how healthy controls (HC) and volunteers with schizophrenia (SZ) respond on correct trials that follow incorrect trials of a difficult visual match-to-sample task. Methods.

HC (n = 21) and SZ (n = 19) completed six event-related, functional magnetic resonance scans (each 10 min., Philips 3 Tesla). The first and second scans (A1) provided no feedback on the match-to-sample task (rectangles with matching or non-matching heights). The third and fourth scans (B) provided feedback regarding the accuracy of each trial. The fifth and sixth scans (A2) provided no feedback with respect to accuracy. All scans were analyzed to provide BOLD activity maps of Correct trials following Correct trials (CC), and Correct trials following Incorrect trials (IC). This presentation concerns only IC trials. Trials were jittered. Results. The groups exhibited similar accuracy levels during A1 scans: NV = 53.2% and SZ = 52.2 %. Both groups improved in accuracy during the B scans: NV = 59.7% and SZ = 62.7 % ($p < 0.04$). During A2 the HC group continued to significantly improve in accuracy, 65.2% ($p < 0.05$). In contrast the SZ group declined to 57.2 %, which was not significantly above the initial A1 accuracy set. Physiological findings across these conditions showed three general patterns. First, both groups engaged parietal regions bilaterally across all three conditions. The SZ group's parietal activity extended anteriorly to the sensorimotor cortex. Second, the HC group manifested strong dorsolateral frontal activity during A1 and A2 but very little during condition B (feedback). This was in contrast to the SZ group, which showed robust dorsolateral frontal activity during set B and no frontal activity during A1 and A2. Third, during B condition HC subjects manifested robust activity increases in the habenula and thalamus, but the SZ group showed strong activity in the visual cortex. Conclusion. Though able to benefit from feedback, the SZ group may be unable to acquire a strategy for perceptual learning that will transfer to trials without feedback.. That disability may derive from their failure to tune parietal neurons during the feedback phase. Their reliance on visual cortex may be a reflection of insufficient cortical tuning.

NEUROPLASTICITY-BASED COGNITIVE TRAINING IN SCHIZOPHRENIA

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Schizophrenic subjects can, after cognitive training, demonstrate behavioral improvement in cognition. Most previous studies, however, have not explicitly provided a neuroscience-based rationale for the selection and development of their remediation methods, despite recent basic science advances in identifying the key neurobiological "active ingredients" necessary to drive massive cortical representational change. The purpose of the present study is to investigate such a neuroplasticity-based approach to the remediation of cognitive deficits in schizophrenia, using a computerized neuroadaptive training program that heavily engages attentional and reward systems in the brain and that makes use of exercises which, in animal experiments, induce generalized cortical plasticity. We report on the first twenty-nine subjects, stratified by IQ and symptom severity, who were randomly assigned to either targeted cognitive training (TCT) or a control condition of graphically interesting computer games (CG). Both groups participated in the intervention for 1 hour per day, 5 days per week, and both believed they were receiving an "active" treatment. All subjects received clinical and MATRICS-based neurocognitive assessments (by personnel blind to group status) at study entry, and after 12, 16, 22, and 26 weeks of intervention. Medium to large effect sizes as a result of the first 12-week module of TCT (focused on auditory processing) were found in the following cognitive domains: processing speed (0.8), attention (0.5), working memory (0.45), verbal learning (0.7), and overall verbal processing efficiency (1.2). A comparison of the total neurocognitive change index for the two groups (mean of z-score changes obtained on Trails A, Trails B, Digit-Symbol Coding, Letter-Number Sequencing, Spatial Span, HVLT) revealed a mean z-score change of 0.4 for the TCT group, and -0.1 for the CG group ($p<.01$). These findings suggest that schizophrenic subjects can show meaningful improvements in key cognitive domains as a result of intensive neuroplasticity-based training. Clinical data and results on the effects of additional specialized training modules (visual processing; executive functioning and cognitive control) will be presented.

ABNORMAL NEURAL RESPONSES TO AMBIGUOUS SOCIAL INFORMATION IN PSYCHOSIS

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Background: Previous evidence suggests that an elevated sensitivity to emotional information may lead psychotic patients to misassign emotional meaning to neutral or ambiguous situations and events. We hypothesize that abnormal communication between limbic and evaluative neural systems—specifically, medial temporal-cingulate circuitry—may give rise to aberrant emotional and social perception in schizophrenia. To test this hypothesis, we measured neural responses to verbal descriptions of social situations with emotional or neutral/ambiguous content in schizophrenic patients and healthy control subjects using event-related functional MRI. Methods: We constructed and validated a set of 405 two-sentence descriptions of Positive, Negative and Neutral social scenarios. Subjects underwent functional MRI scanning (3T) while making valence judgments about the randomly presented sentence-pairs. Functional MRI data were analyzed using: 1) a cortical surface, voxelwise approach 2) a region-of-interest analysis. Results: Behavior: The schizophrenic patients were less accurate than the healthy control subjects in classifying Negative and Positive scenarios; there were no between-group differences in accuracy rates for Neutral scenarios. Functional MRI: The control subjects showed significant activation in the bilateral posterior cingulate cortex to the Negative (relative to the Neutral) scenarios, while the schizophrenic patients displayed the opposite pattern of relative activation, with an increased response to the Neutral (relative to the Negative) scenarios in the right posterior cingulate cortex. Also, transient, elevated activation of the left amygdala was found in the patients, but not in the controls, in response to Negative (relative to the Neutral) scenarios; within the patient group, the activity to Neutral scenarios within the right cingulate gyrus predicted the activity to Negative scenarios within the amygdala. Lastly, the magnitude of responses of the right and left cingulate gyrus to the Neutral condition were significantly correlated with delusion severity within the patient group. Conclusion: Patients with schizophrenia, particular those with delusions, exhibit elevated responses of the cingulate gyrus to neutral/ambiguous social information. Future experiments will explore the relative contributions of cognitive impairment and heightened arousal states to abnormal emotional and social perception in psychosis.

COGNITIVE TRAINING FOR SCHIZOPHRENIA PATIENTS ENHANCES ABILITY TO CONTROL THE INFLUENCE OF NEGATIVE AFFECT ON SOCIAL JUDGMENTS

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Prior research indicates that schizophrenia (SZ) patients misinterpret social cues, usually by ascribing negative valence or negative intentions to ambiguous stimuli. Factors contributing to this misinterpretation are unclear. Here, we investigated whether negative affect influences the social judgments of other people and whether the ability to control negative affect when making social judgments could be enhanced through training. Schizophrenia patients performed a task in which they were first primed with positive, negative, or neutral affect and then judged the trustworthiness of a neutral face. The results show that SZ patients rated the neutral face as significantly less trustworthy after the negative affect prime as compared to the positive or neutral affect prime. This problematic influence of negative affect on social judgment decreased after cognitive remediation training. The results suggest that social judgments, especially concerning the suspiciousness of other people, are influenced by negative affect. Furthermore, cognitive training can help patients regulate the influence of their negative affect on social judgments so that feelings such as paranoia do not lead to social misinterpretations. Data from healthy control subjects on this task suggest that the ability to regulate the influence of negative affect on social judgments is mediated by the lateral prefrontal cortex (PFC). Collectively the findings suggest that behavioral training in cognitive control, which is mediated by the lateral PFC, can help patients regulate the influence of negative affect on social judgments so that they can assess social situations more accurately.

COGNITIVE CORRELATES OF THE HAYLING SENTENCE COMPLETION TEST IN FIRST-EPISODE SCHIZOPHRENIA

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Introduction: The Hayling sentence completion test (HSCT) is a high level semantic processing task where subjects had to complete a sentence in an incongruent manner. Byrne et al. (1999) suggested that the HSCT can help to predict subjects who are at risk of schizophrenia. We study the correlates of HSCT impairment in a sample of first episode schizophrenic patients. Methods: 33 first-episode schizophrenic patients with a mean age of 24.6 years (sd 9.13) and mean education of 10.9 years (sd 2.65) were recruited. In addition to the HSCT, subjects completed IQ, information, verbal fluency, letter number span, visual production, Stroop, logical memory, trial making, six element test and the Wisconsin Card Sorting Test (WCST). Results: The total error in HSCT part B was 10.24 (sd 12.01). This variable was associated with CLANG "poverty" (r= - 0.31, p=0.041), handedness (r=0,209, p=0.022), information (r= -0.343, p<0.001), WCST perseveration response (r=0.363, p=0.007), logical memory immediate (r=0.314, p=0.014) and delay recall (r= - 0.367, p=0.004). The additional time spent on task B as compared to task A was 6.53 minutes (sd 60.5), and this was associated with only logical memory immediate (r= - 0.294, p=0.021) and delay recall (r= - 0.292, p=0.024). It also correlated with SAN attention (r= - 0.243, p=0.03). Discussion: The Hayling sentence completion test measures complex semantic processes. Abnormalities of Hayling performance in schizophrenia is related to a range of other cognitive and clinical abnormalities, notably both handedness and language disorder are related to HCST impairment. In addition to its relationship with verbal cognitive functions, HCST is also associated with non-verbal executive function such as the WCST. Reference: M. BYRNE a1, A. HODGES, E. GRANT, D. C. OWENS and E. C. JOHNSTONE (1999) Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS), Psychological Medicine, 29: 1161-1173

SUBCORTICAL VISUAL DYSFUNCTION IN SCHIZOPHRENIA DRIVES SECONDARY CORTICAL IMPAIRMENTS

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Visual processing deficits are an integral component of schizophrenia (SCZ) and are sensitive predictors of schizophrenic decompensation in healthy adults. The primate visual system consists of discrete subcortical magnocellular and parvocellular pathways, which project preferentially to dorsal and ventral cortical streams. Subcortical systems show differential stimulus sensitivity, while cortical systems, in turn, can be differentiated using surface potential analysis. The present study examined contributions of subcortical dysfunction to cortical processing deficits using high-density event-related potentials (ERPs). ERPs were recorded to stimuli biased towards the magnocellular system using low contrast isolated checks in Experiment 1 and towards the magnocellular or parvocellular system using low versus high spatial frequency sinusoidal gratings, respectively, in Experiment 2. The sample consisted of 23 SCZ and 19 controls. In Experiment 1, a large decrease in the P1 component of the visual ERP in response to magnocellular-biased isolated check stimuli was seen in SCZ compared to controls. SCZ also showed decreased slope of the contrast response function over the magnocellular-selective contrast range compared to controls, indicating decreased signal amplification. In Experiment 2, C1, P1, and N1 were reduced in amplitude to magnocellular-biased low spatial frequency stimuli in SCZ, but were intact to parvocellular-biased high spatial frequency stimuli, regardless of generator location. Source waveforms derived from inverse dipole modeling showed reduced P1 in Experiment 1 and reduced C1, P1, and N1 to low spatial frequency stimuli in Experiment 2, consistent with surface waveforms. These results indicate pervasive magnocellular dysfunction at the subcortical level that leads to secondary impairment in activation of cortical visual structures within both dorsal and ventral stream visual pathways. Although deficits in visual processing have frequently been construed as resulting from failures of top-down processing, the present findings argue strongly for bottom-up rather than top-down dysfunction at least within the early visual pathway. This study was supported in part by a Lieber Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression, USPHS grants RO1 MH66374, R01 MH65350, R03 MH067579, R37 MH49334 and K02 MH01439, and a Burroughs Wellcome Translational Scientist Award.

MULTIMEDIA DVD-BASED CONSENT: A RANDOMIZED CONTROLLED TRIAL

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The goal of this investigation was to evaluate the usefulness of an innovative method of providing informed consent to middle-aged and older persons with schizophrenia. This was a randomized, controlled trial of two procedures for providing informed consent: a DVD-based, multimedia consent procedure, based on cognitive models of learning, incorporating audio, video, still pictures, motion pictures, graphics, animation, and text; and a routine consent procedure. The hypothetical protocol was a simulated study involving relatively high risk and complexity - a randomized, double-blind, placebo-controlled trial of a cognitive-enhancing drug with some potentially serious adverse effects. The primary outcome measures was the subjects' capacity to understand, appreciate, and reason with participation in the hypothetical research protocol presented, using the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) along with a newly developed scale called the UCSD Brief Assessment for Capacity to Consent (UBACC). The study sample was comprised of 145 subjects with schizophrenia or schizoaffective disorder who were older than 40 years of age (mean age 52, 64% men, and 63% Caucasian). The patients who received the DVD consent had significantly ($p < .03$ to $.002$) higher mean scores on understanding (18.9 vs. 15.8 on trial 1 and 22.6 vs. 19.5 on trial 2), appreciation (4.7 vs. 4.1), and reasoning (5.4 vs. 4.8) than the 70 patients who received routine consent ($p < .05$). Patient satisfaction was higher for the DVD consent than for the routine one. The results show that a multimedia consent is not only feasible and acceptable to patients with schizophrenia but it is also associated with better comprehension of consent material related to a high-complexity, high-risk drug trial of the type commonly used for regulatory purposes.

THE RELATIONSHIP BETWEEN CLINICAL VARIABLES AND EXECUTIVE COGNITIVE FUNCTION EVALUATED BY EXECUTIVE INTERVIEW (EXIT) IN CHRONIC SCHIZOPHRENIA

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Objective: Executive cognitive deficits are now considered as one of the core aspect of schizophrenia and may affect the functional status of patients. The Executive Interview(EXIT) is a brief, clinically based neurobehavioral measure designed to assess the executive dysfunction. The goals of EXIT are to discriminate the presence and severity of executive cognitive deficits, to predict executive functions which are related impairments in self-care and functional status, and to predict problem behaviors engendered by executive dyscontrol (Royal et al., 1992).It was developed for elderly population but has been shown to be reliable in schizophrenic patients. This study aimed to examine the correlation between executive deficits and clinical variables in chronic schizophrenia. Methods: A total of 105 chronic schizophrenia patients(41 males, 29 females) were recruited from 3 community mental health centers in Seoul. Measures of assessment were: EXIT, Brief Psychiatric Rating Scale(BPRS), Global Assessment of Functioning(GAF) scale, Sheehan Disability Scale(SDS), Heinrichs Quality of Life Scale(QOLS). Clinical variables including the duration of untreated psychosis(DUP) were collected. Correlation analysis was performed to examine the relationships between EXIT total score and other variables. Independent T-test was performed to compare the clinical variables between the high EXIT scored group(n=65) and the low EXIT scored group(n=40) based on cut-off criterion of 15. Results: The mean age of subjects was 39.9±10.5 years, and the mean duration of education was 10.8±3.3 years. The EXIT total score was positively correlated with age($r=27$, $p<0.01$), DUP($r=0.20$, $p<0.05$) and SDS scores($r=0.25$, $p<0.05$), and negatively correlated with the total scores of QOLS($r=-0.22$, $p<0.05$) and GAF($r=-0.33$, $p<0.01$). When comparing the high and low EXIT scored groups, there were significant differences in DUP, GAF scores, Anxiety-Depression scores of the BPRS, and the total dysfunctional days in SDS($p<0.05$). Discussion: Executive deficits were significantly correlated with older age, higher level of disability, longer DUP, poorer quality of life, and lower global functioning level. The subjects with poor executive function were characterized as having longer DUP and lower global functioning level, and being emotionally more anxious and depressive. These results suggest that executive deficit may be an important factor in determining the level of disability in chronic schizophrenia

OLFACTORY IDENTIFICATION DEFICITS RELATED TO PSYCHOMETRICALLY-DEFINED SCHIZOTYPY

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Existing endophenotypes for schizophrenia have not been sufficiently sensitive and specific, indicating a need for investigation of novel endophenotypes. Olfactory identification deficits have received recent attention as a potentially useful endophenotype for schizophrenia. Reports of olfactory deficits in persons with schizophrenia have been difficult to interpret due to various confounds. Therefore, examination of this deficit in related populations, such as individuals with schizotypal personality features offers an alternative approach that can avoid these potential confounds. Park and Schoppe (1997) reported olfactory identification deficits in undergraduates scoring in the top 10% on the Schizotypal Personality Questionnaire, using the 40-item University of Pennsylvania Smell Identification Test (UPSIT). The current study examined whether this deficit could be detected using the abbreviated form of the UPSIT, the 12-item Brief Smell Identification Test (B-SIT; shown to correlate with UPSIT at around 0.83). Twenty-six undergraduates scoring in the top 10% of the Abbreviated SPQ (SPQ-B; mean age 19.6, SD = 1.1; 62% female) and twenty-six controls (scoring lower than half a standard deviation above the mean; mean age 19.8, SD = 1.6; 62% female) were administered the B-SIT as part of a larger battery of tests. Group differences in number of items correct on the B-SIT between individuals scoring high on the SPQ-B (10.11, SD = 1.40) and controls (10.42, SD = 1.14) did not approach statistical significance, $U = 300.5$, $p = .48$. Additional analyses that examined group differences within each gender (controlling for menstrual cycle in females) also did not approach statistical significance. Results suggest that olfactory identification deficits may not represent a robust endophenotype that is consistently found in samples with schizotypal personality features. Alternatively, the abbreviated form of the UPSIT that was used in the present study may not be adequately sensitive to detecting relatively subtle deficits previously reported in psychometrically-defined community samples.

HIPPOCAMPAL MORPHOLOGY AND MEMORY-RELATED FUNCTIONAL BRAIN ACTIVATION IN SCHIZOPHRENIA AND UNAFFECTED SIBLINGS

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Structural and functional abnormalities in the hippocampus have been implicated in the cognitive deficits present in schizophrenia. Nevertheless, further clarification of the relation between hippocampal structural morphology, functional activation in the region, and cognitive performance is needed. In this study we investigate (1) whether individuals with schizophrenia demonstrate task related functional abnormalities in regions of the hippocampus where abnormal morphology has been detected, (2) whether the degree of morphological abnormality is associated with the severity of functional activity deficits in the hippocampus or other brain regions, and (3) whether behavioral performance on memory tasks is related to morphological or functional abnormalities in the hippocampus. Functional magnetic resonance imaging (fMRI) scans were obtained from individuals with schizophrenia, their unaffected siblings, and healthy controls. All participants performed working and episodic memory tasks with face and word stimuli. High dimensional computational neuroanatomy methods were used to assess hippocampal volume and shape on a subset of participants. We found abnormal task-related brain activity in the right head of the hippocampus in the schizophrenia and sibling groups across all tasks compared to controls, the region of the hippocampus also found to show morphological abnormalities in schizohprenia. Furthermore, we found that the degree of hippocampal shape deformation in the schizophrenia group was negatively correlated with task related activation in the right dorsolateral prefrontal cortex, anterior cingulate, and bilateral parietal regions. Our results suggest a critical relationship between structural and functional brain abnormalities in schizophrenia.

MULTIPLE-OBJECT TRACKING IN PATIENTS WITH SCHIZOPHRENIA AND IN PEOPLE AT HIGH RISK OF SCHIZOPHRENIA

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It has been demonstrated that patients with schizophrenia and people at risk of schizophrenia perform poorly on tasks which require orienting, focusing, maintaining, and shifting of attention. In traditional laboratory paradigms, visual attention selects information from a single location of the environment. However, many typical everyday activities, such as video games, simultaneously watching people in a crowd, or navigating in heavy traffic, require attention to multiple locations of the environment. These functions, which model real-life attentional demands more reliably that traditional laboratory task, have not been investigated in schizophrenia and in "at risk" mental states. To elucidate this issue, we investigated fast and slow multiple-object tracking in patients with schizophrenia (n=30), in people at high risk of schizophrenia (n=27), as defined by the Comprehensive Assessment of "At Risk Mental State" instrument, and in age-, gender-, and education-matched healthy control subjects (n=30). We also assessed the relationship between multiple-object tracking and working memory (spatial and object working memory) and sustained attention/context processing (1-9 version of the Continuous Performance Test). Results revealed that patients with schizophrenia and people at risk of schizophrenia displayed impaired performances on multiple-object tracking tasks as compared with controls. People at risk of schizophrenia outperformed the patients with manifest illness on all tests. Multiple-object tracking performance was related to spatial working memory, but not to object working memory and sustained attention/context processing. These results suggest that multiple-object tracking is impaired in schizophrenia and in people at risk of schizophrenia, and that it is specifically associated with spatial working memory. Impairments of multifocal attention may be an endophenotype of schizophrenia.

WORK PERFORMANCE AND NEUROCOGNITION AFTER COMPUTERIZED NEUROCOGNITIVE SKILLS TRAINING IN CHRONIC SCHIZOPHRENIA

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Cognitive impairments are a core feature of schizophrenia and are related to poor functional outcomes.Neurocognitive skills training programs show modest significant benefits on cognitive functioning, and on longer-term broader functional outcomes, including work. Aims:To evaluate the feasibility and efficacy of neurocognitive skills training in improving cognitive functioning, clinical symptoms, adaptive life skills and work function in long stay psychiatric inpatients. Methods: 84 inpatients with predominantly DSM IV schizophrenia were randomized to either computerized neurocognitive training (COGPACK) providing practice of cognitive functions, or to a control condition. The program consisted of 24 one-hour laboratory sessions occurring approximately 2 times per week over a 12-week period with a weekly discussion group to facilitate transfer of cognitive skills to adaptive life functioning. The control group received similar hours of staff and computer exposure without cognitive training. Assessments:A neuropsychological battery, PANSS, Barnes, SAS and Social Adaptive Functioning Evaluation (SAFE) were administered at baseline,weeks 6,12,24 and 12 months. Results: Mixed model ANCOVA with baseline assessments as covariates did not show significant group effects indicating experimental and control group did not differ over time in symptoms, adaptive functioning, and side effects. Time, but not group by time, effects were found on the SAFE ($F=6.34, df=1,188; p<0.01$),PANSS positive symptoms ($F=7.13, df=1,288; p<0.01$),and Barnes $F=11.98, df=1,288, p<0.001$), indicating improvement. Changes in cognitive measures were evaluated by ANCOVA with baseline measures as the covariate and 3 months endpoint assessment as the dependent variable and group as the independent variable. Significant group effects were found for Trail Making A($F=7.9, df=1,67; p<0.01$),Rey Auditory Learning(Total,Trials 1-5)($F=4.3, df=1,71; p<0.05$),and cognitive composite score($F=3.7, df=1,73; p<0.05$),indicating improvement in the experimental group. Patients in the experimental group worked more weeks ($t=2.1, df=66; p<0.05$)than the control group over the 12-month follow-up. Conclusions:Participation in the cognitive program was associated with improvements in learning, psychomotor speed, and higher participation in a work program. Results support the feasibility and efficacy of cognitive skills training in improving cognitive and work functioning in longer-stay psychiatric inpatients.

COGNITIVE, NEUROPHYSIOLOGICAL AND FUNCTIONAL CORRELATES OF PROVERB INTERPRETATION ABNORMALITIES IN SCHIZOPHRENIA

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Abnormally concrete and idiosyncratic interpretations of proverbs are a hallmark of schizophrenia. This abnormality could be due to aberrant activation of disorganized semantic associations, or to working memory (WM) deficits. We evaluated these hypotheses by exploring the relationships between proverb interpretation and other neurocognitive measures in schizophrenia patients. Eighteen schizophrenia patients and 18 normal control participants (NCPs) were assessed on: proverb interpretation (via the Delis-Kaplan Executive Function System Proverb Test); auditory WM (Letter-Number Span Test); auditory sensory-memory encoding (as indexed by the mismatch negativity (MMN) event-related brain potential); and executive function (Wisconsin Card Sorting Test). Patients were also assessed on symptom factors via the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS), and on functional status (UCSD Performance-Based Skills Assessment). As expected, schizophrenia patients produced less accurate and less abstract descriptions of proverbs than did NCPs. These proverb interpretation deficits in patients were not significantly correlated with disorganization or other symptom factors, but were significantly correlated ($p<0.05$) with impairments in WM, sensory-memory encoding (as indexed by reduced MMN amplitudes), executive function, and functional status. These results are consistent with some role for WM deficits, but not for disorganized associations, in abnormal proverb interpretation in schizophrenia. Proverb interpretation deficits may be part of a syndrome related to generalized frontal cortical dysfunction.

DETERMINING CATEGORICAL DECISION-MAKING CAPACITY STATUS OF RESEARCH PARTICIPANTS: DATA FROM THE CATIE SCHIZOPHRENIA STUDY

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The authors evaluated a framework for determining the categorical capacity status of potential subjects in schizophrenia research. Expert-judgment-based validation of potential capacity thresholds on the subscales of the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR) was evaluated using receiver operator characteristic (ROC) analysis. The participants were 91 patient-subjects—55 enrolled in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and 36 non-CATIE patients—and 40 non-psychotic comparison subjects from the community. Categorical capacity determinations were rendered by majority or better agreement among 3 independent, experienced clinicians. The ROC area under the curve was .94 (95% CI .88-.99) for the Understanding subscale of the MacCAT-CR, .85 (95% CI .76-.94) for the Appreciation subscale, and .80 (.95% CI .70-.90) for the Reasoning subscale. Using the best available estimate of prevalence of incapacity, the actual Understanding scale cutoff score used in the CATIE schizophrenia trial yielded a positive predictive value of 100% and a negative predictive value of 94%. Thus, the CATIE schizophrenia study's use of a cutoff score on a capacity measure to screen for decisional incapacity proved to be efficient and ethically acceptable. Independent validation of MacCAT-CR subscale scores using the expert judgment method may provide a practical, evidence-based method for determining the categorical capacity status of schizophrenia research subjects. However, the validity of such a method depends on context-sensitive implementation with special attention to risk-benefit issues.

ASSOCIATION BETWEEN ATTITUDE TOWARD MEDICATION AND NEUROCOGNITIVE FUNCTION IN SCHIZOPHRENIA

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Introduction: A patient's attitude toward medication is important for medication adherence, which is a key determinant of outcome in schizophrenia. This study examined the association between attitude toward antipsychotic medication and clinical status, particularly neurocognitive function, in patients with schizophrenia. Method: Ninety-two patients meeting the DSM-IV criteria for schizophrenia participated in this study. The attitudes of the subjects toward medication were evaluated using the Drug Attitude Inventory (DAI). Clinical characteristics including psychiatric symptoms and side effects of medication were evaluated. Neurocognitive function was measured using the Mini Mental State Examination (MMSE) and a computerized battery consisting of the Digit Span Test (DST), Verbal Learning Test (VLT), Continuous Performance Test (CPT), Wisconsin Card Sorting Test (WCST), Finger Tapping Test (FTT), and Trail Making Test (TMT), parts A and B. The associations between attitude toward medication and neurocognitive function and clinical characteristics were analyzed. Results: The scores on the DAI were not significantly correlated with the clinical characteristics, such as psychopathology or neuroleptic-induced extrapyramidal side effects. Instead, the scores on the DAI were significantly correlated with the learning index, delayed free recall, and total recall on the VLT, the number of categories completed on the WCST, and omission and commission errors on the CPT; the scores were not significantly correlated with measures on the MMSE, DST, FTT, or TMT. Conclusion: Our findings indicate that a patient's attitude toward medication is associated with neurocognitive function. Specifically, verbal learning memory, executive functioning, and sustained attention were associated with attitude toward medication.

BRAIN ACTIVATION DURING AN ADAPTIVE EMOTION RECOGNITION TASK IN MEDICATED SCHIZOPHRENIA OUTPATIENTS: EVIDENCE FOR IMPAIRED AFFECTIVE PROCESSING

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It has been repeatedly reported that schizophrenia patients show impaired emotional face recognition. However, it still remains unclear whether this deficit is from emotional or cognitive origin.

Brain imaging studies produced inconsistent results. Some papers report reduced others increased activation of limbic structures during the processing of faces with emotional expressions assuming an emotional processing deficit. However, since patients and controls often also show performance differences, reduced activation might be a sub phenomenon of this lower task performance. On the other hand, increased activation might reflect the compensation of impaired processing in some structures. To overcome this shortcoming, we developed an adaptive emotion recognition task. We used pictures of faces where we systematically increased the intensity of the emotional expression by means of computer morphing methodology. During the task completion, the difficulty of the task was adapted to the individual performance level by increasing or decreasing the intensity. Neutral faces as well as faces with four different emotional contents (fear, pleasure, anger, and disgust) were presented to 20 schizophrenia outpatients and 20 matched healthy controls during a functional MRI experiment. As intended by the adaptive algorithm, the number of correct answers did not differ between groups. However, the mean intensity of the faces was slightly higher in the patient group. Analysis of brain activation revealed a reduced activation of limbic structures, namely the amygdala and the orbital frontal cortex in schizophrenia patients. These results are interpreted as reflecting an impaired automatic processing of facial emotional expressions in patients with schizophrenia leading to the observed deficit in emotion recognition.

SAFETY, TOLERABILITY AND PHARMACOKINETICS OF AN EXTENDED RELEASE FORMULATION OF AV965, A 5-HT_{1A} ANTAGONIST FOR COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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AV965 is a potent, selective, 5-HT_{1A} pure receptor antagonist. Animal behavioral experiments indicate 5-HT_{1A} silent antagonists can block or reverse cognitive impairment caused by 5-HT_{1A} agonists, scopolamine, and NMDA antagonists and can enhance performance in learning and memory tests. In addition, 5-HT_{1A} can promote the release of glutamate and acetylcholine. Thus, AV965 could be therapeutically useful for cognitive deficits in schizophrenia. Two randomized, double-blind, placebo controlled, Phase 1 studies were conducted in volunteers to evaluate safety and pharmacokinetics of single and multiple doses of AV965 as a liquid (AV965/NLS-101) or as an extended release (ER) tablet (AV965-102). Study 101 included 72 males and 8 females aged 18-45. Study 102 included 68 males aged 18-65 and 16 elderly males. Subjects were exposed to 5-60 mg once daily and 20-30 mg tid in Study 101 and 30-120 mg once daily in Study 102 for up to 14 days. AV965 single dose pharmacokinetics of the liquid were characterized by a rapid absorption and distribution phase, a long terminal half-life, a large volume of distribution, and generally dose proportional increases in C_{max} and $AUC_{0-\infty}$. Dosing with 60 mg of the liquid resulted in T_{max}, C_{max}, and $AUC_{0-\infty}$ of 1 h, 118 ng/mL, and 707 h*ng/mL, respectively. With the 60 mg ER tablet, dosing resulted in T_{max}, C_{max}, and $AUC_{0-\infty}$ of 5.8 h, 18.7 ng/mL, and 542 h*ng/mL, respectively. Compared to the liquid, for the ER tablet, absorption was delayed and C_{max} decreased to a greater proportion than $AUC_{0-\infty}$. Exposures remained dose proportional with the ER tablet. Food consumption slowed AV965 absorption (liquid and ER tablet) with inconsistent effects on C_{max} and $AUC_{0-\infty}$. C_{max}, T_{max}, and $AUC_{0-\infty}$ were consistently lower in females and higher in elderly males. AV965 was safe and generally well tolerated, using both liquid and ER formulations, in a total of 164 normal individuals. Most adverse events (AE) were mild or moderate and all were transient. CNS-related AEs (paraesthesias and dizziness) were the most frequent and generally dose-dependent. AEs occurred on the first day and decreased with subsequent dosing. No clinically relevant changes in vital signs, ECGs, lab assessments, or physical exams were observed. The ER formulation achieved the goal of reducing C_{max} while preserving overall exposure levels and will be used for studies in patients planned for 2007.

TRANSLATING BASIC RESEARCH ON EMOTION AND SOCIAL COGNITION TO SCHIZOPHRENIA: PROMISES AND PITFALLS

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Disturbances in emotion and social cognition are central to schizophrenia, and research over the last few decades has more clearly specified the nature of these disturbances. Many of these advances have come from research that has translated the approaches and methods from affective science and social psychology to the study of schizophrenia. In this talk, I will demonstrate how basic research on emotion and social cognition can further inform our understanding of the symptoms, course, etiology, and treatment of schizophrenia. To do so, I will review recent data, including my own, that illustrates both the promises and potential pitfalls of translational research approaches in schizophrenia.

THE EFFECTS OF A FATTY ACID AND ANTIOXIDANTS ON NEUROPSYCHOLOGICAL FUNCTIONING IN SCHIZOPHRENIA AND RELATED PSYCHOSES

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BACKGROUND: There is solid evidence of neuropsychological impairment in schizophrenia,covering areas like attention, working memory, learning, long-term memory and executive functions. There is also strong evidence of disturbed membrane phospholipid metabolism and increased oxidative stress in schizophrenia. The knowledge of the links between the neuropsychological impairments and the lipid/oxidative stress disorder is very limited.Also, the effects of fatty acids and antioxidants on cognitive functioning are largely unknown. The present study is part of a larger clinical trial. AIM: To investigate the effects of ethyl-eicosapentaenoic acid (EPA) and /or antioxidants(vitamins E+C) as add-on to antipsychotic drugs on cognition in schizophrenia and related psychoses. SUBJECTS: Forty-six acutely ill patients were included in a randomized, double-blind, 2 x 2 factorial,placebo controlled trial.Thirty-three of these patients were re-tested four months later. Twenty age and sex matched healthy controls were tested at both occasions. METHODS: The neuropsychological battery consisted of tests related to attention (Continuous Performance Test-IP and Stroop Color Naming Test), working memory (Paced Audi-

tory Serial Addition Test), verbal learning and memory (Hopkins Verbal Learning Test), visual memory (Kimura Recurring Recognition Figures Test) and executive functioning (Word Fluency). Data were analysed by means of a Linear Mixed Model programme (SPSS 12), taking into account RBC-polyunsaturated fatty acids (PUFA) at baseline. RESULTS: The two attention measures were significantly linked to treatment, whereas there were no significant associations between the other neuropsychological test variables and treatment. EPA impaired attentional capacity, based on the CPT-IP d'measure. Combining EPA and antioxidants improved it. The harmful effect of EPA was linked to lower PUFA levels. Antioxidant supplementation increased the difference between the conflict and the color reading condition of the Stroop Color Naming Task, thus impairing selective attention. The harmful effect of antioxidants was linked to lower PUFA levels. DISCUSSION: In keeping with symptom impairment shown in the larger trial, adding EPA or antioxidants alone impaired attention measures among patients with lower baseline PUFA. Interventional agents might have caused oxidative stress in these patients. This would impair the NMDA-receptor functioning and damage cellular membranes.

NEURAL MECHANISMS OF BACKWARD MASKING DEFICITS IN SCHIZOPHRENIA

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Introduction: Schizophrenia patients exhibit impairments in visual masking. The object-sensitive area in the lateral occipital lobe (LO) has been proposed as a critical area for the backward masking. In this study, we investigated the neural correlates of impaired visual backward masking in schizophrenia patients. Method: We examined the brain activations of schizophrenia patients and healthy controls during a visual backward masking task using a fast-event related fMRI design. We especially focused on three key visual areas: LO, the motion-sensitive area in the lateral occipital lobe (MT) and early visual processing areas (retinotopic areas, RET). We first identified these three areas using localizer scans in patients and healthy controls. Then we examined the activation of these areas in both groups during a visual backward masking task. In the masking task, we systematically manipulated stimulus onset synchronies (SOAs) while keeping the duration of stimulus and mask constant. Results: Both groups showed improved performance as the SOA increased (i.e., masking became weaker), but performance recovered more quickly in controls with increasing SOA. Regarding the brain activation for controls during the masking task, LO showed parametric increase of activation as the SOA got longer, but MT and RET did not. For patients, the parametric effect of SOA on the brain activity in LO was weaker compared with controls. Similar to controls, patients did not show parametric increase of activation in MT or RET. In addition, schizophrenia patients showed less overall activation in LO compared to controls across all SOAs, but groups did not differ in overall activation in MT or RET. Discussion: The observed parametric increase of activation in LO with increasing SOA is consistent with our previous finding of the critical role of LO in visual masking in normal controls (Green et al., 2005). The results from the current study suggest that dysfunctional LO is associated with impaired visual backward masking in schizophrenia.

ARE FACIAL INFORMATION RETENTION/INTEGRATION DEFICITS IN FIRST-DEGREE RELATIVES OF SCHIZOPHRENIA PATIENTS FURTHER EVIDENCE OF A VULNERABILITY MARKER?

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Schizophrenia patients are observed to produce abnormally 'restricted' visual scanpaths when viewing facial expression stimuli (Loughland et al, 2001), a finding which appears to be diagnostically specific to schizophrenia (Loughland et a., 2002). Healthy first-degree relatives of schizophrenia probands are observed to produce an attenuated form of the visual scanpath deficits seen in schizophrenia (Loughland et al, 2004), suggesting these disturbances may involve a familial transmission component. This NARSAD supported study explored whether scanpath deficits to faces in schizophrenia are associated with dysfunction in information sequencing or information retention/integration, and whether similar deficits might be observed in their healthy first-degree relatives. The pilot sample consisted of 25 schizophrenia, 13 first-degree relatives and 25 non-related healthy control subjects. Scanpaths were recorded while subjects viewed seven facial expression stimuli (happy, sad, neutral, fear, disgust, surprise, anger). In the information sequencing and information retention/integration tasks, a different face stimuli set were used depicting the same seven basic emotions, overlaid by a five-by-five tile matrix. In the sequencing task, subjects removed as few tiles as was necessary for them to identify the facial expressions. In the retention/integration task, removed tiles were immediately replaced as each new tile was selected. The results support previous findings in schizophrenia patients of a restricted visual scanpath strategy for viewing faces, characterised by fixations of longer duration and a shorter raw scanpath length. Disturbances were most apparent in patients for the angry face. In the sequencing and retention/integration tasks, first-degree relatives required significantly more tile removals (N=5) across both tasks than did either the controls (N=3) or patients (N=3), who did not differ from each other. However, with respect to accuracy, subjects differed from each other only in the retention/integration task, where patients and their relatives were twice as inaccurate compared to controls (21.1%, 19.5% vs controls=11.5%). This finding provides further evidence that visuo-cognitive disturbances, particularly with respect to the retention/integration of socially meaningful stimuli, may represent a vulnerability marker for schizophrenia.

ASSOCIATIONS OF MULTIPLE DOMAINS OF METACOGNITION WITH NEUROCOGNTION WITH SCHIZOHRENIA

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Metacognition refers to a range of abilities linked to persons' capacity to think about their own thinking and the thinking of others and involves a range of functions including those referred to as theory of mind and mentalizing. Research has suggested that persons with schizophrenia often experience deficits in metacogntion and that these deficits cannot be explained by a single symptom or global cognitive deficit. Links between metacognition and individual forms of neurocognition remain unclear. A limitation of research to date is that metacognition may contain many semi independent capacities and yet is often measured using single tests which cue persons to

make explicit judgments about laboratory tests. To address these issues we have developed an interview which spontaneously elicits persons' narratives of self and illness and rated these using the Metacognitive Assessment Scale (MAS), a scale which separately assesses self reflectivity, awareness of the mind of the other, decentration and mastery of problems. In the current study we present partial correlations comparing the MAS subscales ratings of these narrative with performance on select subtests of the Weschler Adult Intelligence Scale (WAIS III), the Weschler Memory Scale (WMS III), the Bell Lysaker Emotion Recognition Scale (BLERT) and the Wisconsin Card Sorting Test (WCST), controlling for insight as rated with the Scale to Assess Awareness of Mental Illness. Participants were 60 adults who completed the narrative interview, insight assessment and neurocognitive testing as part of their enrollment in a randomized trial of cognitive behavior therapy. MAS ratings were made blind to insight rating and test performance. Results revealed awareness of one's own thoughts and feelings was linked to performance on the WCST, BLERT, the Visual Reproduction subtest of the WMS III and the Arithmetic and Information subtests of the WAIS III. Performance on the Visual Reproduction was also linked to the Mastery and Decentration scales of the MAS. Results may suggest that neurocognitive deficits may be related to the ability to know one's own thoughts and feelings and that other deficits in other domains of metacognition have more complex origins. Implications for understanding psychosocial dysfunction are discussed.

ASENAPINE REVERSES ANHEDONIA INDUCED BY CHRONIC MILD STRESS BUT DISPLAYS NO HEDONIC EFFECTS IN AN INTRACRANIAL SELF-STIMULATION PROTOCOL

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We explored the effects of asenapine, a novel psychopharmacologic agent being developed for the treatment of schizophrenia and bipolar disorder, in chronic mild stress (CMS)–induced anhedonia in rats and in an intracranial self-stimulation (ICSS) protocol. In the CMS protocol, male Wistar rats trained to consume a 1% sucrose solution were divided into control and CMS groups for the 7-week trial. Both groups were subdivided to intraperitoneal treatment regimens: asenapine 0.06, 0.2, or 0.6 mg/kg twice daily; imipramine 10 mg/kg every day; or vehicle (n=8 per group). In the ICSS protocol, male Sprague-Dawley rats were trained to receive a stimulus via electrode implanted into the ventral tegmental area in response to pressing a lever. A variable interval 3-second schedule was used during extinction/reacquisition and rate-frequency training. Drug tests began after stability was achieved. An ascending rate-frequency protocol with 11 conditions (2 minutes each) was used, with the frequency increasing from 10 to 175 Hz. From the rate-frequency curves, the locus of rise (LOR) and maximal rate of responding (MAX) were calculated. Thirty minutes before testing, rats received subcutaneous treatment with asenapine 0.01, 0.03, 0.1, or 0.3 mg/kg (yielding exposure equivalent to the intraperitoneal doses used in the CMS protocol); cocaine 5.0 mg/kg as a positive control; or vehicle (n=7–8 per group). CMS caused a 34% decrease in sucrose consumption ($P<0.001$). Both asenapine and imipramine were inactive in controls but effective ($P<0.001$) in CMS animals, restoring sucrose consumption to control levels (from week 3 onward for asenapine 0.6 mg/kg twice daily; from week 4 for imipramine). In the ICSS protocol, asenapine 0.1 and 0.3 mg/kg significantly increased LOR (by 5% and 9% from baseline, respectively), and asenapine 0.3 mg/kg significantly decreased MAX (by 59% from baseline). In contrast, cocaine 5.0 mg/kg decreased LOR and left MAX unchanged. Asenapine was as effective as imipramine in decreasing CMS-induced anhedonia, and the ICSS data indicate that this effect was not due to an hedonic profile. These findings suggest that asenapine may have therapeutic utility in bipolar and other affective disorders.

THE COMPLEMENT SYSTEM AND SCHIZOPHRENIA: A HYPOTHESIS

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Complement is a crucial effector system of innate immunity and its activation generates opsonins, inflammatory mediators and cytolytic protein complexes, which are essential for the clearance of microorganisms, immune complexes and necrotic or apoptotic cells. Inappropriate or chronic complement activation is associated with host tissue damage. The roles of complement within the brain have not been studied in detail yet, but are likely to be the same as in other tissues. Recent observations implicate complement in novel, non-inflammatory functions in the brain, and provide a basis for further study of complement-mediated effects on neuroprotection and neurodevelopment. Activities of the complement activation classical and MBL pathways and their components in sera of schizophrenic patients (SP, n=150) vs. healthy subjects (HS, n=200) from the Armenian population have been evaluated using commercial kits (Wieslab, Lung, Sweden, COMPL CP310, MP320), different type of ELISAs and functional activity assays. Parametric and non-parametric statistics were applied to compare data obtained. In SP, the activities of the complement both pathways were increased significantly in comparison with HS. Genetic load, adverse embryonic events, and perinatal events are considered as a neurodevelopmental first hit that leads to schizophrenia vulnerability. The most frequently cited embryonic and perinatal factors include viral illness during the second trimester of pregnancy and perinatal brain damage. Here, the complement system probably plays its main role as a protector from microbial invasions and in clearance of damaged or altered cells. However, evidence for the neurodevelopmental model of schizophrenia includes findings of tissue loss, reduced cortical folding, and structural changes, which is regarded as a necessary neuropathological hallmark of neuronal degradation. These processes might include complement over-activation. Recent, longitudinal brain imaging studies indicate that progressive brain changes are more dynamic in schizophrenia than previously thought, with grey matter volume loss. In this context, from our data we might hypothesize that the complement system could have a dual role in schizophrenia: neuroprotective in aetiology and neurodegenerative in pathogenesis. Acknowledgement: KRM thanks the Royal Society-NATO for fellowship #16312/03B/LD.

REMEDIATION OF FACIAL AFFECT DECODING AND VISUAL SCANPATH DEFICITS IN SCHIZOPHRENIA

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People with schizophrenia are observed to have marked deficits in their ability to identify and discriminate between various facial

expressions of emotion (Loughland et al, 2002). These deficits are commonly interpreted as a dysfunction in the neurocognitive mechanisms that underlie face processing. Previous research by our group shows that people with schizophrenia display abnormally 'restricted' visual scanpaths to face stimuli and attend less to areas of greatest affective saliency (i.e., eye and mouth regions). This restricted visual scanpath strategy in schizophrenia is characterised by fixations of greater duration and a shorter raw scanpath length (Loughland et al, 2002, 2004). Recent research has explored the potential clinical utility of cognitive remediation to improve facial emotion perception in patients with schizophrenia (Penn and Combs, 2000). While the results of this approach are promising, no research to date has focused on the visuo-cognitive deficits that might underlie face perception deficits. This paper reports on the development of an extraocular muscle (EOM) proprioception task and research examining whether proprioceptive retraining of eye movements delivered using visual scanpath technology improves emotion perception in schizophrenia patients by assisting them to develop a more adaptive face viewing strategy. Subjects will be randomly assigned to one of two remediation groups (Group 1: proprioception retraining, Group 2: face perception retraining) for six, thirty minute weekly sessions. Post treatment follow-ups will be conducted at 1 and 6 months in order to explore the potential sustainability of gains made as a consequence of EOM proprioceptive retraining. It is predicted that EOM proprioceptive retraining will produce greater improvements in visual scanpath strategies to face stimuli and affect recognition accuracy than face perception retraining alone, and that these gains will be stable over time at 1 and 6 months post-treatment follow-up. The theoretical underpinnings of this unique line of enquiry will be presented, as will the novel methodology and EOM proprioceptive retraining stimulus proposed for this research. Clinical significance and preliminary findings will be discussed.

N-DESMETHYLCLOZAPINE DEMONSTRATES PRO-COGNITIVE ACTIONS IN EXPERIMENTAL MODELS

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Schizophrenia is characterized by hallucinations, delusions (positive symptoms), flattened affect, apathy and anhedonia (negative symptoms). Furthermore, it is now appreciated that a major determinant of functional impairment in schizophrenic patients is their cognitive deficits. Whereas modern antipsychotic drugs treat positive symptoms well, treatment of the negative symptoms and the cognitive deficits remain substantial unmet medical needs. Among currently available antipsychotic agents, clozapine has superior efficacy against negative symptoms and appears to be uniquely effective in improving cognitive function. Clozapine is metabolized to N-desmethylclozapine (NDMC) with significant inter-patient variability. A compelling case can be made that the metabolite NDMC accounts for the superior efficacy and pro-cognitive effect of clozapine. NDMC possesses pharmacological attributes predictive of superior antipsychotic activity, including dopamine D2/D3 receptor partial agonism, serotonin 5-HT2A inverse agonism, and muscarinic M1 receptor agonism. Further, in schizophrenia patients treated with clozapine, those patients with higher plasma levels of NDMC relative to clozapine experience better outcomes on positive and negative symptoms and exhibit improved cognitive function. Here, we demonstrate that like clozapine, NDMC is active in animal models predictive of antipsychotic activity (MK-801 and amphetamine-induced hyperactivity in mice). However, unlike clozapine, NDMC activates hippocampal MAP kinase, an action that is abolished in mice lacking the muscarinic M1 receptor. Moreover, we show that while clozapine impairs both novel object recognition (NOR) and performance in the radial arm maze (RAM), NDMC does not impair performance in either cognitive assay. Importantly, unlike clozapine, NDMC significantly improves performance in the RAM paradigm, indicating pro-cognitive actions. ACADIA is presently developing NDMC (ACP-104) as a novel treatment for schizophrenia.

EXAMINING DECLARATIVE MEMORY IN SCHIZOPHRENIA

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Schizophrenia is characterized by psychosis, affective symptoms, and diverse cognitive deficits. With respect to specific domains of cognition, deficits in declarative memory are among the best-characterized impairments in schizophrenics. Declarative memory is the aspect of human memory that encodes, stores, and retrieves facts (semantic memory) and experiences (episodic memory). Often declarative memory is invoked flexibly in the novel application of both semantic and episodic facts to scenarios that differ from the original learning environment. In this study we used a modified version of the Rutgers acquired equivalence task (AE) and a modified version of the Stanford conjunctive memory task (CM) to examine putative deficits in declarative memory in SCZ. We compared performances of four groups: schizophrenic volunteers who were on (SV-on) antipsychotic drugs (APDs), off (SV-off) APDs, the combination of both groups (SV-combined), and normal volunteers (NV). The AE was used to dissociate procedural and declarative memory processes, while the CM is currently being used to dissociate explicit and implicit memory processes. Results from AE are complete, and have demonstrated impairments in schizophrenia specific to declarative but not procedural memory, as performance between groups was comparable when remembering previously learned material (NV 98.5+/-2.7%; SV-ON 98.4+/-3.4; SV-OFF 97.2+/-3.5; p=0.82), but not comparable during the flexible use of information (NV 90.8+/-18.0; SV-ON 75.4+/-3.6; SV-OFF 48.7+/-34.4). Compared to NV, this impairment in SV information transfer just missed significance in SV-ON (p=0.056), but was highly significant in SV-off (p=0.003), evidence that APDs partially improve, but do not fully repair memory. During procedural learning, SV-combined required a significantly greater number of trials compared to NV in order to reach the training criterion of 95% (NV 18+/-20.8 trials; SV-combined, 43.8+/-50.8 trials; p=0.001). Results from the CM are not complete, but a similar trend is emerging from preliminary data showing that SV-combined performs worse than NV on explicitly learned sets of face-house pairs, and significantly worse than NV on implicitly related (unlearned) face-face pairs. In summary, results suggest that APD treatment can remediate impairments in declarative memory and that specific impairments in the flexible expression of declarative memory are consistent across cognitive tasks in schizophrenia.

ERPS FOLLOWING REWARD AND NON-REWARD IN SCHIZOPHRENIA OUTPATIENTS

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Recent models of attention suggest that dopaminergic inputs to the medial frontal cortex (MFC) provide a mechanism for the shifting of attention to motivationally relevant stimuli when task demands exceed the capacity provided by automatic processing. Thus, abnormalities of dopamine function in schizophrenia would be expected to interfere with the rapid assignment of motivational salience to ongoing events. Recent ERP studies have demonstrated an enhanced medial frontal negativity (MFN) following penalty/non-reward feedback compared to reward feedback in healthy subjects, consistent with the hypothesized role of dopamine cell function in processing of reward information. Following the work of Potts et al., we compared ERPs following stimuli that predicted reward and non-reward feedback in a sample of schizophrenia outpatients and psychiatrically healthy comparison subjects. Participants completed a passive S1/S2 task in which reward or non-reward was predictable on 80% of trials but deviated from expectancy on the remaining trials. Preliminary analyses from this ongoing study reveal that both groups exhibited an MFN in the 250-350 ms following stimuli predicting non-reward and a positivity in this latency range following stimuli predicting reward, suggesting that the MFC system in schizophrenia is appropriately responsive to the motivational significance of ongoing events. Further analyses will examine the integrity of this signaling system in a larger cohort of subjects and determine whether the amplitudes of these reward-related ERPs are related to symptoms in schizophrenia.

BRAIN REWARD SYSTEM DISTURBANCE IN PSYCHOSIS

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In order to investigate dopaminergic reward systems in psychosis, 14 patients who were experiencing current psychotic symptoms and 14 control volunteers performed an instrumental conditioning task with financial rewards in the MRI scanner. The task involved learning that various abstract stimuli were associated with differing probabilities of gaining reward. Both groups of subjects chose the stimulus most likely to be rewarded most frequently ($p=0.005$, controls; $p<0.04$, psychosis patients), indicating that both groups learnt the required associations. There was no significant difference between groups on choice behaviour. Within groups, participants responded more rapidly on trials in which there was a possibility of gaining a reward in comparison with neutral trials ($p<0.01$ both groups), providing evidence that participants found potentially rewarding stimuli motivationally salient. Psychosis patients responded more rapidly than control subjects to neutral stimuli ($p<0.05$), suggesting that they found such stimuli more salient than control participants did. Both groups showed ventral striatal activation on receiving a reward but patients showed greater activation in the head of the caudate nucleus. As regards the difference between rewarding feedback and neutral feedback, the controls showed greater midbrain ($P<0.001$) and ventral striatal ($P<0.01$) differentiation between these outcomes than did patients. We also fitted a computational model of reward prediction error to our data. This demonstrated greater differential physiological responses to reward and neutral prediction errors in the midbrain ($p<0.001$) and striatum in controls than in patients. In conclusion, in a simple test of incentive processing, there were behavioural and physiological differences between patients with psychosis and controls. One explanation for these results is that patients attributed motivational importance to stimuli which were objectively irrelevant, and that brain responses in psychosis are sensitized to rewards and to irrelevant stimuli, broadly supporting Kapur's aberrant incentive salience hypothesis. Funding provided by a UK Department of Health Research Capacity Development Award, the Wellcome Trust and Medical Research Council.

FARAMPATOR (ORG 24448), AN ALLOSTERIC AMPA RECEPTOR POTENTIATOR, IMPROVES A SUB-CHRONIC PCP-INDUCED DEFICIT IN WORKING MEMORY IN THE RAT

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Background: The NMDA receptor hypofunction hypothesis is increasingly being accepted as relevant to the aetiology of schizophrenia, particularly in explaining cognitive dysfunction (Olney 1999). Drugs that positively modulate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors, are now under study for potential amelioration of cognitive deficit symptoms of schizophrenia. Aim: To assess the ability of a novel AMPA receptor potentiator, farampator (ORG 24448), to improve a sub-chronic PCP-induced deficit in working memory using the novel object recognition-NOR-paradigm. Method: Female hooded-Lister rats received vehicle (n=10; i.p. twice daily) or PCP (n=40; 2mg/kg i.p. twice daily) for 7 days, followed by a 7-day drug-free period before drug treatment. Farampator (1, 3, 10 mg/kg) or vehicle was administered i.p 30 min prior to testing. Testing consisted of a 3min acquisition phase where rats explored two identical objects followed by a 1min intertrial interval. Then in the retention trial, rats explored a familiar and a novel object for 3min.The exploration time(s) of each object in each trial was recorded. Result: In the retention trial saline treated animals explored the novel object significantly more than the familiar object ($p<0.05$). This effect was abolished in the PCP-treatment group, but reinstated by farampator treatment ($p<0.05$). Conclusion: Farampator significantly attenuated the PCP-induced working memory deficit . These results suggest that farampator may have potential for the treatment of cognitive deficit symptoms of schizophrenia.

COGNITIVE FUNCTION IN CHILDHOOD AND EARLY ADULTHOOD WERE PREDICTIVE OF LATER SCHIZOPHRENIA IN A DANISH BIRTH COHORT

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Context: It has been suggested that lower cognitive function is a risk factor for schizophrenia and bipolar disorders. However, the mechanisms underlying these associations are unclear. Objective: This study examines the influence of cognitive function and change in cognitive function during adolescence on schizophrenia, schizophrenia like psychosis and bipolar disorders in adult life and explores possible mechanisms for any associations. Design: Cohort of men born in 1953 followed from 1972 until 2002 with psychiatric outcomes obtained from the Danish Psychiatric Central Register. Setting: Metropolitan area of Copenhagen, Denmark. Participants: 6

923 (all male) cohort members who had completed assessments of cognitive performance at ages 12 and 18 (the latter conducted as part of their conscription medical examination) and had complete data on all covariables considered in the analysis. Results: During follow-up 133 of the men were admitted to hospital and had a discharge diagnosis of schizophrenia or schizophrenia spectrum disorder. Cognitive function measured at both age 12 and 18 years was inversely associated with these disorders (unadjusted hazard ratio per standard deviation of cognitive function at age 12: 0.87 (95%CI: 0.75, 1.05) and at age 18: 0.72 (95%CI: 0.60, 0.86)). Adjustment for birth weight, social circumstances during childhood, indicators of social integration and educational attainment at age 18 years changed these associations only slightly. When cognitive function measured at age 12 and 18 were entered in the same model only the latter was inversely associated with risk of schizophrenia or schizophrenia spectrum disorder. A one standard deviation decline in cognitive function between age 12 and 18 was associated with an increased risk of schizophrenia spectrum disorder (1.32 (95%CI: 1.01, 1.75)). Conclusions: We found inverse associations between cognitive function measured at ages 12 and 18 and adult risk of schizophrenia. The association with cognitive function assessed at 18 years were stronger than those measured at age 12 and a relative reduction in cognitive function between age 12 and 18 was associated with greater risk of schizophrenic disorders suggesting that a reduction in cognitive function may be an early symptom of these disorders.

RECONCEPTUALIZING THE NATURE AND PROGRESSION OF ATTENTIONAL DEFICITS IN SCHIZOPHRENIA: DUAL-TASK INTERFERENCE IN PRODROMAL, FIRST EPISODE, AND CHRONIC PHASES OF SCHIZOPHRENIA

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Attentional deficits are core features of schizophrenia that clearly contribute to functional outcome. The underlying processes and the progression of these deficits remain ambiguous. The attentional dysfunctions have been attributed to limitations in availability or allocation of processing resources that are not specific to type of elementary cognitive process. However, another prominent possibility that has not been previously examined in schizophrenia is that structural processing bottlenecks result in an inability to carry out certain elementary cognitive operations in two tasks simultaneously. Using a multitasking paradigm drawn from cognitive psychology (the psychological refractory period experiment), we are testing the contrasting predictions of these two models in prodromal, first episode, and chronic phases of schizophrenia. Manipulations that separately prolong perceptual, response selection, and response production processes are being used to evaluate the location and extent of structural processing bottlenecks. Findings indicate that slowing in response selection processes interferes with dual-task performance in schizophrenia in a manner that is consistent with a central structural bottleneck. Some measures of dual-task interference show amplified interference in patients, consistent with slower response selection processes. Dual-task interference associated with response production processes also appears to be exacerbated in schizophrenia. The amplified dual-task interference at response selection and response production locations is only mildly present in prodromal patients, becomes more prominent in first episode patients, and appears most severe in chronic schizophrenia patients. Several components predict functional outcome, including overall response time, interference in response selection processes, and slowed response production, particularly in first episode patients. These initial results encourage the further isolation of sources of schizophrenia attentional dysfunction in specific patterns of interference with simultaneous processing. The progression of deficit severity suggests that these cognitive processes may contribute to illness onset and that their impact on functional income may increase from prodromal to first episode periods. These hypotheses will be examined in ongoing longitudinal components of these studies.

MK-801 DISRUPTED ATTENTIONAL PERFORMANCE IN A LATERALIZED REACTION TIME TASK IN RATS – A VALID MODEL OF SCHIZOPHRENIA?

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Attention (or vigilance) is one of the critical domains of cognition that is disrupted in schizophrenia as identified within the MATRICS (Measurement And Treatment Research to Improve Cognition in Schizophrenia) initiative. In the present study, acute N-methyl-D-aspartate (NMDA) receptor antagonist administration, was used to model and induce attentional disturbances of schizophrenia in a lateralized reaction time task (LRTT) paradigm in rats. The LRTT assesses an animal's ability to attend to and detect brief target stimuli. Male Lister Hooded rats were trained to sustain nose pokes of variable durations in the center aperture. After completion of a sustained nose poke, one of four apertures was illuminated after which a nose poke in the lit aperture resulted in a reward (food pellet) and was scored as a correct response (choice accuracy). MK-801 administration (0.08-0.12 mg/kg, s.c.) disrupted attentional performance by reducing choice accuracy and increasing premature or anticipatory responding. Specifically, MK-801 dose-dependently impaired choice accuracy in a manner that interacted with the duration of the target stimuli, as rats were only impaired at the briefest stimulus durations, 0.1 and 0.2 s, respectively. Neither the atypical antipsychotic clozapine (1.3 mg/kg, s.c.) nor the newer antipsychotic aripiprazole (0.31 mg/kg, s.c.) was able to reverse the MK-801 (0.10 mg/kg)-induced attentional deficit. The doses of clozapine and aripiprazole were without effect on attentional performance themselves based on dose-response relations, however, in a range known to produce antidopaminergic effects. Since existing antipsychotics, including clozapine and aripiprazole, have either no or minor beneficial affect on cognitive function in schizophrenia patients, the present paradigm mirrors this clinical unmet need in terms of predictive validity. Therefore, the LRTT paradigm potentially offers the opportunity to discover therapies superior to existing treatment, and future testing of potential novel cognition enhancers is warranted.

SCHIZO-OCD SHOW DIFFERENT COGNITIVE ERP COMPARE TO OCD AND SCHIZOPHRENIC PATIENTS

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Several studies show that OCD and schizophrenia coexist more often than one would expect. It has been suggested that Schizo-OCD

patients may have a subtype of schizophrenia with distinct pathophysiology, treatment response and clinical course. With regard to cognitive functioning, studies on specific deficit produced conflicting results. In Schizo-OCD patients, we can potentially expect to have unique pattern of neurocognitive tasks, an interaction between schizophrenia and OCD, or a simple combination of two. We propose a preliminary study which consider visual ERP' pattern of Schizo-OCD patients, compared to OCD and Schizophrenic patients without OCD symptoms. We used Discriminative Response Task (DRT), which consist on a visual go/no-go paradigm. This task was applied to 11 schizo-OCD patients, 16 OCD patients, 14 schizophrenic patients, and 12 age-matched normal controls, assessed on SCID-CV and Y-BOCS. Our results seem to confirm the hypothesis that Schizo-OCD may be considered a separate cognitive-ERP entity compared to schizophrenic patients. Actually Schizo-OCD patients show distinct ERP profile compared to both schizophrenic without OCD and OCD patients. Particularly Schizo-OCD have larger amplitude in non-target condition than in target condition (like normal subjects), with target P3 amplitude higher than normals in Fz ($p<0,02$) - similar to OCD patients – and non-target P3 amplitude lower than normals in Fz ($p<0,007$), Cz ($p< 0,007$), Pz ($p<0,006$), as the group of Schizophrenic patients. Schizophrenic without OCD have longer latencies and smaller amplitudes compared to the other three groups, demonstrating that Schizo-OCD are not the worst group in terms of cognitive resources recruitment.

UTILITY OF INTERACTIVE CONSENT PROCESS FOR IMPROVING UNDERSTANDING OF RESEARCH PROTOCOLS

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The purpose of this study was to evaluate the utility of an interactive consent process (embedding a brief questionnaire within the process of reviewing research consent forms) with patients considering enrollment in a clinical research study. We linked this consent project with a study of a medication adherence program for middle aged and older patients with schizophrenia (n=63), a study of a cognitive rehabilitation program for older patients with schizophrenia or related psychoses (n=20), a type-2 diabetes clinical drug trial (n=13), and a study of exercise in patients with knee osteoarthritis (n=10). For each protocol we developed a 5-item questionnaire to evaluate participant understanding of key information relevant to informed consent for that trial (generally corresponding to the purpose, procedures, risks, benefits, and voluntary nature of study participation). Administration and scoring of the questionnaires was embedded into the process of reviewing the formal consent forms with each potential participant, e.g., after reading the paragraph regarding the purpose of the protocol with a participant, the person administering the consent paused to evaluate the subject's comprehension of that information. Whenever a subject's response suggested less than adequate comprehension, the relevant information was re-explained, and then comprehension was re-evaluated, with up to two re-explanations. Regardless of patient population or protocol type, a vast majority of participants exhibited adequate understanding of the voluntary nature of research participation after a single explanation. However, for the other four queried elements, at least one re-explanation was generally necessary before 90% or more of the subjects demonstrated adequate understanding. Regardless of protocol type, however, by trial 3, all but one participant manifested adequate comprehension across all five evaluated elements. These results illustrate the importance and efficacy of an interactive consent process, wherein participants' understanding of essential information is queried and re-explanation is provided where needed.

ELEVATED HOMOCYSTEINE ASSOCIATED WITH POORER COGNITIVE FUNCTIONING IN EARLY PSYCHOSIS

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Background: Impaired cognition in neuropsychiatric patients with disorders such as dementia and Alzheimer's disease has been linked with high homocysteine levels. Cognitive dysfunction and, more recently, elevated homocysteine have been identified in individuals with schizophrenia, however there has been limited research investigating their relationship. The aim of the current study was to examine this relationship in a sample of First Episode Psychosis (FEP) patients. Method: Patients aged 15-25 years were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC) at ORYGEN Youth Health. Participants consented to a randomised controlled trial investigating the homocysteine-lowering effects of a B-complex vitamin (folate, B12 and B6) and its effect on cognition. A total of 120 patients were randomised to either the vitamin condition or placebo. Blood samples were taken at baseline and following a 12-week trial period to determine homocysteine levels. The MATRICS 'candidate' neuropsychology test battery was administered at baseline, week 6 and week 12 to assess cognitive performance. Factors potentially influencing homocysteine levels including dietary vitamin intake and methylenetetrahydrofolate reductase (MTHFR) polymorphisms were assessed via Food Frequency Questionnaires and genetic analysis of blood samples, respectively. Results: A significant relationship was found between elevated homocysteine levels and poorer cognitive functioning in the domains of visuospatial ability, speed of processing, visual learning and memory, verbal learning and memory and executive functioning. Conclusion: Elevated homocysteine levels seem to be linked to impairments across a number of cognitive domains in FEP. Genetic variations of MTHFR can lead to elevated homocysteine levels, therefore results on the relationship between MTHFR C677T polymorphisms and cognitive performance in this sample will be presented (genetic blood samples currently await analysis). As vitamin dietary intake may also influence homocysteine levels, dietary data from Food Frequency Questionnaires is currently being examined. Homocysteine-reducing agents such as folate may act to improve cognitive functioning and perhaps ameliorate cognitive dysfunction if administered in the early stages of the illness.

NEURAL CORRELATES OF IMITATION IN SCHIZOPHRENIA: IMPLICATION FOR ACTION UNDERSTANDING AND SOCIAL COGNITION

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BACKGROUND. Schizophrenia (SZ) is associated with difficulties in generating and guiding behavior by internal representations. Mental representation of others' actions, intentions and emotions form

the core of social understanding. A neural mechanism (mirror neurons) has been proposed to account for action understanding and imitation in primates. Human mirror mechanism is mediated by a mapping of the observed action and its motor representation in the circuit that includes the inferior frontal and parietal cortices, structures that are heavily implicated in schizophrenia. METHOD. We examined imitation ability in relation to internal representation and frontal cortical mechanism. SZ and matched controls (NC) were asked to imitate lip movements, manual gestures and facial expressions of others. Connectivity of the white matter tracts was examined by DTI using indices of fractional anisotropy (FA) and mean diffusivity (D). In addition, we examined frontal cortical activation during gesture imitation using near-infrared optical tomography (NIROT). RESULTS. SZ showed significant deficits on all imitation tasks even though they could correctly identify the acts. Imitation accuracy was correlated with verbal working memory (another index of internal representation). Facial expression imitation deficit was associated with reduced social functioning. DTI data showed that both gesture and lip imitation accuracy scores were correlated with FA in the left frontal cortex. NIROT data showed greater frontal activation during imitation in NC than in SZ. These results suggest that reduced white matter integrity and activation of the frontal cortex in SZ are related to their imitation performance. DISCUSSION. Imitation requires internal representation and simulation of others' actions and is important for all forms of learning including language acquisition and social behavior. Imitation errors and their relation to working memory deficit in SZ suggest that generation of internal representation and mirror mechanism may be linked to abnormal social cognition in SZ and that altered frontal cortical connectivity may contribute to deficits in mapping observed action to its representation.

EXPLORING ACTION MEMORY IN SCHIZOPHRENIA: INTERACTIONS BETWEEN SOURCE MONITORING AND THE ENACTMENT EFFECT

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In everyday life, we perform hundreds of actions for which we have strong episodic memory recollection. Laboratory studies have shown that performing actions, compared to reading action sentences, improves the recall and recognition of those actions, a phenomenon dubbed the enactment effect. We have adapted an action memory paradigm in order to examine in a population of schizophrenia outpatients: A) the enactment effect; B) and source monitoring for actions (capacity to distinguish externally-driven from internally-generated actions). Based on the experimental and theoretical literature, we hypothesized that 1) patients would greater benefit from the enactment effect, particularly among those with prominent negative symptoms; and 2) patients would show an acute source-monitoring deficit, particularly among those with prominent positive symptoms. We compared 28 medicated, chronic outpatients matched to a group of control subjects matched on age, SES, and language. Current symptoms were assessed by SANS, SAPS, and BPRS. 84 real common objects were presented successively in front of participants, accompanied by a sentence describing an action and read outloud by participants. Each action was either a) enacted by the participants (self-performed); b) enacted by the experimenter (externally-performed); or c) not enacted by anyone (control condition). We assessed retrieval first with a cued-recall condition, which consisted in presenting again the objects (interleaved with 15 never-studied objects) and in asking subjects to perform the action associated to the object. This step was immediately followed by a four-choice action recognition, and by a source-monitoring test. The most interesting result was the significant difference of source attribution when participants did not recall the action. Schizophrenia subjects, compared to healthy participants, were biased in attributing the source of actions to the experimenter instead of attributing it to the control condition. While the group difference for memory performance was significant, the effect size was moderate, and no significant group difference was observed for the recall of self-performed actions. Interactions with the current symptomatology of the patients will also be explored. These results highlight the importance of exploring memory deficits in schizophrenia to a better understanding of the cognitive processes underlying the symptoms of people with schizophrenia.

DEVELOPING TRANSLATIONAL PARADIGMS TO STUDY EXPLORATORY BEHAVIOR IN NEUROPSYCHIATRIC DISORDERS

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In this study we differentiate between the exploratory behavior of acutely decompensated schizophrenia (SZ) and psychotic bipolar disordered (BD) patients using a human paradigm analogous to the widely used rodent "open field". The human open field is a room in an inpatient psychiatric ward containing a desk, file cabinet, bookcase, 10 engaging objects, and no chair. The subject is asked to wait in the room and is monitored for 15 min. As in our rodent Behavioral Pattern Monitor, we quantify both the amount of the subject's exploratory behavior and the sequential patterns of the behavior. Motor activity levels are measured continuously at a high frequency by an accelerometer embedded in a vest (LifeShirt System,Vivometrics), enabling the differentiation of unpredictable (entropic) from predictable (perseverative) motor patterns. In validation studies using scripted movements, the inverted U-shaped response curve of the dynamical entropy as a measure of perseverative behaviors was orthogonal to measures of the amount of motor activity and analogous to the inverted U-shaped amphetamine dose responses obtained using comparable measures in rodents. Using digital video recording, the subject's interactions with the objects are scored offline and the spatial locations of the subject's center of mass in the environment are sampled at a high frequency (Clever Systems). The x-y coordinate sequences are analyzed using non-linear approaches that generate the spatial d exponent and inform us about the structure of spatial patterns of movement. Results indicate that, relative to healthy controls, SZ patients exhibit a marked reduction in object interaction and exploration, while BD patients exhibit increased object interactions, increased activity, and altered distributions of time spent in different areas. Both SZ and BD patients show reduced complexity in spatial patterns of movement. Thus, SZ and BD patient groups exhibit different behavioral profiles, even during highly psychotic states when they may otherwise be indistinguishable. This paradigm offers an innovative approach to recording exploratory activity in a novel environment, using procedures and multivariate assessments that have been validated in extensive studies of open field behavior in rodents. Studying inhibitory deficits using a cross-species translational approach may be helpful in uncovering neurobiological substrates and genetic bases of psychiatric illness. Supported by MH071916.

ERROR PROCESSING IN SCHIZOPHRENIA: THE ROLE OF WM LOAD

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We investigated whether patients with schizophrenia (SZ) are able to process both positive and negative feedback successfully in a reinforcement learning task. Impairment in one or both of these processes would be consistent with current theories of reward-processing, which attribute reinforcement learning ability largely to midbrain dopamine function, known to be disrupted in SZ. Forty patients with SZ and 31 healthy control subjects completed our computerized learning task. In this task, a modification of the Wisconsin Card Sorting Test, subjects sort stimulus cards by pointing with a computer mouse to a key grid displaying four feature dimensions (rows: form, color, number and background shade) each with four levels (columns: e.g., red, blue, green and yellow). When the subject chooses a dimension for a match, feedback is delivered visually: "+ 2 cents" or "- 2 cents." Subjects sort 42 six-card decks in two conditions (21 decks per condition). Positive-feedback decks test subjects' ability to persist with rewarded behaviors by making a win-stay response once, twice or three times consecutively. Negative-feedback decks test subjects' ability to change penalized behavior by making lose-shift responses to eliminate one, two or three of the four possible sorting rules. Patients' performance was similar to the control group on the positive feedback decks but poorer on the negative feedback decks. However, on the negative feedback decks, the accumulation of negative feedback restricted the ability of subjects in both groups to eliminate possible sorting dimensions, creating a kind of working memory load effect. That is, neither group had particular difficulty using one instance of negative feedback to arrive at a second dimension. Both groups found it more difficult to use two instances of negative feedback to arrive at a third dimension, and here patients were significantly worse than controls. Finally, both groups found it most difficult to use three instances of negative feedback to arrive at the fourth dimension and, again, patients were significantly worse than controls. Performance on this modified card sorting task suggests that individuals' use of negative feedback to guide behavior may be mediated by the memory demands of incorporating multiple instances of feedback, and that this interaction is more pronounced in patients with SZ. This work was supported by NIMH 1 R24 MH072647-01A1 (Gold, PI).

SELF MONITORING, AGENCY AND EXECUTIVE CONTROL IN SCHIZOPHRENIA: ONE GENERAL COGNITIVE DEFICIT ?

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Objective: The aim of this study was to explore whether disordered agency, which relies on self monitoring, could depend on a more general executive deficit in subjects with schizophrenia. Method: 15 DSM-IV schizophrenia patients and 15 matched healthy subjects were administered a computerized action recognition task. Subjects had to make a movement with the mouse which can be seen on a computer screen, but without seeing their own hand. Temporal and angular biases were randomly introduced in the movement on the screen, so that there was a discrepancy between the movement made by the subject and the movement on the screen. After each trial, subjects were asked whether the movement they saw was their own (agency judgement). The task gradually increased in complexity to add executive burden: first, in inhibition, second, in working memory and third in both of them. Results: Patients with schizophrenia neither made more movement errors than healthy controls, nor had longer initial reaction time but were significantly longer in executing the movement. Patients with schizophrenia were globally more impaired in the action recognition task than normal controls. However, executive burden did not increase action recognition errors in schizophrenia patients, whereas it did in normal controls. Conclusion: Our results suggest that executive control and action recognition share some common cognitive processes in normal functioning. However, these two functions appear to be more separated in schizophrenia. From a therapeutic perspective, our results also suggest that cognitive interventions aimed at enhancing executive control and sense of agency should be differentiated.

EARLY VISUAL PROCESSING IN SCHIZOPHRENIA: UNDERLYING STRUCTURE OF VISUAL MASKING PARAMETERS

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Schizophrenic patients consistently demonstrate performance deficits on visual masking procedures. In visual masking, the subject's ability to process a target stimulus is reduced by another stimulus (mask) presented either before (forward masking) or after (backward masking) the target. Several experimental paradigms have been used to study visual masking in schizophrenia. Most early studies have used high-energy masks (i.e., the mask is stronger than the target) and spatially overlapping target and mask. More recently, studies have begun to employ relatively weak (i.e., low-energy) masks, as well as masks that surround, but do not spatially overlap, the target. These paradigms typically produce non-monotonic (U-shaped) functions that demarcate the minimum as the point of the strongest masking effect. Despite the theoretically plausible distinctions among the various paradigms, it remains unclear whether these procedures provide different information regarding visual processing deficits in schizophrenia. The purpose of the present study was to address this issue by examining the underlying structure of visual masking parameters, based on theoretical distinctions among physiological processes involved in these procedures. Data for forward and backward masking components of four masking conditions (target location and identification with a high-energy mask, target identification with a low-energy mask, and target identification with equal energy paracontrast/metacontrast) was collected from 127 patients with schizophrenia and 100 normal controls. Based on the aforementioned distinctions, we compared four models of visual masking using structural equation modeling. Although high zero-order correlations were found among the masking parameters, a four-factor model, in which factors were separated on the type of response (target location and identification), the shape of the function (monotonic and non-monotonic), and the overlap of the stimuli (overlapping and non-overlapping), provided the best fit for the data. The pattern of results was virtually identical for patients and controls. These findings suggest that the four masking procedures used in this study may tap unique effects on visual processing and are not redundant. The results also support distinctions in the mechanisms underlying performance on these measures.

ANTIPSYCHOTICS EXACERBATE IMPAIRMENT ON A TRANSLATIONAL WORKING MEMORY TASK IN FIRST-EPISODE SCHIZOPHRENIA

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Working memory impairments are an established cognitive feature of schizophrenia, yet it remains unclear what component operations of working memory are abnormal in the illness and how they are affected by antipsychotic treatment. This study sought to replicate previous findings of worsened performance on a translational spatial working memory task among first-episode schizophrenia patients after antipsychotic treatment and to extend these findings to examine whether a disturbance in covert attention contributes to patients' impairments. Fourteen antipsychotic-naïve schizophrenia patients performed an oculomotor delayed response task before and 6-weeks after treatment with risperidone (n=11)or olanzapine(n=3). The oculomotor delayed response task is a translational paradigm used to examine the 'online' maintenance of spatial location information in working memory for brief periods of time. Over the delay period during which subjects were required to maintain spatial location information in working memory, visually distracting stimuli were presented at varying frequencies so as to direct attention away from the remembered peripheral location. Fifteen matched healthy individuals were studied in parallel. Patients were less accurate than healthy individuals at remembering spatial location information and increasing covert attention away from remembered locations during delay periods had a greater adverse impact on patients' performance. Moreover, patients' impairments in remembering spatial location information were greater after treatment. This worsening of patients' performance after treatment occurred in the context of clinical improvement and minimal extrapyramidal side effects. Consistent with previous findings, patients' pretreatment deficits on an oculomotor delayed response task were exacerbated by antipsychotic treatment. Impairment of selective attention supporting working memory may contribute to these deficits. Animal studies suggest that alterations in prefrontal dopaminergic systems or thalamocortical drive following antipsychotic treatment may account for our findings.

DISFUNCTIONS OF MEMORY AND SUBJECTIVE STATES OF AWARENESS THAT ACCOMPANY RECOLLECTION IN PATIENTS WITH SCHIZOPHRENIA

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Memory is one of the most impaired cognitive functions in schizophrenia. Its deficits involves mainly the central executive of working memory and episodic memory. Episodic memory can be assessed taking into account the states of consciousness that accompany recognition. One of them is conscious recollection, the other is feeling of familiarity. There are clues suggesting that recognition with conscious recollection is impaired in schizophrenic patients. Different variables, including level of information processing, affect in distinct ways the states of awareness in healthy volunteers, suggesting that they are based in distinct cognitive processes. The main aim of this work was to evaluate comparatively schizophrenic patients to healthy volunteers concerning episodic memory, with emphasis on the states of awareness that accompany recollection, and working memory. Besides, the intention was also to verify whether there is correlation between both kinds of memory. 20 schizophrenic patients and 20 healthy volunteers paired by age, sex and schooling took part in the study. Episodic memory was assessed through a recognition task, with self-evaluation of states of awareness and free recall. Level of processing effect was assessed through instructions associated to words of the recognition task ("Make a Sentence" or "Count the Letters"), which knowingly imply a differentiated information handling. The central executive was assessed through the double task. The groups have not differed on intelligence evaluation. Patients had worse performance in recognition and free recall tasks. In recognition task, the difference between groups has occurred exclusively due to a higher rate of recognition, accompanied by conscious recollection among the healthy volunteers. Both groups have shown level of processing effect, but it was less marked among patients. There was no difference between groups concerning working memory task, or correlation between performance in double task and episodic memory tasks. Level of processing effect in patients was evidenced, though less clear than in healthy volunteers. Also, there was no correlation between performance in double task and episodic memory tasks. These results may have implications for therapy and for research in schizophrenia and cognition. Patients with schizophrenia may benefit from cognitive rehabilitation interventions that take into account the cognitive profile showed by these patients.

COMPARISON OF THE IN VITRO PHARMACOLOGY OF N-DESMETHYLCLOZAPINE (ACP-104) WITH OTHER ATYPICAL ANTIPSYCHOTIC AGENTS

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Antipsychotics produce their specific efficacy and side effect profiles by interaction with multiple receptors in the central nervous system. Interaction with dopamine D2 receptors is a central feature in the activity of most of these drugs. However excessive inhibition of D2 receptors can also lead to extrapyramidal side effects and impairment of cognitive function. Interactions with other receptors such as the 5-HT2A receptor may contribute to an increased efficacy and tolerability of some agents while interactions with other receptors such as histamine, alpha adrenergic and muscarinic may also impact the therapeutic and adverse effect profiles of these agents. Here we summarize the receptor profiles of several commonly used antipsychotic agents as well as that of N-desmethylclozapine, the principal active metabolite of the antipsychotic clozapine. This metabolite (termed ACP-104 in the context of a potential therapeutic agent) has unique pharmacological features that suggest antipsychotic activity with improved efficacy and tolerability (1-4). First, like most all other antipsychotic agents ACP-104 is a dopamine receptor ligand. However, in contrast to

all other antipsychotic agents except for aripiprazole, it is a dopamine D2 /D3 partial agonist. Secondly, like several other antipsychotic agents, ACP-104 is a high affinity 5-HT2A antagonist (inverse agonist). The 5-HT2A / D2 affinity ratio of ACP-104 is similar to clozpaine and is more favorable than that of most other antipsychotic agents. It is notable that while ACP-104 shares with aripiprazole the desirable attribute of D2 partial agonism, ACP-104 is distinct from aripiprazole in that while ACP-104 is a 5-HT2A antagonist, aripiprazole is a 5-HT2A partial agonist. Moreover, in contrast to all other antipsychotic agents, ACP-104 has been found to be a muscarinic M1 receptor agonist suggesting a potential for superior effects on cognitive function - a prediction that is being born out in preclinical studies (5). In addition, ACP-104 has lower affinity for alpha adrenergic and histamine H1 receptors suggesting a lower potential for weight gain, sedation and orthostatic hypotension. (1) Weiner et al. Psychopharm 177: 207-216, 2004 (2) Burstein et al. J Pharmacol Exp Ther 315(3): 1278-1287, 2005 (3) Sur et al. PNAS 100: 13674-13679, 2003 (4) Spalding et al, Mol Pharm, published online Sept 7, 2006 (5) McFarland et al., poster presented at this meeting

THE DOT PATTERN EXPECTANCY TASK AS A MEASURE OF SCHIZOPHRENIA LIABILITY

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Both patients with schizophrenia and their unaffected relatives have been shown to demonstrate impairments in context processing—the ability to represent and maintain task-relevant information in order to guide subsequent cognitive processing. MacDonald et al. (2005) recently reported that a new task, the dot pattern expectancy task, offers a rapid means of assessing this construct, and was sensitive to impairments in both patients and their relatives. We present preliminary evidence from an ongoing family study that supports this claim. A total of 37 patients with schizophrenia, 30 non-psychotic first-degree relatives of patients, and 20 healthy controls have been tested to date. The task involves a total of 80 trials and requires approximately 15 minutes to complete including instructions. The test is an AX CPT where stimuli are Braille letters. A Braille L represents "A" and a Braille H represents "X". Subjects are asked to make a target response to a specific letter sequence (X following an A), and a non-target response to all other stimuli. Targets are present on 70% of trials. Lures consisting of a BX make up 12.5% of the trials, lures consisting of an AY make up 12.5% of the trials, and BY lures make up 5% of trials. Deficits were hypothesized to be shown as increased errors of omission on AX target trials as well as increased false alarms on BX lures. Both patients and relatives demonstrated marked deficits on the task: D' context of 3.3, 1.8, and 2.3 in controls, patients, and relatives, respectively; and BX false alarm rates of 13, 39 and 32%, respectively. Patients showed a significantly elevated target omission rates (12%) compared to 6% in relatives and 4% in controls. The sensitivity of the task likely stems from two sources: 1) like letter versions of the context CPT, the X target stimulus elicits deficits in inhibiting proponent responses; 2) the unfamiliar Braille stimuli demand a degree of precision in working memory representation that is not required by letter versions of the task. These preliminary data strongly support the use of the dot pattern expectancy task as a marker of schizophrenia liability.

DYNAMICAL GLUTAMATERGIC CORTICAL CONTROL OF DOPAMINE-MEDIATED ACTION SELECTION SUGGESTS MEDICATION EFFECTS FOR SCHIZOPHRENIA: A COMPUTATIONAL APPROACH

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Deficits in glutamatergic efficacy are implicated in many genetic and pharmacological studies investigating schizophrenia. Adopting a computational modelling approach, we propose a mechanism whereby background glutamatergic cortical activity modulates tonic striatal dopamine (DA), investigate subsequent effects on behaviour, and explore its applicability to fMRI. Gurney et al's large-scale basal ganglia model of action selection [1] was adapted to include substantia nigra pars compacta (SNc). Operating along functional channels, winning actions are gated at the expense of suppressed losers, according to each channel's salience. This process is modulated by striatal DA, whose levels were dynamically altered via SNc by cortical excitation, and inhibited by striatum and pallidum [2]. The effects of antipsychotic medication were investigated by varying D2 receptor efficacy. Simulations showed that decreased cortical activity lead to DA elevations. This counter-intuitive finding was due to decreased subthalamic activity, which quietened pallidum and thus disinhibited SNc. Acting to increase gain levels, elevated DA compensated for diminished salience-related activity, lowering selection thresholds. Grossly deficient cortical activity reduced DA. Whilst DA was maximally elevated, the selection threshold fell below background cortical activity levels, leading to spurious selection. This overcompensation was countered by D2 antagonism, simultaneously making low-level competitions easier to resolve, though at excessive levels such benefits were erased. We propose that glutamatergic deficits in schizophrenia give rise to negative symptoms, and may engage this compensation mechanism, allowing otherwise difficult selections to occur. Further decreases in cortical activity - perhaps due to environmental factors or excessive synaptic pruning - would lead to overcompensation, and subsequent spurious selection may underlie elements of positive symptomatology. Medication counters this by raising the selection threshold, though if taken to excess can lead to negativity in itself. Given matched selection behaviour, the model can provide predictions of subcortical functional activation, potentially allowing for discrimination between "purely" negative and overmedicated patients. We are now planning to test these predictions in a series of fMRI studies. Funded by the Neuroinformatics DTC (EPSRC/MRC grant). 1.Gurney Biol Cybern 84;6,401-10. 2.Floresco Nat Neurosci 6;9,968-73

THE IMPACT OF TRAINING ON RELATIONAL LEARNING IN SCHIZOPHRENIA

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Objectives. The aims of these studies are: (1)To characterize relational learning using a transverse patterning (TP) problem in schizophrenics and healthy controls;(2)To increase relational learning success in schizophrenics through training; and (3)To investigate neural plasticity associated with different stages of relational learning and memory. Methods. Twenty patients with schizophrenia and 20 healthy controls participated in the behavioral study. Subjects first

performed the standard version, which consisted of 2 conditions, simple discrimination (SD) and TP. TP requires the subject to learn the relationship among three overlapping items. SD served as the control condition and requires the subject to learn the correct item in each of 3 non-overlapping paired items. Subjects then completed a stepwise training version of the TP task. Schizophrenic subjects were assessed with standard psychiatric symptom ratings. Neuroimaging studies are ongoing and consist of (1) fMRI scans during initial TP learning and following 1 week of training; (2) single-voxel 1H-MRS to assess markers of neuronal integrity and glutamatergic function. Results. Schizophrenic volunteers were impaired at learning both TP and SD conditions compared to controls. Average accuracy rates for controls were 88% for SD and 68% for TP. Schizophrenic subjects had accuracy rates of 74% for SD and 54% for TP. When provided with the stepwise training regimen, 95% of controls and 70% of schizophrenics learned the TP problem to criterion. Even with ample training 30% of the schizophrenics never reached criterion. TP performance was inversely related to the severity of psychotic symptoms in schizophrenic volunteers. Preliminary fMRI data reveal that early TP learning is accompanied by a right hippocampal negative signal and a positive signal change in the left inferior frontal area. Discussion. The results from the standard TP task support previous findings of relational learning impairments in schizophrenia. Our results suggest that schizophrenics are slower to learn but have the capacity to reach normal learning performance when provided with training. Ongoing neuroimaging studies will help determine whether the hippocampus and/or other compensatory regions become activated with training to promote relational learning in schizophrenia, and whether 1H-MRS glutamatergic markers predict performance and underlying fMRI activity.

THE TAXONOMY OF AFFECTIVE DYSPROSODIA IN SCHIZOPHRENIA AND ITS RELATION TO ACOUSTIC CUE PERCEPTION: A PRELIMINARY INVESTIGATION

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Affective dysprosodia, or deficits in the perception of emotion through vocal intonation, are an enduring aspect of schizophrenia that are linked to negative symptoms and predicted by sensory processing dysfunction. Yet the taxonomy or affective specificity in patient dysprosodia is unknown. Within prosody in particular, it has been difficult to disentangle emotion specific deficits from differences in emotion intensity perception. Prior research has shown that certain acoustical cues such as fundamental frequency (F0), voice intensity (VOint) and high frequency energy (HF-500) are highly predictive of decoding ability. Here, we examined patients' perception of 5 basic emotions at differing intensity levels in conjunction with intensity ratings. Additionally, we examined the relationship between performance and intensity ratings and acoustical properties of the stimuli in an emotion specific manner. In a sample of 26 patients with schizophrenia/schizoaffective disorder and 17 healthy controls we found the following: Patient decoding was significantly worse for all affective classifications save angry, and there was no significant emotion x group interaction or intensity x group interaction. Correlation analysis between affective decoding and the acoustic properties of the stimuli revealed that patients were significantly less sensitive to changes in F0sd, and that these differences contributed to differential decoding ability of happy, sad and fearful utterances. Analysis of affective decoding misattribution patterns revealed that patients and controls had generally the same types of misattribution errors, and further, that deviations from the control misattribution pattern were in part related to acoustic cue utilization. Finally, patient ratings of emotional intensity were slightly higher than those of controls. These results suggest that patients' affective dysprosodia is not characterized by any experiential deficit or differences along arousal or valence dimensions but rather, stem from aberrant sensorial and cognitive processing.

COGNITION IN DEPRESSION AND MANIA

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Cognitive deficits are a key component of mania and depression. Evidence suggests that cognitive tests tapping 'hot' processing are particularly affected in unipolar depression. The key to understanding these debilitating and life threatening disorders and to developing both preventative health measures and novel effective treatments lies in a thorough understanding of the integration of cognition and emotion and their neural substrates, possibly via the identification of endophenotypes. In addition, identifying factors which provide resilience and developing psychological treatments which focus on relapse from the first episode of depression are essential for effective treatment.

SCHIZOPHRENIA AND SEX DIFFERENCES IN THE SIMULTANEOUS AND SEQUENTIAL PROCESSING OF LANGUAGE AND EMOTION

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Background: Several studies have shown impairments in emotion recognition as well as in language processing in schizophrenia, and these deficits have been associated with poorer social skills. Healthy women outperform men in both areas and preservation of this female advantage has been reported in female patients with schizophrenia. This might explain, in part, the more favourable social course in female patients compared to male patients. However, social functioning in daily life is complex and requires processing of various kinds of information at the same time. Therefore we tested the hypothesis that male patients with schizophrenia are more impaired in the simultaneous and sequential processing of language and emotion relative to female patients. Method: Forty-eight patients with stabilized schizophrenia (24 m, 24 f), treated with atypical antipsychotics, and 48 controls (24 m, 24 f) were assessed with two working memory (WM) tasks. One task tested sensitivity to interference in a dual-task paradigm and required simultaneous operations in two conditions: counting while distinguishing between male/female faces and counting while distinguishing between two emotional facial expressions (anger/fear). The other task tested the capacity to maintain and manipulate information and required sequential mental operations in the same two conditions: distinction between male/female faces and between the facial expressions anger/fear, followed by the decision whether the choice that had been made rhymed with a word presented on the screen (e.g. fear-near). Results: As predicted, male patients were impaired on the emotion condition of the simultaneous task. On the emotion condition of the sequential task, in contrast, all patients were significantly impaired and no sex differences were observed. Conclusions: The

findings suggest (1) that female patients are less sensitive to interference than male patients in the simultaneous processing of language and emotion, (2) that limitations in the capacity of the WM to maintain and manipulate information are similar for both male and female patients.

SOA SENSITIVITY IN SCHIZOPHRENIC AND ALZHEIMER PATIENTS S. SCHUMM*, C. SEBBAN*, G. SIMMAT**, G. FERREY*** * HôPITAL CHARLES FOIX UNITé D'EXPLORATIONS FONCTIONNELLES, IVRY SUR SEINE, FRANCE ** CHU H. LABORIT, POITIERS, FRANCE *** HôPITAL SIMONE WEILL, EAUBONNE, FRANCE

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A series of reaction times have been measured on a personal computer in 35 schizophrenic patients and 14 patients with Alzheimer dementia. In each applied paradigms the same stimuli were used (letters). The patient's responses were obtained by pressing the left or right button of a double switch except for the backward visual masking test where the response was orally given. The paradigms differed by their content since the patient was asked to evaluate the similarity or difference between two presented stimuli, or between a presented stimulus and a target previously learned. The patient was asked to press the right button when his answer was "similar" the left one for "different". Using a model of the cognitive processes taking place for a visual stimulus (derived from the model proposed by Bonnet, 1989),the duration of different steps of this model were evaluated with the raw reaction times. Intrinsic and extrinsic validations of this approach have been done previously (Le Roc'h et al., 1995 ; Sebban et al., 1998 ; Eusop et al., 2001). In the present study both groups of patients a shown significant slowering of the visual stimulus processing. However schizophrenic patients were characterized by a lack of sensitivity to stimulus onset asyncrhony (SOA)when a two stimuli were successively presented. According to the model of working memory, these results could indicated that the alteration of cognitive processes in schizophrenic patients are already present before representations reach the working memory. K. Le Roc'h et al. 1995. La Presse Médicale, 24, supp. 16, 12-18 C. Sebban et al., 1998. L'Encéphale. 190-4. E. Eusop et al., 2001. L'Encéphale. 26: 39-44

NORADRENALINE REUPTAKE INHIBITORS IMPROVE DISCRIMINATION LEARNING IN RATS: ALPHA-1 AND ALPHA-2 SUBTYPE MECHANISMS

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Pre-clinical data indicate that alpha-2 adrenergic receptor mechanisms are important modulators of cognitive functions. For example, alpha-2 adrenoceptor agonists can, under some circumstances, improve spatial working memory function in rodents and monkeys, while alpha-2 antagonists impair it (Arnsten and Li 2005). In addition, enhancements in noradrenergic function secondary to blockade of alpha-2 adrenergic receptors, improve the ability of rats to respond flexibly in tasks that involve the re-mapping of stimulus-reward associations or the shifting of attention (Lapiz and Morljak 2006). Clearly, however, much remains to be discovered about whether and how noradrenaline modulates other cognitive operations dependent upon the prefrontal cortex. To examine this issue, we trained rats to perform 2- or 4-choice instrumental discrimination tasks in 5-choice serial reaction time boxes. In each daily session, rats learned, by feedback only, to respond into one aperture for food (responses into other apertures elicited a time-out). In the 2-choice version of the task, the noradrenaline reuptake inhibitors despiramine (0.5-5.0 mg/kg) and (to a lesser extent) atomoxetine (0.03-1.0 mg/kg), which generally increase noradrenaline levels, enhanced discrimination learning in a dose-dependent fashion. Rats pretreated with the selective alpha-2 adrenoceptor antagonist, atipamezole (0.1-1.0 mg/kg) exhibited a dose-dependent impairment in discrimination learning, while the alpha-2 adrenoreceptor agonist clonidine (0.001-0.01 mg/kg) tended to improve acquisition. Regarding the alpha-1 subtype, the antagonist prazosin (0.1-1.0 mg/kg) tended to improve learning, while the agonist cirazoline (0.025-0.25 mg/kg) impaired it. Therefore, it appears that alpha-2 and alpha-1 receptors exert opposing influences on the control of discrimination learning. We interpret these behavioral improvements as a possible increase in the contextual control over response learning, an effect that resonates with a recent finding from McClure et al. (2006) indicating that alpha-2 agonism improves contextual processing in individuals with schizotypal personality disorder. Taken together, these data indicate that activation of alpha-2 noradrenergic receptors leads to enhancements in some aspects of prefrontal-cortical dependent cognition. Our approach also provides an easily deployed measure with which to probe these mechanisms in rodents.

TIME-COURSE AND NEUROANATOMY OF ABNORMAL REAL-WORLD COMPREHENSION IN SCHIZOPHRENIA

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Deficits in building up an overall representation of meaning of incoming information have been proposed as a fundamental cognitive dysfunction underlying schizophrenia. Prior studies of this dysfunction have focused on language. Clinically, however, schizophrenia is characterized by both verbal and nonverbal abnormalities. We used event-related electrophysiological potentials (ERPs) and event-related functional magnetic resonance imaging (fMRI) to examine the time-course and neuroanatomy of real-world comprehension as 20 patients with schizophrenia and 20 matched healthy participants viewed 80 silent, 8-sec-long movies of common real-world activities. Final movie scenes were either congruous with their preceding context (e.g., a man shaves his face after smearing on shaving cream) or anomalous (e.g., a man strokes a rolling pin across his face after smearing on shaving cream). Relative to the control group, patients showed enhanced increases in (a) the ERP response at approx. 400ms after final scene onset and (b) the fMRI/BOLD response in an inferior prefrontal-temporal network, to anomalous relative to congruous scenes. Similar effects have been previously proposed to reflect processing based on semantic associative knowledge, and hence, these results suggest overactive semantic associative function in schizophrenia. On the other hand, patients, unlike controls, failed to show increases in (a) the ERP response at approx. 600ms, and (b) the fMRI/BOLD response in the dorsolateral prefrontal cortex (DLPFC) and the basal ganglia (BG), to anomalous relative to congruous scenes. In the control group, these responses

resembled the effects that have recently been reported when participants read sentences comprised of semantically related words that nonetheless described impossible actions (e.g., 'the eggs would eat'). We suggest that they might reflect the reevaluation of initial semantic expectations based on the real-world knowledge that is crucial for flexible comprehension. This more exhaustive analysis of incoming information appears to be impaired in schizophrenia. Imbalances between inferior prefrontal-temporal activity and DLPFC-BG activity in schizophrenia might lead to an over-reliance on semantic associations at the expense of flexible, accurate comprehension. This could lead to a tendency to "jump to conclusions", and in turn, to delusions, and the stereotyped, non-context-driven thought that characterize schizophrenia. Support: NARSAD, NIMH MH071635

INFLUENCE OF SCHIZOTYPAL PERSONALITY TRAITS ON NEUROCOGNITIVE DEVELOPMENT

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Deficits in neurocognitive performance are one of the hallmarks of schizophrenia, a finding consistent within clinical samples as well as in related non-clinical groups. Adults who score high on schizotypy measures have demonstrated neurocognitive deficits, suggesting that factors other than the confounds of illness cause these disruptions. It is clear that neurocognitive deficits in psychosis precede the onset of florid symptoms. This study was designed to test the hypothesis that normal cognitive developmental changes during the adolescent period interact with the presence of schizotypy personality traits in a normative sample. Comparing two samples at different stages of development on both psychosis proneness trait scores and neurocognition may help to determine which changes are indicative of the emergence of psychotic symptoms. Recruitment of participants is currently underway from local youth groups and schools within the Manchester area for the younger age range (mid adolescence, ages 15-17) and via email at the University of Manchester for the older group (young adulthood, ages 19-25). At present, 59 participants have completed the O-LIFE scale for measuring psychosis proneness and the Prodromal Questionnaire (PQ). Participants also completed a battery of neuropsychological tests assessing callosal function, language, visuospatial processing and executive function. Preliminary analysis has indicated a developmental change in levels of schizotypy. There was a significant effect of age on O-LIFE subscale Impulsive Non-conformity ($t(57) = 2.22$, $p < 0.05$), with the younger group reporting higher levels. There was also a trend towards a significant effect of age on the subscale Introvertive Anhedonia, with the older group reporting higher scores. The effect of age on the subscales positive, disorganised and general symptoms of the PQ approached significance, with the younger group reporting higher scores. There appears to be a developmental change in scores on schizotypy measures from mid adolescence to young adulthood. With continued recruitment neurocognitive performance in relation to schizotypy measures will be analysed in different age groups. This will enable the investigation of the effects of schizotypy on neurocognitive development and its relationship to the emergence of psychotic symptoms.

NEUROCOGNITIVE CORRELATES OF 50 AND 100 MS AUDITORY GATING IN CONTROLS AND PATIENTS WITH SCHIZOPHRENIA

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Abnormal 50 and 100 ms ratio scores in the event-related brain potential are frequently observed in patients with schizophrenia administered the paired-click paradigm. The clinical significance of an abnormal ratio score is unclear, with most studies finding weak or no relationship between abnormal ratio scores and clinical measures. The lack of findings may be due to limitations inherent to the 50 ms Cz measure – poor reliability and the superposition of activity from multiple brain regions. Examination of activity at specific structures may allow a more direct assessment of the relationship between abnormal ratio scores and clinical measures. 122 channels of magnetoencephalography data and Cz electroencephalography were collected from 59 controls and 71 patients with schizophrenia administered the standard paired-click task. Left- and right-hemisphere 50 and 100 ms superior temporal gyrus (STG) first (S1) and second click (S2) source strength measures were obtained, and S2/S1 ratio scores calculated. Measures also were obtained at Cz. All participants completed a neuropsychological battery containing tests of attention, working memory, long-delay memory, and an IQ estimate. Hypotheses were: 1) 50 and 100 ms Cz ratio scores would be only moderately related to cognitive abilities; 2) as 50 ms STG processes are associated with sensory encoding, higher STG 50 ms ratio scores would be associated with impaired performance on attention measures; and 3) as 100 ms processes reflect sensory encoding and higher order processes, higher 100 ms ratio scores would be associated with impaired performance on all assessed cognitive domains. Supporting Hypothesis 1, Cz 50 and 100 ms ratio scores were not strongly associated with cognitive measures. Contrary to Hypothesis 2, 50 ms ratio scores were not associated with attentional measures. At 50 ms, after controlling for general intelligence, only an association of larger left 50 ms STG ratio scores and more impaired working memory performance in patients was observed. Supporting Hypothesis 3, 100 ms STG ratio scores were related to several cognitive domains in both groups. Overall, the current study suggests that 100 ms STG ratio scores are a good indicator of general cognitive function in patients and controls. The observed associations between sensory gating and neurocognitive performance in the patient population support the STG ratio score measure as a clinically significant endophenotype of schizophrenia.

A POTENTIAL ROLE FOR GLYCINE TRANSPORT INHIBITORS IN AMELIORATING COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA : EFFECTS OF ORG 25935

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Background: The NMDA receptor (NMDAR) hypofunction hypothesis is increasingly being accepted as relevant to the aetiology of schizophrenia, particularly in explaining cognitive deficit symptoms

(Olney 1999). Glycine (Gly) is an essential co-agonist for NMDAR function. Inhibitors of glycine transporter-1 (GlyT1), which is important for glycine reuptake, are now under study as potential new therapeutic agents for the treatment of schizophrenia. Aim: To assess the ability of a novel GlyT1 inhibitor (Org 25935) to improve a subchronic PCP-induced deficit in working memory using the novel object recognition paradigm in the rat. Method: Female hooded-Lister rats received vehicle (n=10; i.p. twice daily) or PCP (n=40; 2mg/kg i.p. twice daily) for 7 days, followed by a 7 day drug-free period before drug treatment. Org 25935 (3, 6, 10 mg/kg; n=10/group) or vehicle was administered i.p. 45 min prior to testing. Testing consisted of a 3 min acquisition phase where rats explored two identical objects followed by a 1min inter-trial interval. Then in the retention trial, rats explored a familiar (from the last trial) and a novel object for 3 min.The exploration time(s) of each object in each trial was recorded. Result: In the retention trial saline treated animals explored the novel object significantly more than the familiar object ($p<0.05$). This effect was abolished in the PCP-treatment group. Org 25935 (3 and 6mg/kg) treated groups significantly attenuated the effects of PCP and increased novel object exploration time ($p<0.05$). Locomotor activity of animals treated with the highest dose of Org 25935 was significantly reduced compared with the vehicle group ($p<0.05$). Conclusion: Org 25935 significantly attenuated the PCP-induced working memory deficit suggesting that GlyT1 inhibitors may have potential in the treatment of cognitive deficit symptoms of schizophrenia

SCHIZOPHRENIA-LIKE COGNITIVE EFFECTS OF CANNABINOIDS

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Cannabis use is increasingly being recognised as a risk factor in the development of psychotic symptoms and the endogenous cannabinoid system is implicated in the pathophysiology of schizophrenia. Cognitive impairments are among the most debilitating symptoms of schizophrenia and most highly predictive of functional outcomes. Cannabis intoxication impairs cognitive processes and there is growing evidence for longer-lasting cognitive impairment with long term or heavy cannabis use, including new data on memory function that will be presented here. Cognitive dysfunction associated with chronic cannabis use is similar in many respects to the cognitive endophenotypes that have recently been proposed as vulnerability markers of schizophrenia. These factors combined indicate a need to further investigate the nature and mechanisms of cognitive impairments associated with cannabis use. The endogenous cannabinoid system plays a significant role in attention, learning and memory in particular, and in mediating inhibitory and excitatory regulatory mechanisms in the brain. There is evidence that the endocannabinoid system is altered in schizophrenia and accumulating evidence of altered functionality in the system following exposure to cannabis or cannabinoids. This presentation will provide an overview of what is known about the long term cognitive effects of cannabis in the context of endophenotypes of schizophrenia, focusing on preattentive, inhibitory, attentive, memory and executive functions. In addition, given the high prevalence of cannabis use among people with schizophrenia, the hypothesis that comorbid cannabis use may exacerbate existing cognitive deficits in this population will be considered. Original data from neuropsychological and functional neuroimaging studies of cannabis users and schizophrenia cohorts with and without comorbid cannabis use will be presented and examined in light of the neurobiology of endogenous and exogenous cannabinoid interactions, neurodevelopmental stages and genetics. The theoretical and clinical significance of further research in this field is in enhancing our understanding of the pathophysiology of schizophrenia and improving the provision of treatments for schizophrenia and comorbid substance use and psychotic disorders.

THE EFFECT OF ANTIPSYCHOTIC DRUG TREATMENT ON REWARD LEARNING AS ASSESSED BY AUTOSHAPING

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Positive symptoms of schizophrenia include such things as hallucinations and delusions, while the negative symptoms include deficits in behavior such as lack of social interest and motivation. The cognitive deficits present in a number of ways including decreased IQ, memory impairment, and disorganized thoughts. The positive symptoms may be effectively treated with antipsychotics, however there is no therapy currently available that effectively treats negative symptoms and disruptions in cognition remain a major area of focus. Typical and atypical antipsychotics have antagonist properties (to varying degrees) at the dopamine D2 receptors. Unfortunately, this interaction also leads to negative consequences, including a dampening of reward processing. Diminished signaling through these receptors disrupts reward learning as assessed by instrumental tasks and acquisition of conditioned reinforcers. An impairment of reward learning may play a significant role in the cognitive deficits seen in schizophrenia. The purpose of this study was to determine the effect of anitpsychotic drug administration on a simple model of Pavlovian learning. We used an autoshaping procedure to assay the effect of haloperidol (HAL; 0.003; 0.01, 0.03, and 0.1 mg/ml) on reward processing. Autoshaping is a paradigm in which an animal is trained to associate a stimulus with a reward. The acquisition of stimulus reward associations is quantified as approach behavior; as the association is formed the animal begins to approach the stimulus despite the fact that the approach does not influence reward delivery. Autoshaping was used in order to determine the capacity of the subject to learn positive and negative associations. It was found that HAL attenuated the ability to discern positive versus neutral cues in a dose dependent manner. This effect was significant at 0.03 mg/ml, and a dose of 0.01 mg/ml completely eliminated responding. These results indicate that reward processing is disrupted in the presence of HAL. After the initial autoshape training the stimulus lights were reversed, so what had indicated reward did not and vise versa. It was found that, surprisingly, HAL treatment did not disrupt reward learning during the reversal. This has implications for the treatment of schizophrenia and the analysis of reward processing data in people with schizophrenia, since the medication itself may have effects on reward learning.

ASTROCYTE TRANSPORTER PARTICIPATION IN THE MK801 MODEL OF SCHIZOPHRENIA

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Background: Proposed models of endophenotypes of schizophrenia involve the malfunctioning of glutamatergic synapses; studies usually focus on neuron function. The present study focuses instead on the role of astrocytes and their molecular contribution to CNS pathology in a NMDA receptor antagonist animal model of schizophrenia.

Key astrocyte transporters are critical for neuronal functions, especially in the metabolic axis of glutamate, glutamine, and lactate. We hypothesized that astrocyte mRNA for L-glutamate, glutamine, and lactate transporters, each respond to MK801. Methods: Adult male C57BL/6 mice (Charles River, 8-12 wks old) were injected i.p. with normal saline with or without (+)MK801 (0.1 mg/Kg). After 2 hr, animals were euthanized via carbon dioxide inhalation followed by decapitation. The brains were rapidly removed, flash frozen in powdered dry ice, and stored at -80°C. Whole brain RNA was extracted using Trizol, and cDNA was prepared using Invitrogen Superscipt procedures. Realtime qPCR methods were employed to quantify mRNA levels against internal 18S RNA, using appropriate specific primer pairs. All experimental procedures were approved by the Univ. of Florida IACUC. Results: In MK801 mice, L-glutamate transporter mRNA encoding astrocytic GLT-1/EAAT2 (SLC1A2) mRNA was significantly ($p < 0.05$) upregulated, while mRNA encoding neuronal and astrocytic GLAST/EAAT1 (SLC1A3) was unaffected, compared to saline. On the other hand, astrocytic glutamine transporter ASCT2 (SLC38A3) was down reglulated. Also, mRNA encoding the monocarboxylate transporters handling lactate, MCT1 (SLC16A1) and MCT2 (SLC16A7), were each downregulated. Discussion: Key astrocyte transporters respond to MK801 inhibition of NMDA receptors in mice. These data suggest astrocytic transporter abnormalities might be important in the pathophysiology of schizophrenia.

POSITIVE EMOTION FAILS TO CAPTURE ATTENTION IN DEFICIT SYNDROME SCHIZOPHRENIA

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Lack of liveliness and interest are hallmark features of deficit syndrome schizophrenia. Although the validity of these symptoms and the deficit classification are well-established, it has yet to be determined whether there are emotional information processing impairments that maintain deficit symptomatology. The current study examined differences in attention bias for emotional information in patients with deficit ($n = 15$) and non-deficit ($n = 20$) syndrome schizophrenia and healthy controls ($n = 25$). Attention bias was measured using a color-word Emotional Stroop task, which included words from multiple basic emotion categories. Results indicated that deficit syndrome patients displayed less overall interference for emotional information (indexed using an emotional – neutral difference score method), and a negative interference score for happiness words. Differences among deficit and non-deficit patients suggest that the attention of non-deficit patients is drawn toward multiple discrete emotions, while deficit patients display less overall attentional bias toward emotional information, and a specific impairment in having their attention drawn toward positive information. Findings have important implications for understanding potential causes of the negative symptoms associated with deficit syndrome schizophrenia and may provide insight into the neurological underpinnings of emotional abnormalities affecting individuals with schizophrenia.

ASSOCIATING AFFECTIVE WORDS IN ALEXITHYMIA

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Alexithymia, or no words for feelings, is an impairment of the ability to identify and communicate one's emotional state. Alexithymia has been described in patients with schizophrenia, in particular in men. In order to elucidate the cognitive-emotional processing underlying alexithymia we investigated nonclinical subjects with either high or low scores on an alexithymia questionnaire. Specifically, we tested the hypothesis that alexithymia would be associated with difficulties in associating emotional words to arbitrary emotional categories. 13 Participants (7f) with high- and 11 participants (6f) with low scores on the verbalizing scale of the Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001), performed emotion related tasks. They were selected from the upper and lower extremes of scores on this scale obtained from 300 individuals. In the affective Simon task participants had to attribute "negative" or "positive", depending on the grammatical category of the word, to affective nouns and adjectives. We also investigated ability to pair emotional facial expressions to words (paired-associate learning), in addition to laterality effects in recognizing emotional expressions in chimeric faces. Alexithymic participants made more mistakes on the affective simon task ($p<0.05$) in general, and on trials where they had to assign "positive" to the stimulus in particular. The alexithymic subjects did not differ from the control group in their ability to pair emotional faces with arbitrary neutral words ($p>0.10$). No group difference was found for the chimeric face task ($p>0.10$). Alexithymia was observed to be associated with difficulties assigning an affective word to an arbitrary category according to worse performance on the affective Simon task. Contrary to the hypothesis of a left hemisphere preference in alexithymic individuals, no difference was observed on the chimeric face task. The results may point to specific dysfunction of the interaction between verbal and emotional systems and are of relevance for understanding such interactions in schizophrenia.

BIOMARKERS IN COGNITION ENHANCEMENT RESEARCH

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Purpose: Performance on clinical neuropsychological tests has been the primary cognitive outcome in pharmacological studies assessing cognitive benefit for schizophrenia patients. This approach may have limitations. Robust sensitivity to drug effects is not well established, tests often tap into generalized cognitive deficit rather than into specific cognitive operations likely to be targeted by new drug treatments, and practice effects and motivational factors can be complex. Neurophysiological and neuroimaging biomarkers may offer advantages, especially for Phase 2 studies, because they more directly assess drug effects on brain systems and they can provide a direct translational bridge for early proof of concept studies. Methods: Neuropsychological and neurophysiological (oculomotor) studies were completed in unmedicated first episode schizophrenia patients, and then patients were retested after 6, 26 and 52 weeks of risperidone therapy. Matched healthy subjects were retested at similar intervals. Functional MRI studies were completed at baseline in the initial cohort of patients, and after acute treatment as well in more-recently recruited patients. Results: Neuropsychological and oculomotor deficits were of a similar degree at pre-treatment baseline in schizophrenia patients, but oculomotor testing was considerably more sensitive to effects of treatment with the antipsychotic drug risperidone. Importantly, oculomotor testing revealed both beneficial and adverse cognitive changes after treatment. Data from neuropsychological tests were highly intercorrelated, suggesting sensitivity to generalized cognitive ability, whereas oculomotor tasks assessed differenti-

ated neurocognitive abilities known to be linked to distinct neural systems. Practice effects were smaller at retest for several oculomotor tasks than for neuropsychological tests, and they were more similar in patients and controls. The robust sensitivity of fMRI to detect baseline deficits will be illustrated, as well as preliminary data showing a high sensitivity for treatment effects on functional brain systems. Conclusions: Biomarkers provide considerable promise as neurocognitive outcomes for novel drug therapies. They are more closely linked to the kind of specific cognitive processes and brain systems likely to be targeted by novel adjunctive procognitive interventions, and they can facilitate translational linkages in early proof of concept studies.

WEAKENED CENTER-SURROUND INTERACTIONS IN VISUAL MOTION PROCESSING IN SCHIZOPHRENIA

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Perceptual deficits including impairments of motion perception are present in schizophrenia but it is unclear what factors cause them and how they influence behavior. In this study, we examined the integrity of suppressive center-surround mechanisms in motion perception of schizophrenic patients. Center-surround suppression is implicated figure-ground segregation and smooth pursuit eye movements (SPEM), visual functions that are impaired in schizophrenia. In healthy individuals, evidence of center-surround suppression is documented by a reduced ability to perceive motion of a high-contrast stimulus as its size increases. This counterintuitive finding is likely a perceptual correlate of center-surround mechanisms in cortical area MT (Tadin et al., 2003). We found that schizophrenic patients have elevated motion discrimination thresholds while performing normally in a shape discrimination task. More importantly, motion discrimination thresholds of schizophrenic patients were less affected by the increases in the stimulus size that normally causes a substantial increase in control subjects' thresholds. This pattern of results indicates that center-surround suppression is abnormally weak in schizophrenia. Moreover, this abnormality was more pronounced in patients with severe negative symptoms. Interestingly, patients with the weakest center-surround suppression actually outperformed control subjects in motion discriminations of large high-contrast stimuli. In summary, our results suggest that schizophrenia is associated with weaker center-surround interactions in motion processing, a finding consistent with motion and contextual processing deficits found in schizophrenia. The observed deficit is consistent with an MT abnormality in schizophrenia and has a potential to disrupt SPEM, figure-ground segregation of moving objects and other visual functions that depend on intact center-surround interactions in motion. Tadin D, Lappin JS, Gilroy LA, Blake R (2003) Perceptual consequences of centre-surround antagonism in visual motion processing. Nature, 424:312-315.

THE IMPACT OF REWARD ON MEMORY IN SCHIZOPHRENIA: A CONTROLLED COMPARISON

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Two experiments were conducted to evaluate the impact of monetary reward on verbal working memory (vWM) and on verbal long-term memory (vLTM). This research was motivated by the observations that negative symptoms (i.e., psychomotor poverty) in schizophrenia are associated with reduced drive and that patients with these symptoms exhibit greater mnemonic impairments. Since in healthy persons monetary reward enhances vWM and vLTM and induces increased neuronal activation of areas implicated in these forms of memory, we were interested in understanding the behavioral effects in schizophrenia. We investigated 50 patients with chronic schizophrenia spectrum disorders compared with 52 matched healthy participants. Gains in neurocognitive performance were evaluated for two levels of vWM difficulty on an nback task and across three aspects of vLTM derived from the California Verbal Learning Test, 2nd Edition (i.e., learning, total immediate recall, and 20 minute retention). Although healthy individuals benefited from reward at a high vWM difficulty level ($F = 7.07$, $p < .01$) schizophrenia patients did not exhibit any improvements in vWM over the non-rewarded baselines ($F = 0.31$, $p > .50$). In contrast, improvement in vLTM retention was induced by reward for both patients and controls ($F = 11.6$, $p = .001$), but reward-related improvements were not observed for learning or immediate recall (all ps > .35). Importantly, patients with less psychomotor poverty, better frontal-striatal cognitive functioning, and those undergoing treatments involving lesser muscarinic and D1 receptor antagonism exhibited the greatest vLTM retention gains. In conclusion, contingent monetary rewards delivered during vWM and vLTM operations effectively moderate aspects of memory performance. However, the influence of reward was relatively limited and depended upon the specific neurocognitive operation examined, symptomatic and pharmacological factors, and whether participants were healthy or suffer from schizophrenia.

A MODEL OF DOPAMINE AND UNCERTAINTY USING TEMPORAL DIFFERENCE

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Does dopamine code for uncertainty (Fiorillo, Tobler & Schultz, 2003; 2005) or is the sustained activation recorded from dopamine neurons a result of Temporal Difference (TD) backpropagating errors (Niv, Duff & Dayan, 2005)? An answer to this question could result in a better understanding of the nature of dopamine signaling, with implications for cognitive disorders, like Schizophrenia. Single cell recordings of dopamine neurons have identified a phasic dopamine burst of activity which is posited to be a reward prediction error, and TD Learning, a form of Reinforcement Learning, provides an explicit method of modelling and quantifying this error. It is likely that disruption to the dopamine system gives rise to an abnormality in information processing by dopamine and some of the symptoms currently associated with schizophrenia, particularly psychosis and deficits in working memory. A computer simulation of uncertainty incorporating TD Learning, and Incentive Salience successfully modelled a Reinforcement Learning paradigm and the detailed effects demonstrated in single dopamine neuron recordings by Fiorillo et al., namely: the phasic activation at the expected time of reward that increased as probability decreased; the sustained increase in activity from the onset of the CS until the expected time of reward, during uncertainty, posited either as uncertainty, or as backpropagating TD prediction errors; and the sustained activation increasing with increasing reward magnitude. In addition, we have demonstrated what a single trial in TD Learning might look like and provide further evidence that ramping of the reward prediction error is not normally found within a trial of a single dopamine firing, but instead arises from averaging

across trials. While we do not rule out the possibility that dopamine may well code for uncertainty, our simulations add further weight to the criticisms of Niv et al. that the effects demonstrated by Fiorillo and colleagues are due to backpropagating TD errors, and not a within-trial encoding of uncertainty. We support claims that the ramping signal is the best evidence yet for the nature of the learning mechanism of a shift in dopamine activity from expected time of reward to the CS. Furthermore, as such fine details of single cell recordings can be captured and explained using TD, we suggest that it is both reasonable and biologically plausible for future models of dopamine and schizophrenia to include TD learning.

THE NEURAL SUBSTRATES OF EMOTIONAL PROCESSING IN SCHIZOPHRENIA: AN EVENT-RELATED FMRI STUDY

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Impairments in emotional processing in schizophrenia have long been described, but the precise mechanisms underlying these impairments, and especially their neural substrates, are still poorly understood. In an effort to further our understanding of these issues, we used event-related fMRI to study the neural circuitry involved in evaluating and responding to emotionally valenced stimuli. Chronic schizophrenia patients and controls subjects were scanned while viewing and rating their subjective reaction to images from the International Affective Picture System (IAPS). A preliminary analysis of data from six patients and four controls suggested that, across the two groups, a network of brain areas frequently implicated in processing of emotional information was robustly activated in response to positively and negatively valenced IAPS stimuli, relative to neutral ones. These areas included ventromedial prefrontal cortex, orbitofrontal cortex, ventral striatum, extended amygdala and insula. This pattern of activation is consistent with the framework of Kring et al., which proposes that the ability of patients to directly experience affect is largely intact, and that abnormalities in the affective domain are, in fact, manifestations of altered representations of the anticipated effects of emotional stimuli. Results form a larger sample of subjects will be presented, including correlations of brain activity with measures of reactivity to emotional stimuli collected during scanning (i.e. subjective ratings and skin conductance response).

RECOLLECTION AND FAMILIARITY JUDGMENTS DURING RECOGNITION IN CHRONIC SCHIZOPHRENIA

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To determine whether schizophrenia patients' deficits in learning and memory reflect reduced conscious recollection and increased reliance on familiarity-based assessment as a basis for retrieval, we administered the Remember-Know (R-K) paradigm, a procedure drawn from basic research on the cognitive neuroscience of episodic memory, to 37 patients with chronic schizophrenia and twenty-one demographically matched healthy controls. During the encoding phase, participants were shown a target word along with an unrelated paired word, followed by line drawings of objects corresponding to the target and paired words, and asked to memorize as much of the information as possible. Participants made a position judgment (right versus left) of the target word to ensure attention during encoding. During the recognition phase, participants judged whether they: [R] remembered the word and recalled explicitly the moment of learning, [K] knew the word, but did not recall the learning episode, or [U] thought the word was unstudied. Twenty five percent of test stimuli were truly unstudied. During the validation phase, participants made forced-choice recognition judgments on two possible paired words and colors of the target picture. Analyses comparing response types indicated significant reduction in R-responses, along with a non-significant increase in K-responses in schizophrenia patients compared to controls, in the context of patients' non-significantly lower overall recognition accuracy on the R-K paradigm. Both patients and controls recalled more contextual details on R compared to K responses, though patients recalled fewer details of the learning episode compared with controls. That is, in patients, successful recognition of a target appears to be based less on an explicit memory of the moment of learning and more on an impression of familiarity, and patients recognize fewer contextual details of the learning episode compared with controls. This pattern suggests that patients with schizophrenia have deficits in organizing and integrating contextual information during learning and/or using contextual information to aid retrieval. We are now using functional magnetic resonance imaging to examine the extent to which these deficits reflect differential disruption of neural systems mediating episodic encoding and/or retrieval processes.

HEARING A VOICE IN THE NOISE: INCREASED TOP-DOWN INFLUENCE ON THE PERCEPTION OF WORDS IN PATIENTS WITH AUDITORY HALLUCINATIONS

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Up to 70% of schizophrenia patients report the occurrence of auditory hallucinations. In the literature, several cognitive mechanisms have been advanced to explain the genesis of this phenomenon. Recent work suggests that a disproportionately large contribution of top-down factors, such as prior knowledge and related perceptual expectations, may be linked to hallucinations. To test this hypothesis, we devised an auditory-verbal discrimination task that relied on such top-down influences and employed Signal Detection Theory to investigate the underlying cognitive mechanisms. Three groups of subjects (hallucinating and non-hallucinating patients and healthy controls) completed the task. They had to decide whether a particular spoken word was identical to a previously presented spoken word, embedded in noise. Thus, subjects had to memorize a sensory trace of the noisy stimulus, and match its mental echo to the perception of the second word. SDT was employed on the accuracy data to calculate Az, a measure of perceptual sensitivity and β, a measure of response bias. Results indicate that hallucinating subjects showed an increased perceptual sensitivity to auditory-verbal stimuli, when compared to non-hallucinating subjects. However, they did not differ from healthy controls. Hallucinating subjects also showed a positive response bias, indicating their general tendency to reaffirm the presence of a suggested auditory stimulus.The high level of sensitivity to auditory-verbal stimuli observed in the task signifies that

hallucinating subjects were better able to tell whether the two presented stimuli matched, than non-hallucinating subjects. Since the task relied heavily on the interaction between internalized sensory states and bottom-up perception and, we conclude that hallucinating patients make more use of top-down processing in the determination of a percept. In addition they showed a positive response bias, which means that hallucinating individuals often made correct matches. However, when they did make a mistake, they usually judged the two items to be the same rather than different. In other words, compared to normal controls and non-hallucinating patients, hallucinating subjects often imagined hearing a certain stimulus, based on the suggestion that it might have been there. In sum, the SDT measures indicate that top-down processing influences concurrent perception of external stimuli to a larger degree in individuals prone to hallucinatory experiences.

SOCIAL COGNITION AND NEUROCOGNITION : INDEPENDENT COGNITIVE DOMAINS IN PSYCHOSIS

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Recent studies have demonstrated that patients with psychosis show deficits in social cognition (cognitive functions related to perception of the self and others), in addition to well established deficits in neurocognitive functions. However, it is still unclear whether these cognitive domains represent two separate endophenotypes or whether there is one overlapping factor underlying both deficiencies. This study wanted to investigate whether deficits of social cognition represent an autonomous area of vulnerability to psychosis, independent of neurocognitive deficits. The sample included 45 patients with a history of psychosis and 54 control subjects (age 18-55), who performed a test-battery consisting of social cognition tasks (Internal, Personal and Situational Attributions Questionnaire (IPSAQ); Action Recognition Task (ART); Verbal Self Monitoring Task (VSMT) and Hinting Task) and neurocognitive tests (Stroop-Color-Word task (SCWT); Trailmaking Test (TMT) and Verbal Fluency). Pearson correlation analyses as well as exploratory factor analyses were conducted for each of the two groups separately. In the patient group, the neurocognitive tasks were strongly and significantly associated with each other ($r>0.43$, $p<0.015$). TMT and Verbal Fluency were additionally associated with the Hinting Task ($r>0.36$, $p<0.05$). Among the social cognition measures, ART was moderately associated with the VSMT ($r=0.29$, $p=0.06$). Performance on the IPSAQ was not related to any of the other cognitive tasks. Results in the control group were largely similar to those in the patient group. Exploratory factor analysis in both groups yielded a three-factor solution explaining 67% of variance. All neurocognitive tasks and the Hinting Task loaded on the first factor (factor loadings > 0.70), the ART and the IPSAQ loaded on the second factor (factor loadings > 0.68), while the third factor was based on the VSMT only (factor loading > 0.95). Neurocognition and social cognition appear to be two separate areas of vulnerability in psychosis. Possibly, social cognition can be located on the affective pathway to psychosis, which is characterised by stress-sensitivity and a predominance of positive symptoms, rather than on the neurocognitive pathway, characterised by brain structural deficits and negative symptoms. However, the lack of significant overlap among the different social cognition measures also suggests that the term 'social cognition' encompasses various cognitive mechanisms.

INCREASED SERUM BDNF LEVELS IN SCHIZOPHRENIC SUBJECTS AFTER INTENSIVE NEUROPLASTICITY-BASED COGNITIVE TRAINING

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Animal studies indicate that increases in brain-derived neurotrophic factor (BDNF) signaling are related to the beneficial effects of cognitive stimulation on brain health. For example, rodents provided access to a running wheel or housed in cognitively stimulating environments exhibit increased levels of BDNF in several regions of their brains (Russo-Neustadt 1999, Young 1999). We measured serum BDNF levels at baseline and after 12 weeks of intervention in 15 schizophrenic subjects undergoing 12 weeks of intensive, computerized, neuroplasticity-based cognitive training exercises and in 14 age and IQ-matched schizophrenic subjects undergoing an active "computer games" control condition. We found that baseline serum BDNF levels were negatively correlated with baseline neurocognitive function in this sample ($r= -0.4$, $p<0.05$). Serum BDNF levels increased by 6% in the subjects undergoing intensive cognitive training, but not the subjects in the control condition, a result which approached significance ($t= -1.5$, $p<0.1$). These findings indicate that: 1) Lowered serum BDNF levels in schizophrenic subjects are associated with poorer neurocognitive functioning; 2) Schizophrenic subjects can show an increase in serum BDNF as a result of the specific effects of intensive neuroplasticity-based cognitive training. We suggest that these increased BDNF levels may be the result of a trophic response in hippocampal and cortical neurons as a result of the intensive training.

MUSIC PERCEPTION AMONG SCHIZOPHRENIA PATIENTS

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Background: Schizophrenia patients often show a deficit in the perception and processing of affective prosody. These deficits could be related to a basic music misperception. The objective of the current study was to evaluate different aspects of music perception in schizophrenia patients as compared to normal controls. Methods: 7 schizophrenia patients and 25 matched normal controls were included. A tool was developed for the current study that included 5 different tasks of musical perception, each including 3 levels of difficulty. Task a, 'absolute locality' requires classifying melodies on the basis of a fixed tone that appears at the end, beginning, or middle. Task b, 'relative locality', requires classifying melodies on the basis of binary note-transitions at the beginning, end or middle. Task c requires classifying melodies on the basis of note repetition. Task d requires classifying melodies on the basis of equal or similar repetitions. Finally task e requires melody classification on the basis of rhythmic pattern. For each task, participants confronted a learning phase of 15 trials in which melodies were classified according to one of the foregoing criteria (not described to the participant). There followed a test phase that consisted of a new set of 15

melodies. The number of corrected answers out of the 15 was counted. Statistical analysis was based on repeated measures, assuming a linear model. Results: In general, schizophrenia patients performed worse than normal controls (Mean correct scores: 9.6 vs. 8.1, F=4.299, p=.047). Performance was unequal between the different tasks (F=2.517, p=.045), with repeated-tone task being significantly easier than relative-locality task and repetition of melody task (p=.002, p=.009, respectively). Yet, no interaction was found between test and group (F=.194, p=.941). The number of correct answers decreased with increase in test difficulty (higher level) (F=7.886, p=.001). Yet again, no interaction was found between level of difficulty and group (F=.875, p=.422). Conclusions: Although schizophrenia patients performed worse than normal controls in the music perception test, there was no specific deficit more pronounced among schizophrenia patients as compared to controls, and the pattern of musical perception was similar between the two groups.

NEUROCOGNITIVE AND OLFACTORY TRAITS IN SCHIZOPHRENIA: FREE-RADICAL INSIGHTS

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Cognitive and olfactory deficits are considered as specific symptom domains of schizophrenia. These at the first glance unrelated traits have common molecular dynamic nature and mechanisms. Cognitive impairments specific to schizophrenia - operational functions and memory with performance processing rate, and olfactory impairment in generalized sense of neural information processing represent subtle dynamic molecular pathways ranging from perturbation in free radicals redox homeodynamics, with hemispheric biochemical dominance/accentuation including alteration of nitric oxide-superoxide complementarity, responsive redox signaling networks, concomitant alterations in genes expression, transcription and apoptosis, redox control of mitochondrial ET chain, membranes permeability, neurotransmission pattern, synaptic circuitry and plasticity to changes in neurogenesis and functional hemispheric asymmetry. Based on free-radical homeodynamics conceptualization,, neurocognitive and olfactory deficits may plausibly manifest predisposition to schizophrenia and represent characteristic markers/vestiges. This analysis may be also important for deeper understanding of schizophrenia etiology and pharmacological intervention.

DISSIMILARITIES IN PREMORBID SCHOOL PERFORMANCE BETWEEN BIPOLAR DISORDER AND SCHIZOPHRENIA: A TWIN STUDY

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Background: There is an ongoing debate whether schizophrenia and bipolar disorder are etiologically distinct disorders. Neurodevelopmental impairments in psychomotor, language and cognitive function show some specificity to schizophrenia and are not seen in those who later develop bipolar disorder. In twin pairs with schizophrenia divergence in school performance occurred 7.5 years earlier than it did in control twins, at 12 years of age, preceding the onset of psychosis by 10 years. Divergence mainly occurred due to underperformance of the twin, who later developed schizophrenia. Underperformance at school might be considered one of the first signs of a latent vulnerability for schizophrenia. Aim: To examine whether a decline in cognitive functioning, specifically school performance, is a risk factor for developing bipolar disorder. Method: Information on developmental divergence in school performance was obtained from 24 monozygotic (MZ) and 29 dizygotic (DZ) bipolar twin pairs and 35 healthy matched control twin pairs. Results: Bipolar patients did not differ on years of education (13.1 years) from their non-bipolar cotwins (12.5 years) or the control twins (13.6 years). Divergence in school performance occurred 6 years earlier in the bipolar twin pairs than in the control twin pairs, at 13.6 years of age. In the discordant twin pairs the developmental divergence in school performance occurred in 44% due to underperformance of the bipolar twin while in 56% the non-bipolar cotwin lagged behind their bipolar twin. Conclusion: This study shows that, in contrast with schizophrenia, bipolar disorder does not involve a decline in cognitive functioning, specifically school performance, preceding the onset of the illness. This study suggests that bipolar disorder and schizophrenia have a different (neurodevelopmental) etiology.

PATIENTS WITH SCHIZOPHRENIA SHOW IMPAIRED REWARD-DRIVEN LEARNING, DESPITE AN INCREASED RATE OF RESPONDING, IN A NOVEL GO-NOGO LEARNING TASK

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Background: Response selection and learning dependent on positive feedback (reward) may involve neural systems somewhat separate from those underlying behavior driven by negative feedback (punishment). We hypothesized that dysfunctional D1-transmission in schizophrenia (SZ) may lead to selective impairment in reward-driven ("Go") learning. Such a deficit in Go learning may occur in the presence of an overall increased rate of responding (a Go response-bias), brought on by excessive dopamine (DA) tone in the striatum. In contrast, the ability to withhold a response to an aversive stimulus ("NoGo" learning) may be unimpaired in medicated SZ patients. Method: We tested 37 SZ patients, and 25 matched controls, on a novel probabilistic Go-NoGo paradigm (Frank et al., 2006). In an acquisition phase, subjects were presented with 6 colored patterns 30 times each. For 3 of the stimuli, subjects would most often gain points by making Go responses (space-bar presses, which were reinforced 90%, 80%, and 70% of the time, for stimuli A, B, and C, respectively). For stimuli D, E, and F, Go responses would usually lead to lost points (70%, 80%, and 90% of the time, respectively). Subjects could avoid losing points by withholding space-bar presses, as non-responses were associated with a neutral outcome. In a post-acquisition test phase, subjects were shown each of the training stimuli 6 times, along with 11 combinations of the training stimuli (e.g., B on the left and E on the right) 3 times each, and received no feedback for their choices. Results: During the acquisition phase, patients made significantly more Go responses than controls (69% v. 61%; t=2.27, p<0.05). Despite their general tendency to make more Go responses, patients actually made fewer Go responses to Go training pairs in the test phase than controls (68% v. 80%; t=1.98, p=0.05). Controlling for the rate of Go-responding to neutral novel stimuli (44% v. 38%), patients showed a greatly reduced tendency to make appropriate Go responses (t=2.313, p<0.05), although patients and

controls showed a similar tendency to withhold responses when appropriate (t=0.704). Conclusions: These results are consistent with a selective deficit in reward-driven learning in SZ, not attributable to a reduced rate of responding. The Go bias shown by SZ patients may reflect excess tonic DA, which could reduce the fidelity of phasic DA signals, often linked to learning. Support: NIMH P30 MH068580-01, 1 R24 MH72647-01A1

LOSS OF PARVALBUMIN-POSITIVE INTERNEURONS PREDICTS DEFICITS IN CORTICAL GAMMA RHYTHM GENERATION IN ANIMAL MODELS OF SCHIZOPHRENIA-LIKE COGNITIVE DYSFUNCTION

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Psychiatric illnesses, particularly schizophrenia, are associated with disrupted markers for interneuronal function. Deficits in interneuron markers are particularly prevalent in prefrontal cortex and are also seen in medial temporal structures such as entorhinal cortex and hippocampus. The interneurons particularly affected in schizophrenia play a critical role in generating cortical rhythms in the EEG gamma band (30 – 60 Hz) – an oscillation associated with sensory processing and short term memory. We investigated a possible link between these two observations in entorhinal cortex and hippocampus using three models of psychiatric illness: 1) Lysophosphatidic acid 1 receptor (LPA1) deficient mice. 2) Antagonism of the NMDA subtype of glutamate receptor. 3) Maternal separation. Neither LPA1 receptor deficiency nor NMDA receptor antagonism induced any change in gamma rhythms generated by kainate in hippocampal slices. In contrast, a dramatic decrease in the power of gamma oscillations was seen in superficial but not deep medial entorhinal cortex layers in both models. Immunolabelling for GABA, parvalbumin and calretinin in medial entorhinal cortex from LPA1-deficient mice showed a c.40% reduction in total GABA- and parvalbumin-containing neurons but no change in number of calretinin-positive neurons. This deficit was specific for layer II. No change in these markers was seen in the hippocampus. Acute NMDA receptor blockade, which selectively reduces synaptic drive to LII entorhinal interneurons, also disrupted gamma rhythms in a similar manner in superficial entorhinal cortex. Maternal separation caused a more profound deficit in gamma rhythm generation than LPA1 KO or NMDA antagonism. In addition to a decrease in gamma rhythm generation in medial entorhinal cortex, a marked decrease in gamma rhythm generation in lateral entorhinal cortex and hippocampus was also seen. These data demonstrate an area-specific deficits in gamma rhythmogenesis in a range of animal models of psychiatric illness and suggest that loss, or reduction in function, of specific interneuron subtypes having a large NMDA receptor expression may underlie this network dysfunction.

TOO MUCH OR TOO LITTLE? HIGH-FREQUENCY NEURAL SYNCHRONY IN FIRST EPISODE SCHIZOPHRENIA

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Background: From an integrative neuroscience perspective, schizophrenia is characterized by a breakdown in the neural mechanisms for binding information into a coherent whole (1). Gamma (40Hz) phase synchrony is a candidate mechanism for neural binding, associated with the emergence of conscious awareness. In first episode schizophrenia, we examined a) Gamma synchrony to emotionally significant stimuli, presented at different levels of awareness and b) whether disturbances in synchrony are specific to the Gamma band. Method: 56 first episode schizophrenia (FES) patients were compared to 112 matched healthy controls, and the context of normal variation in 1,008 controls spanning a wider age range, from the Brain Resource International Database. Phase synchrony in multiple frequencies (focusing on the Gamma band) was extracted from EEG recordings to expressions of fear and happiness presented under conscious (>200ms) and nonconscious (10ms, with backward masking) perception conditions. Results: Healthy controls showed a sustained enhancement in Gamma synchrony over parietal occipital regions for consciously perceived emotion stimuli, but an enhancement over the temporal cortex for nonconscious perception. In FES, stimulus-lock reductions in Gamma synchrony were observed in the context of generally excessive synchrony over frontal and temporal regions, and a reversal of the normal lateralization of synchrony, regardless of awareness level. Conclusion: The findings suggest that distinct mechanisms of neural synchronization determine level of awareness for biologically salient signals of emotion. A general excess of synchrony in FES, regardless of awareness, may contribute to the inability to differentiate relevant from irrelevant stimuli, and consequent misattributions of emotional salience. These findings support an integrative neuroscience model of impaired neural binding in schizophrenia and complement evidence for a reversal of normal frontal-temporolimbic functional connectivity in FES (2). 1. Williams LM (2006). An integrative neuroscience model of 'significance' processing. J Integrative Neurosci., 5, 1-47. 2. Das, P et al. Dysfunctions in the direct and indirect thalamo-amygdala pathways during facial emotion perception in schizophrenia: a functional connectivity approach (under review). Acknowledgments: Pfizer fellowship (LMW) and Brain Resource International Database (www.brainresource.com), coordinated by BRAINnet (www.brainnet.org.au).

MET/MET CATECHOL-O-METHYLTRANSFERASE GENOTYPE ASSOCIATED WITH INCREASED RESPONSE INHIBITION DEFICITS

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The Catechol-O-methyltransferase (COMT) gene Val158Met polymorphism alters the metabolism of dopamine (DA), via enzyme activity, and consequently has an impact on cognitive function. There is also evidence that this polymorphism confers risk for schizophrenia-spectrum disorders. However, genetic association studies of the Comt Val158Met polymorphism in cognition have produced inconsistent results. Bilder and colleagues (2004) posit that this variability is due to the differential effect of the Comt Val158Met alleles on different types of cognitive tasks. The Comt 158Met allele encodes a low-activity isoform of COMT, and, as proposed by Bilder et al., enhances performance on sustained behaviours (i.e., goal-directed action/cognition) through the accumulation of DA at tonic levels. The Comt 158Met allele is also proposed to blunt the phasic pattern of DA bursts, thereby impeding the resetting of behavioural programs. The Comt Val158 allele, in contrast, codes for a high-activity version of COMT that rapidly metabolizes DA, resulting in a phasic pattern of DA concentration in the synapse. Consequently, the

Comt Val158 allele is hypothesized to facilitate the resetting of behavioural programs while disrupting the maintenance of goal-directed behavior. Thus, these alleles each confer both cognitive advantages and disadvantages, depending on extant task demands. This model predicts that individuals with the Met/Met genotype will perform poorly on measures of response inhibition (RI), since such tasks necessitate rapid behavioral resetting. In the current study, this hypothesis was tested by comparing the RI abilities of both healthy and schizotypal undergraduates as a function of their Comt genotype. Consistent with our prediction, persons with the Met/Met genotype had significantly more inhibition errors, relative to Val/Val and Val/Met subjects. Importantly, our RI tasks allow for the systematic manipulation of two putative sources of RI errors: perceptual similarity of discriminative task stimuli and response prepotency. Data suggest that Met/Met individuals were disproportionately impaired as response prepotency increased. Met homozygotes also showed increased error rates in response to increased stimuli similarity; however, this effect was less marked. Due to sample size constraints, this interaction was not significant. However, with sufficient power this finding will likely prove significant.

VISUOSPATIAL ASSOCIATIVE MEMORY DECLINES FOLLOWING A FIRST EPISODE OF PSYCHOSIS: DATA FROM THE EPPIC LONG-TERM FOLLOW-UP STUDY

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One of the strongest findings in neuropsychological studies of schizophrenia is memory impairment, but the timing of this impairment is still unclear. In addition, the tools used to assess memory function have been varied and may not have assessed functions dependent on plastic brain regions. Previously, we have shown that visuospatial paired associative learning (VSPAL) is not impaired in first episode schizophreniform psychosis patients, although there were severe deficits in patients with schizophrenia of more than two years duration compared to controls. Verbal paired associative learning (VPAL) however does seem to be affected earlier in the disorder, with little difference between first episode and chronic illness. In this study we sought to investigate longitudinal change in associative memory in first episode psychosis patients, using a visual associative learning test (visuospatial paired associates from the CANTAB). 23 patients and 17 controls completed the test at two timepoints (mean time between assessments = 6.5 years, range = 5.3 – 9.2 years). The assessment of the patients at baseline was completed soon after the onset of their first psychotic episode. Repeated-measures ANCOVA showed a significant decline in VSPAL function in the patient group (Time x Group interaction $F[1,34]=8.98$, $p=0.005$). Repeating these analyses after dividing the patient group into remitted (n=15) and non-remitted patients (n=8) showed that the decline in VSPAL function was specific to the non-remitted group (Time x Group interaction $F[2,33]=4.56$, $p=0.018$: Non-remitted; mean errors at baseline = 35.8, at follow-up = 53.9: Remitted; mean errors at baseline = 25.2, at follow-up = 31.5). These data support our previous cross-sectional study, and suggest that there are cognitive functions that decline with continued psychotic illness. It remains to be seen whether these progressive impairments are associated with structural brain changes.

USE OF ANCOVA FOR ASSESSING PATIENT-CONTROL DIFFERENCES IN SOURCE MONITORING BIASES

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In previous studies of source monitoring in schizophrenia, guessing estimates were partialled out of source monitoring measures using multinomial modelling, but this methodology resulted in a restricted set of estimated parameters. In the current source monitoring study we overcame these limitations using Analysis of Covariance (ANCOVA), by entering the appropriate count of false positives as covariates when they met statistically determined criteria. Subjects were 51 patients with schizophrenia or schizoaffective disorder, and 20 controls. For the source memory task, encoding involved solving computer-presented anagrams with clues (e.g., "A scaly reptile - SANEK"), or receiving the solution from the computer or the experimenter. Recall involved indicating whether a presented word is New, or was previously generated by the Computer, Experimenter, or Self. The dependent measures were as follows: (1) Item Recognition: old items correctly labelled old. (2) Source Discrimination: old items attributed to the correct source. (3) Internalization Bias: old items originating from the Experimenter or Computer, but attributed to the Self. (4) Externalization Bias: old items originating from the Self, but attributed to either the Experimenter or Computer. (5) Confusion of External Sources: old items originating from the Experimenter or Computer, but attributed to the wrong Experimenter or Computer source. A specific covariate was used for each dependent variable: (1) Recognition and (2) Source Discrimination: the count of false positives. (3) Externalization Bias: the count of Experimenter and Computer responses to new items. (4) Iternalization Bias: the count of Self responses to new items. (5) Confusion of External Sources: the count of Experimenter and Computer responses to new items. The Results suggested that when comparing patients to controls, impairments on item recognition and source discrimination were observed. When comparing patient groups split on hallucinations, a bias toward attributing self-generated items to an external source was observed. Using ANCOVA to partial guessing estimates out of source monitoring error types is recommended for source monitoring studies investigating group differences, and suggests that previously reported null results may be attributable to a failure in separating guessing from source monitoring measures.

EXPLORING FACIAL AFFECT PROCESSING DEFICITS IN SCHIZOPHRENIA USING THE N170 AND GAMMA BAND RESPONSE

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Introduction: Schizophrenia patients exhibit deficits in a wide range of social cognitive tasks, including facial affect processing. However, it is unclear whether the deficit in facial affect recognition is due to processing of basic facial features or due to processing of affect features. The face-specific N170 event-related potential and the gamma band response were used to examine facial affect processing and basic facial feature (i.e., gender) processing deficits in schizophrenia. Methods: Data from 26 schizophrenia patients and 27 normal comparison subjects during a basic facial (gender identification) and facial affect identification (emotion identification) tasks were collected. Participants, in separate

blocks, identified either the gender or the specific emotion of faces. We examined two phenomena: the N170 event related potential and the evoked gamma band (30-50 Hz) response. Results: For the N170 response during emotion identification there was no significant difference between groups. However, patients' N170 during gender identification was significantly lower over both hemispheres compared to the control subjects. Within-subject t-tests revealed that patients produced a significantly larger N170 during emotion identification vs. gender identification whereas controls showed similar amplitudes for both tasks. Normal controls produced a significantly larger N170 during both tasks in the right hemisphere whereas patients did not show this lateralization. Findings for the gamma band response were opposite to those of the N170: normal controls showed significantly greater activity compared to patients during the emotion identification task, whereas activity during the gender identification task was comparable between both groups. Discussion: The results from the N170 reveal that schizophrenia patients have a deficit during non-emotional judgment of faces (i.e. gender) but the N170 is enhanced when judging the emotional content of the face. However, patients had lower gamma activity than controls during emotion processing. Because gamma activity is associated with binding of features, these results suggest problems in visual organization of emotional information. The results help to clarify the nature of facial affect processing deficits in schizophrenia. Patients show a neural response of normal amplitude to emotional stimuli, but the processing does not appear to be as well-organized as in controls.

EMOTIONAL BINOCULAR RIVALRY IN SCHIZOPHRENIA

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Binocular rivalry occurs when dissimilar images are presented to corresponding visual fields of the two eyes. As they compete for perceptual dominance the observer's perception switches between the two alternatives. Previous research suggests that the rate of switching during binocular rivalry is associated with psychotic symptoms but cognitive (e.g. learning, attention) and affective (e.g. emotional content of stimuli, mood state) context can also modulate dominance duration and switching rate. We investigated the relationship between affect and binocular rivalry in healthy controls and individuals with schizophrenia or schizoaffective disorder (SZ). We hypothesized that affective stimuli would alter the percept duration and rivalry switching rate. A face and a radial grating stimuli were presented to the opposite eyes. Subjects were asked to view the stimuli and to indicate their perceptual experience (e.g. face or grating or mixed) by button presses. The perceptual switching rate and dominance duration were measured. Face stimuli consisted of 4 expressions for each of 4 identities (happy, sad, angry, neutral). Clinical symptoms and mood state were assessed in the same session. Preliminary analyses show no group differences in perceptual dominance or switching rate across the 4 emotional conditions. However, in the SZ group, the rate for each condition was associated with increased negative affect. Reduced perceptual dominance duration was associated with increased psychotic symptoms and depression scores for all conditions in the SZ group. In healthy controls, no correlations were found between mood and binocular rivalry. These results suggest that psychotic and emotional disturbances in individuals with schizophrenia may increase sensitivity towards the affective context of visual stimuli, which in turn, influences binocular rivalry and perceptual awareness.

STRESS REACTIVITY AND AFFECTIVE MODULATION DURING THE PRODROMAL, FIRST-EPISODE AND CHRONIC PHASES OF SCHIZOPHRENIA

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Substantial evidence indicates that stress contributes to the etiology, expression and course of schizophrenia. Significant questions persist, however, concerning the behavioral, physiological and clinical consequences of stress exposure, patient characteristics that might predict stress reactivity, and pathways that could account for sensitivity to perceived psychological threat. This research draws from basic research in health psychology and the study of emotion to consider how stress and emotional reactions might contribute to the onset of schizophrenia, progression of the illness, and functional outcome. To examine the consequences of exposure to psychosocial stress, the Trier Social Stress Test (TSST) was administered to prodromal, first-episode and chronic schizophrenia patients along with samples of matched healthy comparison subjects. The groups were not found to differ in baseline levels of salivary cortisol, possibly due to the effects of antipsychotic medications. Cortisol levels increased in response to the TSST, but these changes did not differ as a function of group. Among the patient groups, higher resting levels of cortisol were associated with poorer daily functioning. To further investigate the impact of psychological threat, affective modulation of the startle eye blink reflex was utilized as an index of the appetitive and defensive motivational systems. Replicating and extending prior research, a normal pattern of affective modulation was observed across all three phases of illness; pleasant or appetitive visual images attenuated the amplitude of the startle eye blink reflex and unpleasant or aversive images potentiated the reflex relative to a neutral response. In addition to reflecting motivational priming, startle modulation appears to be affected by the intensity of activation associated with the arousing qualities of a stimulus. Examination of the startle reflex to specific emotional content of the pictures generally revealed an enhancement of affective modulation to pleasant and aversive images as arousal levels increased. The strength of association between affective modulation and functional outcome was found to vary as a function of phase of illness and the motivational priming system that was activated. Fundamental aspects of stress reactivity and the emotion response, therefore, appear to remain largely intact across the prodromal, first-episode and chronic phases of schizophrenia.

NEUROPSYCHOLOGICAL DEFICITS IN AFFECTIVE AND NON-AFFECTIVE PSYCHOTIC PATIENTS: RESULTS FROM AESOP EPIDEMIOLOGICAL COHORT

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Background: Patients with schizophrenia exhibit pervasive neuropsychological dysfunction evident already at the first psychotic

episode. However, it is not clear if similar deficits are also present in other psychotic disorders, especially affective psychosis. Methods: Data came from the AESOP study, comprising a large epidemiological cohort of first-onset psychosis patients. We compared schizophrenia (n=106), schizoaffective (n=14), bipolar/manic (n=41), depressive psychosis (n=48), brief psychotic disorder and psychotic disorder NOS (n=26), and delusional disorder (n=10) patients to healthy controls (n=264) on 18 neuropsychological measures selected to assess six major domains: (1) memory (verbal and visual) (2) academic verbal abilities (3) attention, concentration and mental speed (4) executive functions and working memory (5) language (6) visual constructual/perceptual abilities. Additionally, premorbid intelligence, current full-scale IQ, performance IQ and verbal IQ were assessed. Results: Schizophrenia and schizoaffective patients performed significantly worse ($p<0.001$) than controls on almost all measures but were not different from each other. The group with psychotic depression was indistinguishable from that of schizophrenia. Subjects with bipolar/manic disorder performed significantly better than those with schizophrenia and psychotic depression. Further, in comparison to healthy controls bipolar/manic performance was impaired only on verbal learning, block design, digit symbol and category fluency. Conclusions: Early in the course of disease schizophrenia is distinguishable from bipolar/manic psychosis but not from depressive psychosis by global and specific neuropsychological functioning.

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EARLY WITHDRAWAL AND TRANSDERMAL NICOTINE EFFECTS ON PERFORMANCE-RELATED COGNITIVE FUNCTIONING IN SCHIZOPHRENIA

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Persons with schizophrenia (SZ) represent the psychiatric group with the greatest rates of cigarette smoking, with estimates as high as 90%. While the reasons for this high percentage in SZ are not yet fully understood, recent evidence has identified self-medication as a hypothesis. One reason for self-medication may include attempts to compensate for neuropsychological deficits, considered to be primary in this disorder. Attentional and performance-related functions, including speed of processing and accuracy of responding, are understood to be impaired in SZ. Therefore, in this study, we sought to elucidate the potential relationship between smoking behavior and cognitive function. A total of 21 persons with SZ and 14 age-matched comparison (NCL) male smokers were recruited from the VA Boston Health Care System – Brockton Division and community-based populations. Subjects were administered the Attention Network Test (ANT) to assess three divisions of attention (alerting, orienting, executive), reaction time (RT) and accuracy (ACC). Across subjects, administration of the ANT was performed at three nicotine conditions including baseline (without cigarettes for at least 1 hour), early withdrawal (without cigarettes for 8 hours) and patch (3hr application of 21mg Nicoderm CQ transdermal nicotine patch). As expected, overall RT in SZ ($M = 777.9$ms) was slower than NCL ($M = 606.3$ms), $F(1, 33) = 10.62$, $p < .01$. RT change variable computations suggested significantly greater improvement for SZ ($M = 87.38$) at nicotine patch compared to baseline than NCL ($M = 37.14$), $F(1,33) = 4.21$, $p < .05$. Overall rates of ACC tended to be more impaired in SZ (93.3%) than NCL (97.9%), with SZ (91.6%) significantly less accurate than NCL (97.2%) at early withdrawal, $t26 = 2.18$, $p < .05$. Importantly, following nicotine patch, ACC rates were insignificantly different to the NCL group. Therefore, nicotine withdrawal demonstrated a greater negative impact while nicotine administration showed a greater positive impact in SZ. Differences between groups on networks of attention were insignificant. These findings suggest a greater impact of nicotine in SZ on neurocognitive functioning in context to performance-related areas. Funding support provided, in part, by a Schizophrenia Dissertation Fellowship, Supreme Council 33°, Scottish Rite Masonic Organization; Manfred Meier Neuropsychology Scholarship, American Psychological Foundation, Division 40 – Clinical Neuropsychology.

INTERRUPTED GRASPING PERFORMANCE UNDER A VISUAL ILLUSION: A TMS STUDY TO INDUCE SCHIZOPHRENIA-LIKE DEFICITS

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Previous studies indicate that deficits in visually-guided reaching movements among patients with schizophrenia (SCZ) are mediated by abnormalities in the dorsal visual processing stream. For example, in healthy individuals grasping movements are typically resistant to visual illusions whereas patients with SCZ are more susceptible. Repetitive transcranial magnetic stimulation (rTMS) can be used to induce transient neural lesions. This study, therefore, induced transient lesions in healthy subjects with rTMS delivered to dorsal structures that have been associated with inaccurate grasping in patients with SCZ. Fifteen healthy participants completed a visual illusion paradigm where they either grasped or estimated the vertical dimension of blocks whose size was distorted by the presence of neighbouring objects. Participants received either active or sham 1 Hz rTMS delivered at 100% resting motor threshold to the following: 1) dorsal cortical structures (i.e., anterior intraparietal cortex; AIP) responsible for grasping movements; and 2) the ventral cortical structures (i.e., lateral occipital cortex; LOC) responsible for object recognition. Our results demonstrate that grasping movements were disrupted following rTMS stimulation applied to AIP. In particular, participants' peak grip aperture, while grasping target blocks, was scaled in accordance with the visual illusion. In contrast, rTMS applied to LOC interrupted estimation performance. That is, participants demonstrated peak estimates that were reflective of the target block's true size and, therefore, were not modulated by the visual illusion. Notably, however, estimation performance was also interrupted by rTMS stimulation applied to AIP in the same manner; therefore, alteration in estimation performance cannot be attributed to ventral stream disruption alone. Our results demonstrate that rTMS-induced lesions of the dorsal stream in healthy subjects produce disruption in grasping movements that are similar to those seen in patients with SCZ. These results strengthen the evidence suggesting that dorsal brain circuitry is involved in the pathophysiology of SCZ.

NEUROCOGNITIVE MARKERS OF 6 MONTH CLINICAL OUTCOME IN FIRST EPISODE PSYCHOSIS

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Background: Cognitive dysfunction has been shown to be related to and predictive of functional outcome in people suffering from their first episode of psychosis (FEP), however, the relationship between cognitive dysfunction and clinical outcome remains open to discussion. The early identification of cognitive markers in non-responders may allow for alternative treatments and/or medications resulting in a more favorable outcome. Method: This study is part of an ongoing behavioral and imaging project of the Prevention and Early Intervention Program for Psychoses (PEPP) of the Douglas Hospital, McGill University in Montréal, Canada. Eighty-two patients with FEP and 22 healthy controls were used in this six-month outcome analysis. Responders were defined as those with global measures of two or less (mild) on the Scale for the Assessment of Positive Symptoms (SAPS) and three or less (moderate) on the Scale for the Assessment of Negative Symptoms (SANS). All subjects had undergone standardized clinical and neuropsychological assessments. The neuropsychological assessment included the Wechsler Adult Intelligence Scale (WAIS), Wechsler Memory Scale (WMS), Stroop, Trail Making Tests A and B, d2 Attention Test, Verbal Fluency, and Tower of London. The evaluation also included the Hinting Task, the Social Intelligence Tests, and the Iowa Gambling Task. Results: Non-responders ($N = 40$) were compromised in areas of verbal memory (Logical Memory I – immediate recall and Logical Memory II – delayed recognition of the WMS, $ps < 0.05$), spatial memory (Corsi Spatial

Span Total of the WMS, ps < 0.05), and executive functioning (Stroop Interference, ps < 0.05) as compared to responders and controls. In addition, none of the compromised areas were significantly different between responders and controls except for the Logical Memory I – immediate recall. Furthermore, the Full IQ and Verbal IQ measures of the WAIS only differed between the non-responders and controls (p < 0.05). All measures were independent of symptoms at the time of testing. Conclusions: This study revealed that a specific number of cognitive measures taken at baseline could differentiate between non-responders and responders but not between responders and controls at six months. This outcome suggests that those with dysfunctions in memory and executive functioning should undergo alternative treatment or be monitored more closely for alternative medications to produce a more favorable outcome.

CONSEQUENCES OF CANNABIS USE ON EXECUTIVE FUNCTIONS IN METHAMPHETAMINE INDUCED PSYCHOSIS

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Methamphetamine (MA) abuse is associated with neurotoxicity in fronto-temporal-striatal regions and related cognitive deficits. However, MA is seldom abused in isolation, and cannabis is the most common secondary drug abused by MA users. Gonzalez et al. (2004) found a trend suggesting worse global cognitive functioning in non-thought disordered MA users who lacked a history of cannabis dependence compared to MA users with past cannabis dependence. Thus cannabis use might be neuroprotective in non-thought disordered MA users. The present study aimed at elucidating the relationships between cannabis and MA abuse on executive abilities in persons with MA induced psychosis. It was hypothesized that cannabis use would moderate the effects of MA on cognition. Fifty-two individuals with MA induced psychosis completed a battery of executive functioning tasks, including measures sensitive to the integrity of the orbitofrontal circuit (OFC; Iowa Gambling Task) and of the dorsolateral prefrontal circuit (DLPFC; CANTAB's ID/ED Shift task). Exclusion criteria included inability to communicate in English and intoxication at testing. Regression analyses were used to predict executive functioning. After controlling for age and premorbid intelligence, years of MA use, years of cannabis use, and their interaction were entered as predictors. Neither duration of MA nor duration of cannabis abuse predicted ID/ED performance. In contrast, increased duration of MA abuse predicted poorer gambling task performance (R2=0.185, p=.001), whereas increased duration of cannabis abuse predicted better gambling task performance (R2=0.092, p=.021). The interaction terms were not significant in either the ID/ED or the gambling task analyses. Our study suggests that the impact of chronic substance abuse on executive functions depends upon the particular function evaluated. The functional integrity of DLPFC as indicated by ID/ED performance is not related to the drug exposure durations or their interaction. In contrast, duration of MA abuse strongly predicts greater OFC dysfunction and duration of cannabis abuse modestly predicts improved OFC functioning as indexed by the gambling task. The hypothesis that cannabis use attenuates the neurotoxic effects of MA abuse was not supported, as indicated by the lack of a significant interaction between the duration measures. That is, the impact of cannabis abuse and MA abuse on OFC functioning emerged as independent predictors.

PREDICTING REAL WORLD OUTCOMES FROM DISCRETE FUNCTIONAL AND COGNITIVE ABILITIES

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Significant deficits are found in many cognitive domains for the vast majority of schizophrenia patients. Previous studies have left some question as to whether global cognitive impairment or discrete domains affect functional outcomes, and none have addressed distinctions within and between ability and performance domains. This study examined the relevance of specific cognitive domains, derived from data reduction techniques, to discrete functional abilities and functional outcome domains. Schizophrenia patients (n=212) were examined with a comprehensive neuropsychological battery (NP), two measures of functional ability (interpersonal and adaptive), and rated on domains of real world functional performance by an objective third-party. Exploratory and confirmatory factor analyses and path analytic procedures were used to determine cognitive factors and their direct and mediated effects on different functional outcomes. Four empirically-derived cognitive factors (attention/working memory, processing speed, verbal memory, and executive functioning) had differential correlations with interpersonal and adaptive skills and with real world performance. Path analyses revealed direct effects of the attention/working memory, processing speed, and executive functioning domains on interpersonal skills, while adaptive skills were predicted by verbal memory, processing speed, and attention/working memory. Real world interpersonal behavior was predicted by negative symptoms, self-reported depression, and interpersonal skills, but not directly by cognitive skills. Real world performance in community behaviors was predicted by adaptive skills and also by a direct effect of processing speed. In contrast to previous reports, we found differential predictors of functional abilities and functional performance from discrete domains of cognition. These cognitive domains were differentially related to interpersonal and adaptive skills, while processing speed affects real world social behavior both directly and through its influence on skill acquisition. Treatments that target specific cognitive or functional skills might result in changes in very specific outcome domains, rather than promoting global functional improvement. Assessment and treatment needs will be discussed accordingly.

OLFACTORY IDENTIFICATION DEFICITS REMAIN STABLE FOLLOWING A FIRST EPISODE OF PSYCHOSIS: DATA FROM THE EPPIC-LONG TERM FOLLOW-UP STUDY

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Objective: Previous investigation reveals stable olfactory identification deficits (OID) at 6 months following first onset of psychosis

(Brewer et al, 2001), and more recently, in an ultra-high-risk group that later developed a schizophrenia spectrum disorder (Brewer et al, 2003). As a potential premorbid marker of transition to schizophrenia, the utility of OID in mapping development and compromise of limbic-prefrontal pathways, particularly in orbitofrontal regions, is important for tracking the relative integrity of circuitry implicated in the course of psychosis following early onset. Method: In this study we sought to investigate longitudinal change in olfactory identification in first episode psychosis (FEP) patients using the University of Pennsylvania Smell Identification Test (UPSIT) relative to Controls (CTLs). Results: Our preliminary data from 14 FEP and 9 CTLs (mean time between assessments = 73.4 months, range = 61.4 – 85.2 months) showed no change in performance over time (FEP T1 = 30.5 [SE = 1.3]/T2 = 31.2 [SE = 0.9]; CTL T1 = 32.4 [SE = 1.7/T2 = 31.7 [SE = 1.2]). Conclusions: These data support our previous longitudinal study and suggest that there is no change in OFC function with continued psychotic illness. Interaction between OFC and other neural networks implicated in the degenerative aspects of schizophrenia requires further exploration. The findings are discussed in the context of utilising olfactory models of function to track emerging onset of psychopathology. Brewer et al, 2001, Am J Psychiatry, 158, p107-115; Brewer et al, 2003, Am J Psychiatry, 160, p1790-1794.

SERIAL ORDER PROCESSING IN FIRST-ONSET SCHIZOPHRENIA: A CORRELATIONAL ANALYSIS OF ERROR PATTERNS AND CLINICAL SYMPTOMS

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A characterisation of the cognitive factors contributing to short term memory deficits in schizophrenia and their relation to clinical symptoms is key to further understand the behavioral manifestations associated with schizophrenia (Conklin et al., 2005). A predominant hypothesis put forward to account for the patterns of memory deficits observed in patients with schizophrenia is that of a greater susceptibility to saturation. In order to pinpoint the source of memory deficits, we propose a thorough analysis of errors committed in verbal (Elvevag et al., 2001) and spatial (Fraser et al., 2004) memory tasks in combination with examining the impact of saturation and distraction on performance. Furthermore, the link between cognitive performance and clinical symptoms is investigated. The sample consisted of 15 outpatients in recent-onset schizophrenia and 21 healthy controls. The effect of distraction upon memory performance was tested by interleaving irrelevant items within a sequence of to-be-remembered items – the sandwich effect (Hitch, 1975; Tremblay et al., 2005) – and that of saturation was examined by comparing sequences of 5 and 7 items. Participants were required to perform serial recall, that is, they had to remember sequences of items (digits or dots) and the order in which they were presented. Performance deficits were analysed with output analysis of errors (Henson, 1998) considering intrusion, transposition and omission for all conditions. The PANSS was used to assess the clinical symptoms in patients. Independent-sample t tests were computed on the cognitive parameters to determine group differences. There were significant differences on transposition and omission errors. Correlationnal analyses were performed to evaluate the association between memory errors and the five dimensions of the PANSS. The results indicate that transpositions errors in the presence of distraction are related to negative and hostility components of the PANSS. However, indexes of saturation did not correlate with any of the clinical symptoms. The results are interpreted in light of the concept of contextual disturbance proposed by Hemsley (2005). Our comprehensive analysis of errors in relation with clinical symptoms may shed some light on etiology and has implications for future cognitive and clinical studies.

REDUCED CENTER-SURROUND INTERACTION IN MOTION PROCESSING OF SCHIZOPHRENIA: EVIDENCE FOR ALTERED SPATIAL ORGANIZATION OF THE VISUAL SYSTEM

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Brain disorganization is hypothesized as a core dysfunction associated with schizophrenia. While generally consistent with findings in different fields such as compromised neural connection in postmortem schizophrenic brains and some clinical symptoms, this hypothesis needs to be tested by a link between specific behaviors and their underlying neural mechanisms in patients. In basic neurobiological studies of the visual system, center-surround interaction represents a ubiquitous neural mechanism of which neurons compares visual signals in one spatial region with those in the immediately surrounding region. This neural mechanism is characterized by antagonistic interactions between the responses to central and to surrounding visual stimuli. The perceptual correlate of the center-surround neural mechanism is a suppressive modulation of a surrounding visual stimulus on the perception of a central visual stimulus. We examined the suppressive effect of surround on motion perception at the center in schizophrenia patients (n=24), as well as in normal controls (n=25). Subjects judged the direction of a circular random dot pattern (RDP, center) at various stimulus coherence levels (strength of motion signal), with and without presence of another concentric RDP (surround). The presence of the surround shifted the perceptual judgments of the center towards the opposite direction of the surround at low and intermediate coherence levels in both subject groups, but the magnitudes of the perceptual shift were significantly larger in the patients. The abnormally large perceptual shifts in the patients were not correlated with psychotic status (measured with PANSS scores) or antipsychotic medication (measured with CPZ equivalents), nor with neurocognitive functioning (measured with intelligence quotients). These results show that the normal suppression of the surround on motion perception of the center is weakened in schizophrenia. The weakened center surround interaction suggests that abnormal perceptual behaviors in schizophrenia patients can be linked to specific local neural interactions, which may involve certain types of neurotransmission such as GABA-mediated inhibition. The link between the abnormal motion perception and the center surround neural mechanism provides evidence for altered spatial organization of the visual system in schizophrenia.

ERRONEOUS BELIEFS: HOW DO DELUSIONS IN PSYCHOSIS DIFFER TO CONFABULATIONS ARISING FROM ACQUIRED BRAIN INJURY?

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Traditionally a delusion has been defined as a belief which is considered incredible to others, held with firm conviction, intolerant of contradictory evidence, a source of subjective distress and involving

personal reference. Delusions are the hallmark symptom of psychosis. A rare phenomenon seen in people with acquired brain injury (ABI) is spontaneous confabulation which is where a false memory is recited by the patient following no prompting. Spontaneous confabulators hold strong convictions about the veracity of their memory and at a qualitative level, a confabulation can appear to be similar to a psychotic delusion. The neuropsychological nature of both delusions and confabulations remain unclear despite their interest to researchers and clinicians. Several theories abound linking delusions to executive dysfunction, reduced inhibition, poor memory or poor emotional processing. This study compared people with delusions in psychosis to spontaneous confabulators with ABI on a wide range of neuropsychological tests to decipher the similarities and differences. 2 confabulators and 4 participants with psychotic delusions were tested on a range of neuropsychological tests measuring various aspects of executive functioning, and memory. All participants showed difficulties in mental flexibility, response inhibition and executive functioning and there was little to distinguish delusional content from that of a spontaneous confabulation. However two distinct mechanisms which clearly distinguished spontaneous confabulations from delusions emerged; a) only the spontaneous confabulators failed Schnider's confabulation memory test (Schnider et al 1999) that requires the suppression of proactive interference b) only deluded participants reported high levels of distress associated with their delusional beliefs. In summary, content of both spontaneous confabulation and delusional beliefs might arise from some common dysfunction in prefrontal cortex, but there appear to be some distinct cognitive and emotional processes involved too. The finding that emotional distress is needed for an erroneous belief to become delusional supports Freeman and Garety's (2004) model of delusions.

ARE THERE PEOPLE WITH SCHIZOPHRENIA WHO HAVE NO COGNITIVE DEFICITS?

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It has become well established that cognitive impairment is a very frequent accompaniment of schizophrenia but is not invariable. However, even when patients score within the average range on IQ tests, it is claimed that their profile of performance is abnormal. We tested this in three cohorts; A large clinical sample, and two epidemiological cohorts of psychotic patients (The Suffolk County cohort (USA) and the Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) cohort (UK). The clinical sample was designed to include over sampling of a unique sub-group of patients – those with above average premorbid IQ (>110) who do not show evidence of post-illness cognitive decline. We found that the profile of those with high IQ and no decline, as compared to those with high IQ and decline and those with average IQ, still betrayed evidence of impairments on simple and complex reaction time tasks and certain subtests of the Wechsler Adult Intelligence Scales pertaining to processing speed, although episodic memory and executive function was unimpaired. These data have implications for theories which place cognitive deficits at the core of the schizophrenic disorder and also shed light on which deficits, if any, are specifically implicated and which are part of a general deficit.

PREFERENTIAL SEMANTIC FLUENCY IMPAIRMENT IN SCHIZOPHRENIA: RELATIONSHIP TO SYMPTOMS

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Semantic and phonemic fluency are two tasks thought to impose comparable demands on executive functioning, with semantic fluency imposing additional demands on the semantic system. Larger semantic than phonemic fluency impairment in schizophrenia has been a consistent finding, suggesting that the disorder is associated with semantic system dysfunction. However, the relationship of this dysfunction to particular symptoms of schizophrenia remains unclear. Goldberg and others have suggested that semantic impairment underlies disorganized symptoms, in particular formal thought disorder (FTD). Although past studies employing FTD and non-FTD groups have supported this hypothesis, the influence of other symptoms was not investigated, raising the possibility that symptoms correlated with FTD were responsible for observed differences. To further evaluate the hypothesis of semantic impairment in FTD, the current study examined the relationship of preferential semantic over phonemic fluency impairment to a variety of schizophrenic symptoms, including FTD. 74 patients diagnosed with schizophrenia from inpatient (n = 9) and outpatient (n = 65) hospital settings in the Midwest were tested. All patients received the Scale for the Assessment of Negative Symptoms (SANS)/Scale for the Assessment of Positive Symptoms (SAPS), the phonemic and semantic conditions of the Controlled Oral Word Association Test (COWAT), and the vocabulary test from the Shipley Institute of Living Scale (SILS) as a measure of premorbid IQ. A semantic difference score was calculated by subtracting phonemic from semantic fluency performance, and Pearson correlation coefficients were computed between the semantic score and various symptom ratings. There was no association between semantic processing and positive thought disorder ($p = .665$). A statistically significant association between semantic processing and level of hallucinations ($r = .355$, $p = .002$) was observed. The relationship between hallucinations and semantic processing remained significant after inclusion of premorbid IQ, disorganized symptoms, or negative symptoms as covariates. The results revealed an association between semantic impairment and severity of hallucinations, but not FTD, in schizophrenia. This suggests that semantic impairment and hallucinations may share underlying cognitive mechanisms or neural pathology, a hypothesis that warrants further investigation.

ATTENTION AND SENSORI-MOTOR INTEGRATION DYSFUNCTIONS IN SCHIZOPHRENIA: A PLAUSIBLE CAUSE FOR AN ABNORMAL SENSE OF AGENCY IN SCHIZOPHRENIA?

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In a recent study, we reported that patients with schizophrenia revealed a problem both in motor fluency and in the modulation of attention focus, during simple object-manipulative tasks (Delevoye-Turrell et al. Schizophrenia Research 2006). Following Gallagher's definition of the pre-reflective sense of agency (Gallagher Trends In Cognitive Sciences 2002), our question was to assess whether the sense of agency and in some way, the

implicit-awareness of our body in action could not be directly dependent on well functioning processes of attention and/or sensori-motor integration. Thirty healthy adults and 30 patients with schizophrenia with high ratings on the "delusion of control" items of the PANSS, participated in the study. During session 1, the collision paradigm was used to gain an objective measure of the pre-reflective sense of agency in all subjects (paradigm from: Delevoye-Turrell et al. NeuroReport 2002). Here, the subject' task was to arrest the fall of a pendulum with a load cell which measured the grip force level used throughout the trial. The pendulum was released either by the subject (S=self imposed) or by the experimenter (E=externally imposed). To succeed in the task, grip force had to be increased in anticipation of the impact. For each individual, the sense of agency was objectively taken as the efficiency difference between S and E. During sessions 2 and 3, subjects performed simple object-manipulative tasks under simple and dual-task conditions as well as a battery of clinical test that evaluated the degree of normal function for motor reaction, motor planning, motor awareness and attention focusing. The objective measure of the sense of agency (i.e. the efficiency difference between S and E) was highly correlated with the "delusion of control" items from the PANSS. Second, the degree of abnormality in the pre-reflective sense of agency was not correlated with attention or with sensori-motor integration problems but rather with a combination of the two. Furthermore, the degree of abnormality in the sense of agency was negatively correlated with the degree of motor awareness. The findings presented here fit well within Van Hoof's pathophysiological model of schizophrenia and stresses the importance of assessing the implicit awareness of the body in action for a better understanding of psychiatric illness. This research is financed by the French Research Agency (ANR 2006-2009).

OVERLOOKING THE OBVIOUS: A META-ANALYTIC COMPARISON OF DIGIT SYMBOL CODING TASKS AND OTHER COGNITIVE MEASURES IN SCHIZOPHRENIA

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In focusing on potentially localizable cognitive impairments, the schizophrenia meta-analytic literature has overlooked the largest single neuropsychological impairment: on digit symbol coding tasks. We compared the magnitude of the schizophrenia impairment on coding tasks to impairments on other traditional neuropsychological instruments that have received greater research attention. Articles were located through searches of MEDLINE and PsycINFO electronic databases and reference lists from identified articles. We searched English language studies from 1990 to present comparing performance of schizophrenia patients and healthy controls on coding tasks and cognitive measures representing at least two other cognitive domains. Of 182 studies identified, 40 met all criteria for inclusion in the meta-analysis. Means, standard deviations, and sample sizes were extracted for digit symbol coding and 36 other cognitive variables. Additionally, we recorded potential clinical moderator variables, including chronicity/severity, medication status, age, and education; and potential study design moderators, including coding task variant, matching, and study publication date. Main analyses synthesized data from 37 studies comprising 1,961 schizophrenia patients and 1,444 comparison subjects. Combination of mean effect sizes across studies using a random effects model yielded a weighted mean effect (Hedges' g) for digit symbol coding of g=-1.57 (confidence interval -1.66 to -1.48). This effect compared to a grand mean effect of g=-0.98 and was significantly larger than effects for widely used measures of episodic memory, executive functioning, and working memory. Moderator variable analyses indicated that clinical and study design differences among studies had little impact on the coding task effect. Comparison with previous meta-analyses suggested that current results were representative of the broader literature. Subsidiary analysis of data from schizophrenia relatives also suggested prominent coding task impairments in this group. The five-minute digit symbol coding task, reliable and easy to administer, taps an information processing inefficiency that is a central feature of the schizophrenia cognitive deficit and deserves systematic investigation.

MEMORY PROCESSES AND LEVEL-OF-PROCESSING EFFECT IN A LIST LEARNING PARADIGM IN ADOLESCENTS WITH PSYCHOSIS

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Several studies reveal episodic memory deficits in adolescents with psychosis. However, cognitive mechanisms underlying these impairments have not yet been fully investigated in this population. In the current study, episodic memory was assessed in 16 inpatients adolescents with psychosis and 20 gender- and age-matched controls. Participants had to learn word lists with varying levels of processing at encoding: no cues, syllabic cueing and semantic cueing. Performance was measured with free and cued recalls. Results showed that patients had impaired free recall across all learning conditions. Furthermore, they did not seem to benefit from semantic cueing at encoding, contrary to controls. However, patients showed a greater advantage from cueing at retrieval, but performance remained below that of control participants. These findings suggest that episodic memory deficits may be related to both encoding and retrieval difficulties in adolescents with psychosis. Furthermore, level-of-processing manipulations seem to have differential effects on memory processes in adolescents with psychosis than in healthy individuals. This study was supported by the Fonds de la Recherche en Santé du Québec and the Fonds facultaire d'enseignement et de recherche (Université Laval) awarded to Marie-Claire Doré.

PREDICTORS OF OUTCOME IN A SOCIAL LEARNING PROGRAM FOR PATIENTS WITH SCHIZOPHRENIA: COGNITION

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Social learning programs (SLP, token economies) have been shown to be effective for patients with treatment refractory schizophrenia. The goal of these programs is to teach skills to patients that they will need in the community. It is unknown who will benefit most from SLPs. Cognition predicts community functioning, but how cognition predicts a patient's course in a SLP is unknown (primary aim).

Furthermore, it is not known if cognition changes during the time in a SLP. The Second Chance Program is a 30-bed SLP that treats patients who cannot be discharged from state psychiatric hospitals in New York; the length of stay is 6-12 months and two-thirds of patients have significant community tenure. Recently, all patients in the program were asked to participate in cognitive testing using a computerized system (IntegNeuro) which covers the main cognitive domains that are impacted by schizophrenia and overlaps significantly with the MATRICS battery. Approximately 50% of the patients agreed to and completed testing. In addition, symptoms were measured by the PANSS and SANS. The main outcome measure is the number of points per week earned by a person. This was determined to be the best measure of overall functioning since points are earned for skill areas (self-care, room care, meal behavior), groups, and socially appropriate behavior on the unit (activities, conversations, helping). Points are lost for treatment noncompliance and socially inappropriate behavior (isolation, bizarre behavior, manipulation, verbal abuse). The points determine the privilege level for the next week. The initial analysis compared initial cognitive scores for 14 subjects to changes in points for a 9-week period after the cognitive testing. Using Spearman's correlation coefficients, changes in points were compared to positive and negative symptoms and aspects of cognition. With the small sample size there were no significant results. However several measures approached significance: verbal interference had a positive correlation (rho 0.442, R2=0.2, p=0.11), learning time had a negative correlation correlation (rho –0.376, R2=0.14, p=0.185), and maze performance also had a negative correlation (rho –0.354, R2=0.13, p=0.21). These results indicate less impulsivity and better executive functioning and learning potential will lead to improved performance in a SLP. These results will be extended with more subjects and longer period of measure after the cognitive testing.

A COMPARISON OF BASIC AND SOCIAL COGNITION BETWEEN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Studies comparing cognitive function in schizophrenia and schizoaffective disorder have yielded mixed results, though a majority suggests few if any cognitive differences between the two disorders. In the current paper, we compared basic and social cognitive performance in individuals with schizophrenia and schizoaffective disorder. Data from 272 participants (199 schizophrenia and 73 schizoaffective disorder) allowed sample comparisons on measures of executive function, verbal and nonverbal memory, and processing speed, as well as two measures of social cognition. An overall MANOVA of basic cognitive tasks was not significant, indicating that the schizophrenia and schizoaffective disorder samples performed similarly. Individuals with schizoaffective disorder performed significantly better than those with schizophrenia on the social cognitive tasks, Theory of Mind ($p < .002$) and affect recognition ($p < .008$). The finding of better social cognition may be an explanatory factor contributing to the often-noted superior course and social functioning outcomes of schizoaffective disorder relative to schizophrenia. Lack of basic cognitive differences, on the other hand, may reflect the relatively more distal relationship between basic cognition and functional outcomes.

SELF-SERVING BIAS IS INVERSELY RELATED TO DEPRESSIVE SYMPTOMS IN SCHIZOPHRENIC PATIENTS

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The purpose of the study was to evaluate the relationship between symptomatology, awareness of illness, and self-serving bias (SSB, a tendency to excessively attribute positive events to internal causes and negative events to external causes) among psychotic patients. A total of 44 outpatients with schizophrenia (31 male (70.5%), 13 female (29.5%), mean age,SD: 15.1,9.2, range 18-62 years) formed the sample. The following measures were used: Positive and Negative Symptoms Scale (PANSS), Scale to assess Unawareness of Mental Disorders (SUMD), and Attributional Style Questionnaire (ASQ). Emotional discomfort (P=0.001), which is directly related to depressive syndrome, and cognitive syndrome (P=0.013) were the only psychopathological variables that significantly accounted for a substantial proportion of the variance in SSB, Emotional discomfort accounted for 23.5% of the variance in reversed SSB and cognitive syndrome for 9.7% of the variance in reversed SSB. No significant relationship was found to exist either between unawareness of illness and SSB (P=0.849). The results of the study suggest that among schizophrenic patients a reversed SSB is closely related to the presence of depressive symptoms.

DO CONCEPTS BASED ON PSYCHOTIC SYMPTOMS PREDICT NEUROCOGNITIVE OUTCOME IN RECENT-ONSET SCHIZOPHRENIA?

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Cognitive impairments are largely independent of clinical symptoms, but strongly linked to functional outcome. Several concepts based on positive psychotic symptoms are well-accepted prognostic factors for long-term outcome and treatment response. Long duration of untreated illness (DUP), early onset of the illness and insidious onset have been associated with poorer outcome. Our aim was to examine the role of these variables based on psychotic symptoms as predictors of neurocognitive performance in a group stabilized recent-onset psychosis patients. One hundred thirty-one neuroleptic naive patients with first-episode schizophrenia spectrum disorder were administered a comprehensive neurocognitive test battery and assessed for duration of illness, age of onset, premorbid adjustment and various clinical measures. Cognitive data set was grouped into eight separate factors through an exploratory factor analysis. The method of factor extraction was Principal Components Analysis with an oblique rotation (Promax). Spearman correlations were calculated. Additionally, age of onset was divided into three groups: early onset (<20 years), middle onset (20 to 30 years), late onset (>30 years), and analysis of variance (ANOVA) was used for comparing means. Stepwise multiple regression analyses were used to assess the independent contribution of these concepts to each cognitive factor. Solely, age of onset was significantly associated with cognitive outcome. Earlier age of onset was related to a lower level of verbal comprehensive abil-

ities (r=.251; p=.006), but no differences were found in ANOVA between the three epochs of onset (early, middle and late). Multiple regression analyses displayed age of psychosis onset as a predictor of motor dexterity factor (B=-5.692; β=.251; p=.007). However, this relationship accounts for only a minor portion of the variance of this cognitive dimension after controlling for a number of potentially confounding variables. Concepts based on psychotic symptoms, such as DUP, age of onset or acuteness of onset, have a negligible value as predictors of cognitive outcome in recent-onset schizophrenia.

SEX DIFFERENCES IN OLFACTORY FUNCTION IN PATIENTS WITH EARLY PSYCHOSIS

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Female superiority on many measures of olfactory function has been amply described in the general population. Whether olfactory deficits in patients with schizophrenia or related psychotic disorders are more common in males than females continues to be debated. The purpose of this study was to examine whether a male/female difference in olfactory function was observed in patients with psychotic disorders. To this end, we assessed a sizeable sample of subjects differing by sex and diagnostic status (psychosis vs. healthy controls) in order to compare olfactory identification ability. 353 patients with first episode psychosis (258 males and 95 females) along with 89 healthy controls (45 males and 44 females) were assessed bi-rhinally using the University of Pennsylvania Smell Identification Test (UPSIT). All subjects were between the ages of 10 and 35. Amongst the four subject groups, no age differences were noted. Patients had been ill, on average, for 26.9 months, while 31% had been antipsychotic drug-naïve at the time of olfactory testing. On UPSIT score, males performed more poorly than females, and patients underperformed healthy controls, but no significant interaction was noted between the two variables. This pattern remained consistent when age of the subjects was taken into consideration. Neither smoking status nor exposure to antipsychotic medication had any effects on olfactory test scores. The data suggest that sex differences in olfactory identification ability do exist in patients with psychotic disorders, but can be accounted for by simple male-female differences in olfactory performance. Large sample sizes are required in order to detect these differences in a patient sample due to the moderate effect size.

Mean UPSIT scores (+sd)

	MALE	FEMALE
PATIENT	34.3(4.5)	35.9(3.0)
CONTROL	35.7(2.8)	37.3(2.5)

Sex main effect F(1,438)=11.4, p<.002
Diagnosis main effect F(1,438)=8.9, p<.004
Sex by diagnosis interaction: F(1,438)=.006, p=ns

NEUROCOGNITIVE ENHANCEMENT THERAPY AND SUPPORTED EMPLOYMENT: EFFECTS ON NEUROPSYCHOLOGICAL TEST PERFORMANCE AT ONE YEAR

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A year long program of cognitive training called Neurocognitive Enhancement Therapy was used to remediate cognitive deficits in a sample of people with schizophrenia who were participating in a supported employment program. Sixty-two stable outpatients with schizophrenia or schizoaffective disorder recruited from an urban community mental health center were randomly assigned to a 12 month program of supported employment (SE) or neurocognitive enhancement therapy (NET) + SE. SE was a modified individual placement and support (IPS) program. NET included computer-based cognitive training exercises, a social information processing group and a work feedback group. Participants completed a comprehensive neuropsychological (NP) test battery at intake and again 12 months later. Participants receiving NET+SE demonstrated better scores at one-year follow-up on measures of executive function, working memory and social cognition. MANCOVA on executive functioning variables indicated an overall significant model (F(5,51)=2.52, p<.05). The NET condition scored significantly higher on several variables in the model including: categories complete (F(1,55)=9.18, p<.005; effect size=.51) and percent conceptual level (F(1,55)=4.81, p<.05; effect size=.34). Results of the MANCOVA on working memory variables indicated an overall significant model (F(2, 56)=3.03, p<.05). Digit span was the only significant variable in the cluster (F(1,57)=5.91, p<.05; effect size=.51) with the NET condition demonstrating better scores. Results of the MANCOVA on social cognition variables indicated an overall significant model (F(2,55)=3.09, p<.05). Hinting Task was the only significant variable in the cluster, favoring the NET condition (F(1,56)=4.18, p<.05; effect size=.43). Augmenting supported employment with a multifaceted cognitive remediation program led to better NP performance at year one. Funding for this study is provided by the National Institute of Mental Health.

PASSIVE/APATHETIC SOCIAL WITHDRAWAL AND ACTIVE SOCIAL AVOIDANCE IN SCHIZOPHRENIA: DIFFERENCE IN UNDERLYING PSYCHOLOGICAL PROCESSES

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Objective: There is no universally accepted definition of which symptoms comprises the negative syndrome. Social withdrawal is considered a core feature of negative symptoms commonly differentiated into Apathetic/Passive Social Withdrawal and Active Social Avoidance. In this study we wished to examine if the two symptoms dimensions are characterized by difference in the underlying psychological processes of Object Relations (OR) and Reality Testing (RT). Method: 272 outpatients with the diagnosis of schizophrenia and schizoaffective disorders from Connecticut VA Medical Center and Yale University School of Medicine (87 % male, mean age 43,1 years) were evaluated using the Bell Object Relations and Reality Testing Inventory (BORRTI) (Bell, 1996). The N4 item on PANSS (Key et al., 1987) Negative scale was used to measure Passive Social Withdrawal and G16 on General Psychopathological scale to measure Active Social Avoidance. Results; There were significant correlations between N4 and the BORRTI OR subscale of Insecure Attachment (IA, r=-.17) and RT subscale Hallucinations and Delusions (HD, r=-.12). There were also significant correlations between G16 and OR subscale Alienation (AL, r=.28) and Insecure Attachment (IA, r=19), as well as RT scale Reality Distortion (RD r=.27), Uncertainty of Perception (UP, r=.17) and Hallucinations and Delusions (HD, r=.21). Conclusions: There are significant differences in the patterns of OR and RT between Passive and Active social withdrawal in this study suggesting that patients with Passive

Withdrawal seems to have less interest in relationships while patients suffering from Active withdrawal are more influenced by more psychotic symptoms but also have a tendency towards less basic trust. The results support the idea that the negative syndrome includes Passive/apathetic Social Withdrawal but not Active Social Avoidance. References: Bell MD, (1996) Bell Object relations and reality testing inventory (BORRTI) manual. Los Angeles: Western Psychological Services Key, S.R., Fizbein, A. and Opler, L.A. (1987) The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophrenia Bulletin, 13, 261-276.

A CROSS-SECTIONAL STUDY OF ADIPONECTIN IN PATIENTS WITH SCHIZOPHRENIA

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Background: Adiponectin is a recently identified adipocyte-derived protein associated with metabolic abnormailities such as obesity, insulin resistance and diabetes. Metabolic disorders are a growing concern in patients treated with antipsychotic medication. Methods: Fasting adiponectin levels were assessed in a cross-sectional sample of 294 patients with schizophrenia treated with antipsychotic medication. The patients are enrolled in a prospective study evaluating the metabolic effects of antipsychotics. All underwent an extensive metabolic screening, including an oral glucose tolerance test. Results: Adiponectin levels are correlated with BMI, and differ significantly between patients with normal weight, overweight or obesity ($p=0.0001$). Patients meeting criteria for the metabolic syndrome, either with NCEP ATP-III criteria (28.2%) or with the more recent IDF criteria (35.7%), have significantly lower adiponectin levels than patients without a metabolic syndrome ($p=0.0001$). Patients without glucose abnormalities (82.7%) have significantly higher adiponectine levels compared to patients with glucose abnormalities (IFG and/or IGT, 9.9%) or patients meeting ADA criteria for diabetes (7.5%) ($p=0.004$). Adiponectin levels are lowest in diabetic patients. After controlling for BMI, antipsychotic medication significantly influences adiponectin levels ($p<0.01$). Adiponectin levels are significantly lower ($p<0.05$) in patients treated with olanzapine. Conclusions: In schizophrenic patients, adiponectin levels vary in the same way as described in the normal, overweight and obese non schizophrenic population. Also, adiponectin levels in schizophrenic patients with and without metabolic syndrome mirror what is observed in the general population. Preliminary data suggests that the antipsychotic treatment may influence adiponectin regulation, a finding that should be verified in longitudinal studies

COGNITIVE BENEFITS OF ZIPARASIDONE VS. CLOZAPINE IN TREATMENT RESISTANT SCHIZOPHRENIA: A RANDOMIZED DOUBLE-BLIND COMPARATIVE STUDY

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Background: Recent data from the CATIE schizophrenia trial has suggested that there may be few differences in cognitive effects of antipsychotic medications. However, assessment of such effects can be complex, due a number of confounds, including subject characteristics and dosage of the treatments. In specific, treatment resistant patients may show a substantial dissociation between clinical and cognitive benefits, with clozapine sometimes showing fewer cognitive benefits. This study compared the cognitive and clinical benefits of clozapine and ziprasidone in patients with a history of failure to respond to previous antipsychotic treatments. Methods: Patients with a documented history of either failure to respond to multiple previous adequate antipsychotic treatments or intolerance of treatment were randomized in double-blind fashion to either clozapine (n=74)or ziprasidone (n=73) in a single country (Italy), multi-site trial. Efficacy assessments included the Positive and Negative Syndrome Scale (PANSS) and a cognitive assessment battery examining episodic memory (RAVLT), executive functioning (Stroop test), and processing speed (Trail-making test Parts A and B). Results: Both groups demonstrated statistically significant improvements ($p<.05$) in total PANSS scores and several of the PANSS subscales, with no differences between the groups. Analyses of the cognitive variables found statistically significant within group improvements for ziprasidone in learning and delayed recall and recognition on the RAVLT and Trail Making Part B. Clozapine treated patients improved on the RAVLT, but not on the trail making test and neither group improved on the Stroop test. Weight and total cholesterol were significantly lower at endpoint in the ziprasidone treated patients. When patients recruited for treatment resistance only were compared across treatments, there were no changes in the efficacy profiles. Discussion: This study indicated that cognitive and clinical measures improved following treatment with ziprasidone in patients with a history of either treatment resistance or intolerance. While cognitive improvements were only found for a subset of items in the battery, processing speed and episodic memory may be related to functional disability. These findings are consistent with several prior comparative studies on the cognitive effects of atypical antipsychotics.

VERBALLY GIFTED SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS: DIFFERENCES IN FUNCTIONAL STATUS, BUT NOT COGNITION?

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Cognitive impairment is highly prevalent in schizophrenia and considered a primary mediator of functional outcome (Green et al., 2000; Heinrichs, 2005). Nonetheless, a proportion of patients overlap with healthy controls on any given cognitive task. Interpretation of normal and even above normal neurocognitive test performance in schizophrenia patients is controversial. Patients may have declined from premorbid or potential performance levels that were even higher. However, it is also possible that standard cognitive tasks are insensitive to core processing deficits or that impairment on these tasks is not obligatory in all forms of the illness. We analyzed data from 112 patients who met DSM-IV criteria for schizophrenia or schizoaffective disorder and found 20 patients with age-scaled Vocabulary (WAIS-III) scores of at least 14 (i.e. "superior"). A sample of 67 non-psychiatric controls also yielded 20 cases who met this requirement. Verbally superior patients (Vocabulary M = 15.25, SD = 1.25) and controls (Vocabulary M = 15.15, SD = 1.39) did not differ significantly in first language learned, proportion of males, proportion of foreign births, or parental occupational status (Chi-squared tests $p > .05$). Moreover, patients and controls did not differ significantly (t tests with Bonferroni adjustment $p > .05$) in age and education, or in

verbal (WAIS-III Vocabulary) or non-verbal ability (WAIS-III Matrix Reasoning), auditory working memory (WAIS-III Letter-Number Sequencing), processing speed (WAIS-III Symbol Search), verbal fluency (COWAT), verbal memory (California Verbal Learning Test), word reading (WRAT3) or functional skills (University of California Performance Skills Assessment). However, verbally superior patients and controls differed ($p < .001$) in functional independence in the community (Multidimensional Scale of Independent Functioning). These data are not accommodated easily within "decline" theories of normal or above normal neurocognitive performance in schizophrenia and raise questions about the strength and complexity of relations between cognitive impairment and outcome.

A COMPARISON OF CLINICIAN AND PATIENT RATED MEASURES OF INSIGHT INTO THE NEUROCOGNITIVE AND PSYCHOTIC SYMPTOMS OF SCHIZOPHRENIA

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The purpose of this study was to compare clinician and patient rated measures of patients' awareness of their neuro-cognitive and psychotic symptoms. Schizophrenia is typically associated with a lack of insight into illness, the need for medication, and the social consequences of the illness. Recent evidence also suggests there is poor insight into the neuropsychological deficits that are so prevalent in schizophrenia. Assessment of insight has traditionally taken the form of clinician or patient rated scales; while patient rated scales have the advantage of ease of administration, it is not clear if they capture the same constructs as clinician rated scales. We compared clinician and patient ratings of insight into psychosis and neuropsychological deficit, using a sample of 75 subjects with schizophrenia. The MIC, a novel instrument with clinician (MIC-CR) and self report (MIC-SR)) versions, was used to measure level of awareness of neuropsychological dysfunction, and the SUMD and IS were used as clinician and self report measures of insight into psychotic illness. Results demonstrated a significant correlation between the clinician rated measure, the SUMD and the patient rated measure, the IS ($r=-0.494$, $p<0.001$). Similarly, the clinician rated version of the MIC was significantly correlated to the patient rated version ($r=-0.669$, $p<0.001$). Relationship of all four measures to objective measures of dysfunction will be presented. Clinician and patient rated measures of insight in schizophrenia appear to capture similar constructs.

EFFICIENCY OF THE BACS AND CATIE NEUROPSYCHOLOGICAL BATTERIES IN ASSESSING COGNITION AND ANTIPSYCHOTIC TREATMENT RELATED CHANGE IN COGNITION DURING THE CAFÉ CLINICAL TRIAL

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While clinical trials in schizophrenia have become more sophisticated in evaluating cognitive treatment effects, few studies have compared assessment approaches. This study was designed to compare the efficiency with which two neuropsychological batteries estimated cognitive abilities and change in cognition. Participants were first episode psychosis patients who completed baseline (n=367) and 12-week (n=219) assessments with the BACS (Brief Assessment of Cognition in Schizophrenia) and CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) neuropsychological batteries as part of the Comparison of Atypicals in First Episode schizophrenia (CAFÉ) clinical trial. Exploratory factor analysis revealed that both batteries were characterized by a single factor of cognitive ability for both baseline performance and change in cognitive performance after treatment. Efficiency analysis showed that both batteries evaluated this generalized deficit adequately, although the BACS battery did so in half the time. Given that a unitary factor characterized baseline cognitive abilities in schizophrenia spectrum disorders as well as cognitive improvement after antipsychotic treatment, brief assessments of the procognitive effects of antipsychotic treatments may provide efficient neuropsychological measures in clinical trials. Advantages of shorter batteries include reduced costs associated with administration time and scoring, reduced demands for sustained patient cooperation during cognitive testing, and fewer missing data points. However, should adjunctive therapies target specific cognitive deficits such as reasoning, episodic or working memory, a multi-factorial approach to neurocognitive assessment may be more appropriate given that domain specific cognitive outcomes would need to be evaluated.

EXECUTIVE FUNCTIONING IN FIRST-EPISODE ADOLESCENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: A COMPARISON WITH FIRST-EPISODE ADULTS AND HEALTHY CONTROL SUBJECTS

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Previous studies indicate that early-onset psychosis is related to poorer cognitive functioning than adult-onset psychosis. These studies are, however, retrospective in that all subjects are examined in adulthood, not directly investigating the development of cognitive deficits. We wanted to examine the developmental trajectory by comparing executive functioning in first-episode adolescents with first-episode adults. Adolescents (12-18 years) and adults (≥ 19) with first-episode psychosis are included at the time of their first contact with a psychiatric department. Diagnoses are based on DSM-IV criteria. Symptom level is assessed using the PANSS and the Global Assessment Scale. Executive function is assessed with Wisconsin Card Sorting Test, using the numbers of categories completed and number of perseverative errors. 60 healthy adolescent controls and 200 healthy adult controls have also been included in the study. Data collection has been completed for the adult clinical group (n= 111). At present (September 10, 2006) 24 first-episode adolescent have been included, and by January 2007 we expect to have data on 30 subjects. Statistical analyses will be undertaken to explore the possible group differences, and the results will be presented at the conference.

PERSONALITY TRAITS ASSESSED WITH THE TEMPERAMENT AND CHARACTER INVENTORY IN SCHIZOPHRENIA

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The Temperament and Character Inventory (TCI; Cloninger et al, 1993) is a well-established self-report questionnaire measuring 4

temperament dimensions and 3 character dimensions. However, surprisingly few studies have used it to examine the personality of patients with schizophrenia, and none in Japan. Moreover, possible gender differences in personality among patients with schizophrenia have not been well documented. We administered the TCI to 86 patients with schizophrenia and age- and gender-matched 115 healthy controls to characterize personality traits in patients with schizophrenia and to examine their relationships with clinical variables, particularly gender. Compared to controls, patients demonstrated significantly lower novelty seeking, reward dependence, self-directedness and cooperativeness, and higher harm avoidance and self-transcendence. Male patients showed even lower novelty seeking, reward dependence, self-directedness and cooperativeness, and higher harm avoidance than female patients, although only harm avoidance reached statistical significance. Personality dimensions were moderately correlated with symptom dimensions assessed by the Positive and Negative Syndrome Scale (PANSS, Kay et al, 1987), e.g., self-transcendence was positively correlated with positive symptoms. These results suggest that schizophrenia patients have unique personality alterations, which appear to be present across cultures because the personality deviance of schizophrenia patients in the present study is fairly consistent with prior two studies in differential cultural groups (Guillem et al, 2002; Boeker et al, 2006). This personality of schizophrenia patients may, at least in part, be affected by illness severity. The greater personality deviance of schizophrenia males in the present study might be related to their severer illness as shown by poorer premorbid functioning, earlier age at onset, and severer cognitive deficits compared to female counterparts, all of which have been reported in prior studies (Castle et al, 1993; Leung and Chue, 2000).

COMPREHENSION OF IDIOMS WITH MULTIPLE MEANINGS BY PATIENTS WITH SCHIZOPHRENIA

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Introduction: Schizophrenic patients often interpret idioms literally, especially when the latter have multiple meanings, eg. literal and figurative (Titone et al, 2002). It was argued that this literal bias was due to a failure to suppress the literal meaning, which is always accessed during figurative processing. Alternatively, the graded salience hypothesis (Giora, 1997) states the primacy of the salient meaning (either literal or figurative) during idiomatic processing. By controlling the literal and the figurative salience of multiple meaning idioms, we tested the hypothesis that difficulties to suppress the salient rather than the literal meaning, would better explain impaired idiomatic processing in schizophrenic patients. Method: 15 schizophrenic patients (DSM IV, APA, 1994) and 15 control participants performed a semantic decision task. Idioms with literal (n=20), figurative (n=20) and equal literal/figurative salience (n=40) were followed by a word target related to its salient or non salient meaning. These experimental idioms were included in a list of 240 sentences. Each sentence was followed by semantically related or unrelated word targets. The interval between a sentence prime and a target word was 300 ms. Participants had to judge if the word target was semantically related to the prime sentence. Main results: In both groups, participants judged the semantic relationships between idiom-primes and word-targets based on the salience rather than on the literal plausibility of the idioms. Salient meaning (either literal or figurative) was more rapidly and more accurately accepted than the non salient meaning ($p<.0001$). Control participants show partial activation of the non salient meaning (65% of correct responses), contrary to schizophrenics who show no such activation (50% of correct responses). When idioms had equal figurative/literal salience, control participants show evidence of activation of both meanings, contrary to schizophrenic patients whose performances were near to chance level. Conclusion: Idiomatic salience, more than literal plausibility, plays a crucial role in idiomatic processing. We show that during comprehension of idioms with multiple meanings, schizophrenic patients make normal access to the salient meaning, either literal or figurative. We discuss several hypotheses about the cognitive mechanisms which might explain the impaired activation of non salient or equally salient meanings of idioms by schizophrenics.

STABILITY OF NEUROCOGNITIVE DEFICITS IN PRODROMAL AND FIRST EPISODE SCHIZOPHRENIA

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Schizophrenia is a devastating illness that emerges during a crucial period of neurodevelopment. Early identification of individuals in the prodromal phase and first episode of schizophrenia using vulnerability markers for psychosis may add important insight into neurodevelopmental processes. Vulnerability markers, including a neurocognitive battery, were selected because of established deficits across schizophrenia spectrum groups, high reliability in repeated testing and evidence of heritability. Methods: Subjects at risk for schizophrenia (AR N=38), based on family history of schizophrenia plus a decline in functioning or the new onset of subsyndromal psychotic symptoms, were compared to first episode schizophrenia patients (FE N=13) and normal comparison subjects (NC N=20) at baseline then at 6 month follow-up. The neurocognitive battery included the domains of executive functioning, verbal memory, processing speed, working memory and general intelligence. Composite Z scores were created for each domain as well as a composite neurocognitive index that were assessed for stability and change over time. Results: In repeated assessment, stable group differences were present in the composite neurocognitive index ($F[2,70]=9.27$, $p<.001$) as well as across neurocognitive domains ($F[2,68]=7.82$, $p<.001$) with the AR sample performing intermediate to FE and NC subjects ($p<.05$). The significant group by domain by time effect ($F[8,272]=1.99$, $p<.05$) was then deconstructed. All neurocognitive domains were stable with moderate to good test-retest correlations ($r=.60$-$.89$). Significant group effects were found for verbal learning, executive functioning, working memory, and general intelligence ($p<.05$). Significant time effects were found for the verbal learning and processing speed domains ($p<.005$) perhaps reflecting practice effects. Interestingly, on further analysis, there was a significant group by time interaction ($p<.05$) in the verbal learning domain. While the NC group remained stable over time, the AR and FE groups had a significant improvement in their verbal learning performance from baseline to follow-up. Discussion: The neurocognitive deficits observed in both at risk and first episode subjects are stable with repeated testing. Although still significantly impaired, the AR and FE groups showed improvement in verbal memory performance beyond that seen in the NC that may be secondary to early treatment in the course of their illness.

PROGRESSION OF INTELLECTUAL DEFICITS IN EARLY ONSET PSYCHOTIC PATIENTS: A FIVE-YEAR, LONGITUDINAL FOLLOW-UP STUDY

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The objective of the study was to examine the progression of cognitive deficits in early onset psychotic patients in a 5-year longitudinal, follow-up study. The current presentation includes preliminary results of the progression of IQ deficits in 10 patients. Forty percent of the patients showed deterioration of performance IQ raw scores, and 30 percent showed deterioration of total IQ raw scores at follow-up. No patients showed deterioration of verbal IQ raw scores. Logistic regression analyses revealed that low total IQ at baseline predicted deterioration (vs. increase/no change) of total IQ raw scores at follow-up (marginally significant, $\chi 2=3.550$, df=1, p=0.06; accounting for between 29.9% - 42.4% of the variance, with correct overall predictions=90%). Low parental income also predicted deterioration of total IQ raw scores (marginally significant, $\chi 2=3.669$, df=1, p= 0.055, accounting for between 30.7% and 43.5% of the variance, with 80% overall correct predictions). Also marginally significant, gender predicted deterioration of performance IQ raw scores ($\chi 2= 3.555$, df=1, p=0.059; accounting for between 29.9% and 40.4% of the variance, with overall correct predictions = 80 %), with females less likely to show deterioration. Few psychotic symptoms (SAPS Psychotic Dimension) at baseline also predicted decline of performance IQ raw scores (marginally significant, $\chi 2=3.656$, df=1, p=0.056; accounting for between 30.6% and 41.4% of the variance, with an overall 80% prediction accuracy). The results are suggestive that a considerable proportion of early onset psychotic patients lose intellectual knowledge and skills within the first few years following illness onset.

NEUROPSYCHOLOGICAL FUNCTIONING IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Objectives: bipolar disorder and schizophrenia patients have been shown cognitive impairments when compared with control subjects. This study was aimed to test the hypothesis that patients with remitted bipolar disorder show neuropsychological impairment. Methods: This issue was addressed by comparing remitted DSM-IV diagnosed bipolar disorder, schizophrenia and controls on several clinical and neuropsychological measures. Clinical state was assessed using the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), and Montgomery-Asberg Depression Rating Scale (MADRS). Neuropsychological measures included the KWIS, WMS-III, Korean California Verbal Learning Test (K-CVLT), Wisconsin Card Sorting Test (WCST), Rey-Osterrieth Complex Test (RCFT), and Color Trails Test (CTT). Thirty-two subjects with remitted bipolar disorder, twenty-four remitted schizophrenia and twelve normal controls were studied. Results: Analysis of Variance (ANOVA) revealed no differences across groups on age, education and IQ. With respect to neuropsychological test performance, bipolar disorder patients and schizophrenic patients were similar and both groups were impaired compared to normal controls. Two diagnosed groups have persistent impairments in neuropsychological function, particularly in the domains of declarative memory. Conclusions: The results provide support for the view that remitted patients with bipolar disorder suffer cognitive impairment.This study showed similar cognitive impairments between bipolar disorder and schizophrenia.

MEMORY FUNCTIONING IN SCHIZOPHRENIA: WHAT IS IMPAIRED? WHAT IS SPARED?

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The present study assessed a range of memory processes in persons with schizophrenia to examine the relative impairment of function compared with healthy adults. Participants included 40 schizophrenia and schizoaffective disorder outpatients matched for age and gender with 25 healthy community residents. Subjects ranged in age from 18 - 55 years. All participants were administered a broad-based battery to assess the following memory processes: (a) verbal learning, (b) working memory, (c) semantic memory, (d) remote memory, (e) verbal retention, and (f) implicit memory. To minimize administration order effects, the battery was divided into three parts and the administration order of components was counterbalanced across subjects. To facilitate interpretation of results across memory domains and to create a memory deficit profile, all raw scores were converted to z-scores using the means and standard deviations of the community resident group. For domains with more than one measure, a composite z-score was calculated by taking the average of the z-scores from the individual measures within that domain. The primary analyses of profile level and shape were performed using a MANOVA with diagnostic group (patients vs. controls) as the between-group variable and memory function as the within-subjects variable. In the schizophrenia group, follow-up within-subjects contrasts were performed on each function to further examine areas of relative strength and weakness. For each contrast, the mean z-score for a particular memory domain was contrasted with the mean z-score for all remaining memory domains. The results showed that verbal learning, working memory, semantic memory, and remote memory were significantly impaired in patients compared with community residents. However, no significant group differences were found in verbal retention and implicit learning. Follow-up contrasts within the schizophrenia group revealed verbal learning and working memory to be most impaired. The findings suggest a complex pattern of memory functioning in schizophrenia, with marked impairments noted in verbal learning and working memory and a relative sparing of verbal retention and implicit memory.

FAMILY HISTORY AND COGNITIVE FUNCTIONING AT INTAKE PREDICT SHORT-TERM FUNCTIONAL OUTCOME IN FIRST-EPISODE PSYCHOSIS

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Objective: To determine whether baseline cognitive functioning predicts functional outcome at 3-months in first-episode psychosis (FEP). Method: Sixty-nine (n=69) individuals experiencing a FEP were recruited from the Early Psychosis Prevention & Intervention Centre at ORYGEN Youth Health within a week of intake and

assessed on measures of cognition, psychopathology & functioning (BPRS, SANS, CGI, GAF, SOFAS), at baseline and 3-months. The cognitive battery included the Stroop, Trail Making, WAIS-R, WMS-R, & CANTAB tests. Results: Participants improved on all clinical measures [paired-samples t-tests, $p < 0.001$ for CGI, GAF, SOFAS, BPRS total, SANS total, subscales of SANS alogia, avolition-apathy, anhedonia-asociality; $p < 0.01$ for affective flattening; $p < 0.05$ for attention]. Cognitive functioning also improved significantly on all measures except for Trail Making Part A, Stroop A, and CANTAB Spatial Recognition. Linear regression analyses were conducted with the GAF, SOFAS and CGI as dependent variables, and the clinical and demographic measures (e.g. duration of untreated psychosis, age at illness onset, gender, diagnosis, antipsychotic dose, premorbid IQ, family history) as the independent variables. Family History ($p=0.026$; 15% of variance explained) was the best predictor of GAF at 3-months, and BPRS total baseline ($p=0.016$) best predicted the SOFAS at 3-months. The model for CGI was not significant. When the cognitive measures were added to the models Trail Making Part A replaced Family History as the strongest predictor of GAF at 3-months ($p=0.005$; 18% of variance explained), BPRS total remained the strongest predictor of SOFAS at follow-up ($p=0.002$), and Trail Making Part A was the strongest predictor of CGI at follow-up ($p=0.002$). Conclusion: Family history of psychosis and visual attention/psychomotor speed performance are the best predictors of short-term global outcome, explaining 15% and 18% of the variance, respectively. Aspects of cognitive functioning at intake were also associated with severity of illness.

SOCIAL COGNITION AND NEUROCOGNITION IN STABLE BIPOLAR DISORDER AND SCHIZOPHRENIA

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Introduction: Bipolar disorder (BAD) and schizophrenia (SZP) represent common psychiatric disorders with, at times, similar symptoms during acute illness. Since the earliest descriptions, SZP has been distinguished from mood disorders by worse outcome and cognition. It remains unclear whether differences represent state dependent impairments. We compared cognitive functions in matched persons of BAD and SZP who are stable with respect to symptoms, treatment and living status. Methods: Participants: 12 stable bipolar I patients (BAD) (M:F=7:5, mean age=37.83+10.71) with history of psychotic features were recruited from the Bipolar Clinic and compared to 12 patients from the Schizophrenia Center of the University of Pennsylvania, case matched for age, ethnicity, gender, age at onset of illness, and education. The majority of subjects were employed or students. Clinically stability was defined as living with family or independently, no hospitalization for >6 months, no increase in antipsychotics or mood stabilizers for >3 months before assessment. Procedure: Patients were evaluated for general psychiatric symptoms, depression and mania. Each participant completed a computerized assessment of social cognition, including emotion discrimination and differentiation, and neurocognition, including abstraction, attention, language and spatial abilities, verbal and spatial memory. Cognitive performance of each group was expressed in z-scores compared to performance of healthy controls. Comparisons of symptoms between groups were performed using paired t-tests, comparisons of social and neurocognition were performed using Wilcoxon Signed Rank tests. Results: BAD and SZP groups did not differ on general psychiatric symptoms, depression and mania ratings. Schizophrenia specific symptoms were marginally higher in SZP. BAD and SZP groups did not differ in performance on domains of social cognition, and neurocognition. Discussion: When matched according to demographics and clinical stability we failed to confirm the concept of greater or more specific cognitive impairment in SZP. Our findings are limited by small sample sizes. Reported differences in cognition between patient groups may reflect a more general discrepancy in cognition. In addition, worse outcome in SZP may be mediated by more prominent negative symptoms.

NEUROCOGNITION AND REAL-WORLD SOCIAL FUNCTIONING IN SCHIZOPHRENIA: WE ARE NOT MEASURING AND REMEDIATING ALL THE "RIGHT STUFF"

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While the role of impaired neurocognition in accounting for real-world social functioning in schizophrenia is generally established by now, the overlap is far from complete. Moreover, little is known about the potential mechanisms that bridge between (both social and non-social) cognition and functional outcome. The aim of this study was to aid in closing this gap by developing and validating a novel, more ecologically valid approach for assessment of neurocognitive and social-cognitive deficits in schizophrenia. The current study was motivated by the view that metacognitive processes of self-monitoring (the process by which subjects routinely assess the accuracy of their knowledge) and self-directed action (the degree to which these assessments affect their decision to actually report an answer and at what level of elaboration) are fundamental determinants of competent functioning in the real world. Based on preliminary pilot data (Koren et al., 2004; Koren et al., 2005), we hypothesized that: (1) both the concurrent and longitudinal prediction of impaired social functioning will be significantly improved when adding to conventional measures of cognitive and social-cognitive abilities ("performance quantity"), measures of how much the products of these processes can be trusted ("performance accuracy"), which depend on metacognitive processes of self-monitoring and self-directed action; and, (2), metacognitive abilities will be more sensitive to changes in clinical (particularly, psychotic) symptoms. To assess these hypotheses, a novel metacognitive approach was adapted for use with convetnional tasks in three areas— executive functioning, verbal memory, and theory of mind (ToM). The tasks were administered to a group of 45 schizophrenia patients upon admission and six months later. Patients were examined at both baseline and follow-up assessments with symptom ratings and measures of social adjustment. Our results showed that change in metacognition is a better predictor of functional outcome following symptomatic stabilization than change in cognitive functioning. These results suggest that: (1) metacognitive factors play an important role in real-world outcome over and beyond that of cognitive abilities per se; and, (2) remediation efforts, both pharmacological and behavioral, should be targeted at this level of cognitive functioning.

THE EFFECT OF ANTIPSYCHOTIC TREATMENT ON THEORY OF MIND

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Background: Deficits in a patient's 'theory of mind' (TOM) have been proposed to lead to psychosis – however, it remains unclear if TOM

deficits constitute a trait- or a state-related deficit and whether they respond to antipsychotic treatment. Further, it is unclear if the change in TOM and change in psychosis are related or independent of one another. Methods: In the cross-sectional component of this study 71 patients with psychotic disorders were included and TOM ability was measured using a hinting task in which subjects had to infer real intentions behind indirect speech. In the longitudinal study, a different cohort of seventeen neuroleptic-free patients, were included wherein they received antipsychotic treatment for 6 weeks and the effect on psychotic symptoms and TOM was measured every two weeks. Associations between TOM and psychopatology were assessed and mixed effects model was used to investigate the rate of change over time. Results: PANSS total scores were significantly associated with TOM scores. In particular, the hinting task was not associated with positive symptoms, but was significantly associated with negative symptoms and general symptoms. The longitudinal arm of the study showed that both PANSS positive scores and TOM improved after medication was started, particularly during the first 2 weeks of antipsychotic treatment but, these changes were not associated. The TOM response at 2 weeks of antipsychotic treatment reached similar values as the one obtained in the crossectional sample. Conclusions: While TOM and psychotic symptoms are related to each other, antipsychotic treatment impacts each independently – suggesting a dissimilar cognitive or neurobiological substrate for the two.

Change in PANNS (total, positive and negative) and TOM over time

	Baseline Scores (sd)	2 weeks change	2-4 weeks change	4-6 weeks change	Total change
PANSS-T	86.68 (9.84)	-12.68 [1]	-9.41	-7.1	-29.28
PANSS-P	24.78 (3.04)	-4.21 [2]	-3.1	-2.73	-10.05
PANSS-N	18.47 (5.25)	-2.42	-1.34	-1.23	-5
TOM	14.57 (4.3)	2.92 [3]	0.93	0.49	4.35

1 Significantly different from baseline (t=-3.73 df=48 p=0.0005)

2 Significantly different from baseline (t=-4.14 df=48 p=0.0008)

3 Significantly different from baseline (t=2.95 df=48 p=0.029)

COGNITIVE IMPAIRMENTS IN PATIENTS WITH SCHIZOPHRENIA SHOWING PRESERVED OR COMPROMISED INTELLECTUAL FUNCTIONING: RESULTS FROM AN EPIDEMIOLOGICAL COHORT

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Patients with schizophrenia may show intellectual deterioration from premorbid levels, and different degrees of intellectual decline may relate to different patterns of neuropsychological performance. Using the National Adult Reading Test (NART) and two subtests of the Wechsler Adult Intelligence Scale - Revised (Vocabulary and Comprehension), we estimated premorbid and current verbal intelligence in an epidemiological sample of 105 patients with a first episode of schizophrenia/schizoaffective disorder and 257 healthy controls. Patients and controls were classified in one of four categories: Good-Stable (premorbid and current IQ>=90 and decline<10 points); Poor-Stable (premorbid and current IQ<90 and decline<10 points); Deteriorated–to-Good (decline>=10 points and current IQ>=90); and Deteriorated–to-Poor (decline>=10 points and current IQ<90). Using ANCOVA to partial out the effects of age, gender, ethnicity and education, we compared each patient group with their healthy control counterparts on tasks of perception, verbal and visual memory, processing speed, working memory and executive function. Compared to their healthy counterparts, all patient groups showed significant deficits in processing speed and in one or more tasks of working memory and executive function; only the Deteriorated-to-Poor patients showed a generalized impairment. We conclude that: (a) Deficits in processing speed represent a core impairment in schizophrenia; (b) deficits in working memory and executive functions are central to the disorder but impaired processes are not uniform; (c) only schizophrenia patients combining poor current verbal intelligence and measurable decline from premorbid levels show a generalized impairment.

COGNITIVE FUNCTION IN PATIENTS WITH FIRST EPISODE OF SCHIZOPHRENIA: LONGITUDINAL STUDY

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The cognitive deficit is recognized as a core characteristic of schizophrenia. There has been a wide debate about the nature, the time of onset and long-term process of the cognitive impairment in schizophrenia. The goal of the study was to compare the profile and stability over time of individual parameters of cognitive functions during the period of one year from the onset of schizophrenia depending on the course of the illness. The study included 27 patients with the first episode of schizophrenia according to ICD–10. The comprehensive neuropsychological test battery was administered in the onset of the disease and then one year after. In all patients, there were examined the most important aspects of cognitive functions - intellect; psychomotor speed, focused concentration of attention and global performance capacity; memory; visual and auditory reaction time; executive functions. The criteria for remission were met by 22 patients (81%) when their clinical status was assessed one year after the first episode of schizophrenia; the remaining 5 patients were evaluated as non-remitters (19%). Our results show that remitters have a potential for cognitive deficit improvement for at least one year after their first episode of the illness, especially as to executive and memory functions. On the other hand, the group of non-remitters was not found to improve in terms of cognitive function during the year. The level of cognitive functions during the first episode of schizophrenia did not differ between later remitters and non-remitters. One year after the first episode of schizophrenia non-remitters had worse auditory reaction times; no other significant differences between remitters and non-remitters were found. It may be summed up that cognitive deficit showed a trend to improvement for one year after the first episode of schizophrenia, the tendency being more prominent in remitters. The differences between cognitive performance between remitters and non-remitters are, however, not very prominent in the early stage of schizophrenia. This work was supported by the Ministry of Education Czech Republic (MSM0021622404.

NEUROCOGNITION PREDICTS SYMPTOM REMISSION IN SCHIZOPHRENIA

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In cross-sectional studies neurocognition and symptom ratings in schizophrenia patients are frequently found to be independent. A longitudinal approach may be helpful in clarifying the relationships between symptoms and neurocognition. In the "Schizophrenia Process Study" performed at the University of Bern, Switzerland, symptom courses of 43 schizophrenia spectrum patients were observed during treated psychotic episodes for a mean duration of 86 days. A 10-item scale for daily symptom assessment was applied (Today's Evaluation of Psychopathology, TEP). The rating scale was composed of four factors: psychoticity, excitement, affective symptoms and negative symptoms. Daily ratings of symptoms were performed during the community-based inpatient treatment. Individual courses were analyzed by time series regression yielding mean values of symptoms, slopes of symptom changes and estimates of symptom fluctuations for each patient. Symptoms and global functioning assessed after one month and at the end of treatment were used as dependent variables. A comprehensive neurocognitive assessment was used to test for associations between neurocognition and symptom patterns. Results revealed specific relationships between neurocognition and the longitudinal symptom patterns. A specific problem with verbal memory, intrusion errors during recall, was associated with worse outcome regarding positive symptoms and functioning. Errors in the Stroop Color and Word test showed a similar association with unfavorable outcome. Comparing the relative predictive value in the four symptom domains, neurocognitive factors were associated most strongly with psychoticity and least with affective symptoms. A "fine-grained" longitudinal approach to the evolution of symptoms may be helpful, if not necessary, for uncovering common factors underlying neurocognition and symptoms.

INSIGHT IN SCHIZOPHRENIA: THE ROLE OF 'THEORY OF MIND'

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Insight in psychiatric illness can be conceived of as the capacity "to see ourselves as others see us" (David, 1999). According to this account, impairment of the general capacity to appreciate other people's mental perspectives will cause poor insight. Theory of mind (ToM) tasks are the classic empirical test of a general capacity to appreciate other mental perspectives. Against this background, this study examined the relationship between insight and ToM task performance in schizophrenia. Thirty schizophrenic patients and 26 healthy controls, matched on age, gender and IQ, completed three ToM tasks that were selected to vary the modality of the eliciting stimuli (visual vs. verbal) and the response mode (nonverbal vs. verbal). Instructions also varied with respect to how direct or indirect they were. Relatively more direct instructions referred to others' thoughts or intentions, whereas indirect instructions made no reference to others' mental states. The three ToM tasks included a picture sequencing task, a cartoon-based humour appreciation task, and a story comprehension task. Insight in patients was assessed using the Kemp and David (1996) Schedule for the Assessment of Insight, Expanded (SAI-E). While the patients performed more poorly than the controls on all ToM tasks, only the two indirect tasks (picture sequencing, humour appreciation) generated performance measures that intercorrelated significantly in the patients. Furthermore, it was deficits on these two indirect tasks, rather than deficits on the more direct story comprehension task, that predicted poor insight. Findings suggest that indirect ToM tasks best tap an unprompted, perhaps implicit, monitoring of other people's mental perspectives that is compromised in schizophrenia, leading to the impairment of insight. David, A.S. (1999). "To see ourselves as others see us": Aubrey Lewis's insight. British Journal of Psychiatry, 175, 210-216. Kemp, R., & David, A. (1997). Insight and compliance. In B. Blackwell (Ed). Treatment compliance and the therapeutic alliance. (pp. 61-84). Amsterdam: Harwood Academic Publishers.

VERBAL MEMORY IN FIRST EPISODE PSYCHOSIS: RELATIONSHIP TO IQ, EXECUTIVE FUNCTION AND ONE YEAR OUTCOME

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Cross sectional studies of schizophrenia find strong evidence that verbal memory is impaired and that this is related to contemporaneous measures of poor outcome. Less certain is whether verbal memory impairment is independent of generalised or specific forms of cognitive impairment and whether verbal memory function predicts and is therefore causally related to poor outcome. As part of the West London First Episode Psychosis Study, 176 patients and 109 healthy controls completed the Rey Auditory Verbal Learning Test (RAVLT) which provides measures of immediate recall, learning and delayed recall of a word list. Subjects also performed computerised tasks (CANTAB) of spatial span, spatial working memory, attentional set shifting and planning, as well as tests of premorbid and current IQ. Scores were standardised to the performance of the control group using z score transformations and patients were coded as showing either 'poor' or 'intact' performance (divided around 1 standard deviation below the control mean). Controlling for current IQ, patients with poor performance on both verbal immediate recall and learning showed significantly poorer performance only on spatial working memory errors. When spatial span was entered as an additional covariate, the relationship between working memory errors and verbal immediate recall remained significant. Long term verbal memory performance was independent of all measures of executive function. There were no relationships between any measure of verbal memory at presentation and age at onset of psychosis or duration of untreated psychosis. Further, when clinical and social function was assessed one year later in 99 available patients, none of the baseline verbal memory measures predicted social function or response to treatment. Of all neuropsychological measures, only a measure of cognitive flexibility (extradimensional set shifting errors) predicted social function at one year. These data suggest that, in first episode psychosis patients, immediate recall of verbal material is dependent on working memory efficiency and verbal learning is dependent on working memory span. However, long term verbal memory appears to be an entirely independent function. Further, unlike cross sectional measures, verbal memory at illness onset is not related to any measures that are considered to reflect the severity of future outcome.

A STUDY OF ITEM AND ASSOCIATIVE MEMORY IN SCHIZOPHRENIC PATIENTS AND THEIR NON AFFECTED FIRST DEGREE RELATIVES

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Cognitive deficits are a core feature of schizophrenia (SZ) (Elvevag & Goldberg, 2000) and are also present, to a lesser degree, in non affected relatives (Snitz, MacDonald, & Carter, 2006). So-called episodic memory, which is critical to most daily cognitive activities, is one of the most consistent and significant deficit both in patients and relatives. This memory system refers to when and where a specific event took place and is concerned with two types of information (1) item only (item memory) and (2) association between an item and its context (associative memory). In SZ, both item and associative memory seem to be impaired; the latter to a greater extent than the former (Achim & Lepage, 2003). The contribution of item and associative memory to the episodic deficit is uncertain in non affected relatives. This study is aimed to characterize episodic memory in patients with SZ and their non affected parents by disentangling the contribution of item and associative memory. Patients with SZ (n=19), their parents (n=27) and the control participants of parents (n=27) and of patients (n=19) performed an episodic memory task similar to the one of Rizzo et al. (1996). In this task, 30 words are presented in different locations on a grid. The first part is a force-choice recognition task on target information (words). The second part is a forced-choice recognition task aimed at evaluating associative and non associative contextual memory. In the associative part, the participant must identify which word was in a specific location (the three words presented are familiar, so the participant has to remember the association between the word and its location). In the non associative part, the participant must determine where a specific word was located on the grid (here remembering the association is not essential because only one location is familiar). Only the patient group showed a lower recall performance on the item memory condition (d=0.77). The performance of patients and of parents was lower than that of controls on the associative contextual memory condition (d=0.69 for parents and d=0.62 for patients). Associative memory is defective in patients with SZ and their non affected parents. Item memory seems to be impaired only in patients. In conclusion, associative memory seems to be a better candidate for genetic studies. This study was supported by the FRSQ and the Fondation de l'Université Laval awarded to Andrée-Anne Lefèbvre.

MISPERCEPTION OR MISINTERPRETATION? SOCIAL COMMUNICATORY DYSFUNCTION IN SCHIZOPHRENIA, AND ITS SENSORY ANTECEDENTS

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Social cognitive impairment is an enduring and debilitating aspect of schizophrenia. This dysfunction hinders those it afflicts in their ability to integrate into society, form interpersonal relationships, and remain gainfully employed. Over the past fifty years, researchers have attempted to study these deficits by assessing emotion perception of facial and vocal gestures. Recent attention to sensory deficits within the visual and aural modalities has raised the possibility that social cognitive impairment in schizophrenia may result from both misperception and misinterpretation. This may reflect low-level and feed-forward, as well as higher-order and "top down" dysfunction. We conducted a series of studies with the aim of relating elemental audio-sensory processing deficits to the perception of vocal affect (prosody) in patients with schizophrenia. These studies revealed the following results. First, we observed large effect size (1.6 sd's) deficits in affective prosodic perception that were associated with poor global functioning. Second, we found that within-modality sensory disturbance (specifically-pitch perception) performance, as well as executive processing, predicted affective prosodic dysfunction. Third, we observed that both pitch perception deficits and dysprosodia in patients were associated with white matter integrity estimates within fiber pathways of auditory processing regions in the brain. Fourth, we observed that prosodic deficits extended to the perception of sarcasm and counterfactual intent in interpersonal communicatory discourse. In addition to these affect-related prosodic deficits, we also found large effect size deficits in the perception of non-affective prosody distinctions, such as decoding interrogative versus declarative intent, and recognition of differential stress patterns within speech ("stress prosody"). Like their affective counterparts, audio-sensory processing and executive processing disturbance also significantly predicted non-affective prosodic deficits. Taken together, these findings suggest that schizophrenia dysprosodia reflects a social communicatory dysfunction that is caused by neural deficits across multiple levels of cognition. This dysfunction begins with a deficiency in perception of core elemental acoustic cues and compounds with higher cognitive dysfunction. This results in perceptual deficits of affective, as well as non–affective vocal intent in the illness.

RECOVERY OF WORKING MEMORY FUNCTIONING IN FIRST-EPISODE PSYCHOSIS: RELATIONSHIP TO FAMILY HISTORY OF SCHIZOPHRENIA

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Introduction: Identification of cognitive vulnerability/trait factors using genetic high-risk samples has been criticised due to the low transition rate to schizophrenia. Another approach is to study individuals prior to, or at the onset of frank psychotic symptoms, with a prospective longitudinal design to assist in identifying trait/risk factors. Method: Sixty-nine (n=69) FEP patients were recruited from the Early Psychosis Prevention & Intervention Centre at ORYGEN Youth Health and assessed on measures of psychopathology, functioning and cognition at baseline i.e., within a week of intake, and 3-months (n=46). The cognitive battery included the Stroop, Trail Making, WAIS-R, WMS-R & CANTAB tests. The FEP patients were grouped according to family history of schizophrenia [FAMSCZ]. Results: Analysis of variance was performed to examine for group differences on the demographic,

psychopathology and cognitive measures. At baseline, there was a significant main effect of FAMSCZ for premorbid IQ (F1,45=4.34, p=0.043) only, favouring higher scores in the 'no family history' group. At 3-months, significant group main effects were found for Stroop Part A (F1,33=7.51, p=0.010), Spatial Working Memory (SWM) Between-Search Errors Total (F1,32=7.60, p=0.010) and SWM Strategy (F1,32=6.22, p=0.018) only, again favouring better performances in those without a family history. These results remained statistically significant after controlling for premorbid IQ (except SWM strategy, p = 0.06). Significant group main effects were also found for the SWM Between-Search Errors Total (F1,32=4.67, p=0.039) and SWM Strategy (F1,32=4.27, p=0.047) change scores, with far greater improvement over the first 3-months of treatment in those without a family history. Conclusion: Our results confirm that deficits in verbal intellectual functioning, attention/speed and working memory are associated with a family history of schizophrenia, as is a slowed or minimal recovery in working memory function during the initial treatment phase.

CHANGES IN NEUROPSYCHOLOGICAL FUNCTION OVER TIME IN PATIENTS WITH FAMILIAL SCHIZOPHRENIA AND FAMILIAL BIPOLAR DISORDER

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Introduction: Studies have established that progressive grey matter reductions occur in several brain regions in Schizophrenia with the greatest tissue loss occurring in the early years of the disorder. Studies of established schizophrenia show less consistent findings and few have compared the issue of diagnostic specificity. This study sought to study whether progressive grey matter volume loss occurs in people with established schizophrenia from high density, multiply affected families and to examine whether similar changes occur in individuals with bipolar disorder. Methods: Participants with DSM IV schizophrenia or bipolar disorder were recruited from families where there was at least one other first or second degree relative with the same diagnosis. All individuals were scanned twice using a 1.5T GE LX MRI Scanner using identical image acquisition parameters. Whole brain grey matter loss over time was calculated using the FSL software package. Changes in regional grey matter density were estimated using SPM2. Changes in grey matter density were related to several clinical and cognitive variables measured at baseline and at follow-up assessment. Results: Fifty two people received repeat scans on average 3.5 years apart. Whole brain grey matter loss was evident in both patient groups. However, no regional grey matter loss could be demonstrated to be greater in the schizophrenia group compared to controls. In bipolar patients, progressive grey matter loss was found in the hippocampus which was significantly greater than in controls. These findings were related to several clinical and cognitive measures serially measured at each imaging assessment. Conclusions: Focal grey matter loss was not demonstrated in patients with established schizophrenia, in contrast to the findings in first episode psychosis and high-risk studies. Hippocampal reductions were however evident in subjects with bipolar Disorder, reflecting progressive grey matter loss, remodelling or loss of neuropil in these subjects. Clinical and cognitive correlates of these changes will also be presented at the forthcoming meeting.

DO PATIENTS WITH SCHIZOPHRENIA HAVE INSIGHT INTO THEIR NEURO-COGNITIVE SYMPTOMS?

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The purpose of this study was to determine if people with schizophrenia have insight into their neuro-cognitive deficits. Insight into the psychotic symptoms of illness has been found to be poor among individuals with schizophrenia. Less is known about insight into the neuropsychological deficits which are associated with schizophrenia. Evidence suggests that neuropsychological performance is linked to functional outcome and treatment regimens are currently being created to address these cognitive deficits. Insight is a significant factor in treatment compliance and treatment outcome, thus it becomes important to have a means to determine insight into neuro-cognitive deficits. In order to assess insight into neuro-cognitive dysfunction, 75 subjects were administered the MIC-CR and the MIC-SR, two novel clinician report (CR) and self report (SR) measures that assess insight into neuro-cognitive impairment. Subjects were also administered the BACS to objectively assess neuropsychological status and the WRAT-3 reading subtest to assess premorbid status. Results demonstrated 79% of subjects had cognitive impairment. Poor agreement (kappa<.07) was found between the subjects' report to clinicians of cognitive impairment on MIC-CR and actual cognitive functioning and subjects' self report of cognitive impairment on the MIC-SR and actual cognitive functioning. Likewise, poor agreement (kappa <. 1) was found between an objective measure of attention and the report of attention abilities on the MIC-CR and MIC-SR, an objective measure of memory and the memory subscales on the MIC-CR and MIC-SR, and an objective measure of executive functioning and the executive functioning subscales on the MIC-CR and MIC-SR. The majority of neuropsychologically impaired subjects (61%) were rated by clinicians as lacking insight into their deficits. The average sample insight scores on the MIC-CR were consistent with partial insight both overall and within cognitive domains. Based on these results we conclude that many individuals with schizophrenia have limited insight into their overall neuro-cognitive status as well as their specific deficits in attention, memory, and executive functioning.

EVIDENCE FOR NEUROPSYCHOLOGICAL NORMALITY IN A SUBGROUP OF PATIENTS WITH SCHIZOPHRENIA

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Neuropsychological research has demonstrated that cognitive impairment occurs in a large proportion of schizophrenia patients. However, some reports have identified subgroups of patients performing within average limits on cognitive tasks, giving rise to the controversial possibility that impaired cognition is not an obligatory component of schizophrenia (Kremen et al., 2000; Palmer et al., 1997). These reports have been countered by others (e.g., Wilk et al. 2005) arguing that any normality observed in test performance is more apparent than real and unable to survive careful profile analysis and sampling considerations. To explore the issue, we assessed 118 patients with schizophrenia/schizoaffective disorder and 62 community control participants. Neuropsychological "normality" was defined as an age-corrected scaled score of at least 8 on four subtests

of the Wechsler Adult Intelligence Scale (3rd ed.; WAIS-III; Wechsler, 1997; Vocabulary, Letter-Number Sequencing, Matrix Reasoning, and Symbol Search) and a t-score of at least 40 in terms of total words recalled over the first 5 trials of the California Verbal Learning Test (2nd ed.; Delis et al., 2000). Thirty percent of the patient sample met this criterion and allowed for the subdivision of the patient sample. The neuropsychologically impaired (NI), neuropsychologically normal (NN) and community control (CC) groups did not differ in age, gender, first language learned, or country of birth. An index of the number of significant WAIS-III subtest discrepancies, or "scatter," did not differentiate the groups. The NN and CC groups had significantly higher estimated WRAT3 Reading scores and more years of education than the NI group. In addition, the University of California Performance Skills Assessment (Patterson et al., 2001), a measure of life skills and functional capacity yielded similar scores in the NN and CC groups, with both groups outperforming the NI group. However, the Global Support rating from the Multidimensional Scale of Independent Functioning (Jaeger et al., 2003), a measure of the degree of independence in community living, differentiated all 3 groups. These results provide further evidence that a proportion of patients with schizophrenia perform normally on many standard cognitive tasks. The study of the illness, its treatment and outcome will be advanced through careful analysis of this intriguing subgroup.

INCREASED PSYCHOTICISM AND REDUCED NEGATIVE AFFECT IN YOUNG CANNABIS USERS

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Cannabis use is implicated in increased risk for schizophrenia and some neuropsychological deficits but it is unclear whether pre-existing liability for psychosis may be a major factor. In addition, while many studies have documented acute effects of cannabis on cognitive functions and mood, it is unclear whether there are long-term residual effects. We assessed personality traits (psychoticism, neuroticism, schizotypal personality) mood, perceived stress and neurocognitive functions in healthy young cannabis users and age- and education-matched nonusers. All subjects were screened for polydrug use, psychiatric and neurological disorders. Current cannabis users showed highly elevated score on the Eysenck Personality Questionnaire (EPQ) psychoticism scale and reduced negative affect on the Positive and Negative Affect Schedule (PANAS) but they showed no increase in schizotypal personality trait as indexed by Schizotypal Personality Questionnaire (SPQ). When we divided the cannabis users into moderate vs. heavy users, both groups showed elevated psychoticism and reduced negative affect compared with nonuser controls but moderate users showed increased suspiciousness on the schizotypal personality questionnaire compared with the nonusers. The three groups did not differ on positive affect, perceived stress or neuroticism. However, current cannabis users were found to have better performance on verbal fluency measure compared to non-users. Current users and non-users did not differ in estimated intelligence. These results suggest that cannabis use is associated with increased psychosis proneness but not specifically to schizophrenia-related traits. We observed an interesting residual effect of cannabis use on mood. Positive affect was not affected but cannabis users showed reduced negative affect. In moderate users, reduced negative affect was observed despite increased paranoia. These subjects are currently being tracked for one year to observe the interaction between personality traits and cannabis use as they unfold over time.

INSIGHT AND COGNITION IN FIRST ONSET SCHIZOPHRENIA AND AFFECTIVE PSYCHOSIS

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Background: In schizophrenia, there is some evidence that reduced general cognition and some specific aspects of cognition such as decreased frontal lobe functioning are associated with poor illness awareness and the ability to relabel symptoms as psychotic. However, it is not clear if there are similar associations of cognition and insight in other psychotic disorders. We examined insight and cognition in an epidemiological sample of first-onset schizophrenia and affective psychosis patients. Methods: 110 patients with ICD-10 schizophrenia (mean age=28, male=76) and 72 patients with ICD-10 affective psychosis (bipolar depression or depressive psychosis, mean age=33, male=30), were recruited from London, Nottingham and Bristol as part of the AESOP first-onset psychosis study. Patients were rated on David's insight schedule and a neuropsychological test battery rating IQ, working memory, attention and verbal learning. Results: In schizophrenia reduced illness awareness correlated significantly with lower Full Scale IQ, lower Performance IQ, reduced Verbal Learning, poorer Ravens CPM performance and slower Trail Making A performance. In affective psychosis, reduced illness awareness was associated with slower Trail Making B performance but no other cognitive measure. In schizophrenia, poorer symptom relabelling was associated with lower Full Scale IQ only, while in affective psychosis poorer symptom relabelling correlated significantly with lower Full Scale IQ, lower Performance IQ, poorer working memory, verbal learning and Ravens CPM performance. Conclusion: In both schizophrenia and affective psychosis reduced cognition function was associated with lower levels of insight. However, in schizophrenia the pattern of association was most evident in illness awareness, while in affective psychosis the cognition-insight association was most evident in symptom relabelling. This may suggest that differences in the patterns of cognitive disruption seen in schizophrenia and the affective psychoses may lead to different patterns of symptom and illness awareness experienced by patients during an episode of psychosis.

NEUROPSYCHIATRIC FACTORS ASSOCIATED WITH DECISIONAL CAPACITY IN SCHIZOPHRENIA

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It has been shown that the majority of individuals with schizophrenia possess adequate decisional capacity to provide informed consent for research participation. Additionally, it has been demonstrated that both global neurocognitive function and schizophrenia symptom severity

are associated with ability to provide consent. This study was conducted to determine the specific aspects of neurocognition that are most closely tied to decisional capacity. This information may have important implications for the development of interventions aimed at improving decisional capacity in this population. Participants were 68 individuals with schizophrenia. All were asked to pretend they were being considered for a clinical drug trial. Informed consent materials were then presented for a hypothetical, randomized, double-blind, placebo-controlled trial of a hypothetical cognitive-enhancing agent, and decisional capacity was assessed with the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Neurocognitive function was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and selected subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III). Symptom severity was assessed with the Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptoms (SANS/SAPS). Results showed that, after controlling for age and education, the two specific aspects of neurocognition that were most strongly associated with decisional capacity were reasoning/problem-solving ability (partial $r = .399$, $p < .01$) and immediate memory (partial $r = .431$, $p < .001$). Regarding symptom severity, both negative (partial $r = -.449$, $p < .001$) and disorganized (partial $r = -.282$, $p < .05$) symptoms of schizophrenia were associated with decisional capacity. When neurocognitive and symptom severity variables were entered together into a multiple regression model predicting decisional capacity, immediate memory, reasoning/problem-solving, and negative symptoms remained significantly associated with decisional capacity (R-Square Change = .505, $p < .001$). Given that immediate memory and reasoning are significantly associated with decisional capacity, these findings underscore the importance of presenting consent materials with repetition and structure, thereby maximizing the participant's ability to recall and reason with consent form information in an effective manner.

THE COURSE OF NEUROCOGNITION AND SOCIAL FUNCTIONING IN INDIVIDUALS AT ULTRA-HIGH-RISK FOR PSYCHOSIS

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This study evaluates the course of neuropsychological test performance and its association with clinical symptomatology and psychosocial functioning in individuals identified as ultra-high-risk (UHR) for psychosis. It was hypothesized that a subgroup of individuals would show deterioration in cognitive performance over the follow-up period and that such decline would be associated with concomitant decline in clinical and functional status. Thirty-five UHR individuals were identified from consecutive referrals to the UCLA Staglin Music Festival Center for the Assessment and Prevention of Prodromal States (CAPPS), using the Structured Interview for Prodromal Syndromes (SIPS). All completed follow-up assessments 8.3 months, on average, after initial assessment. Participants were administered a neurocognitive test battery as well as measures of role functioning (Strauss-Carpenter Outcome Scale, NAPLS Role Functioning Scale) and social functioning (UCLA Social Attainment Survey, NAPLS Social Functioning Scale) at baseline and follow-up. UHR subjects showed significant cognitive deficits at baseline in the domains of processing speed, verbal learning & memory, visual learning & memory, and motor speed, and there were 2 profiles of cognitive change over time. Half of the UHR patients demonstrated improvement in social and role functioning over the follow-up period, with 30-40% showing clinically significant functional improvement. The other half showed either stability or decline in functioning over the follow-up period. These 2 groups did not significantly differ in neurocognition at baseline, but did show distinct patterns of change in neurocognition over time. Patients who improved functionally also showed improvement in processing speed and visual memory as well as decreased clinical symptoms, on average, over the follow-up period. Patients who did not improve functionally showed stable clinical symptoms and cognitive performance over time. Although the degree of neurocognitive deficits at baseline in UHR patients does not differ according to short-term functional outcome, the course of neurocognitive change over the first 8 months of follow-up differentiates patients with good and poor functional outcomes. Based on these findings, we hypothesize that neurcognitive improvement in the first 6-8 months after ascertainment discriminates a "false-positive" UHR group from a group that is truly UHR for onset of psychosis.

CONTRIBUTION OF THEORY OF MIND AND EXECUTIVE FUNCTIONS TO SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Deficits in higher order cognitive functions have been hypothesized to contribute to social impairment in schizophrenia. However, few studies have examined theory of mind ability and the specific components of executive functioning to assess their independence or their strength as predictors of social functioning. This study aims to clarify which higher order cognitive functions relate to social functioning and to assess the magnitude and independence of the relationships among the predictors. At present, data have been collected from 28 schizophrenia outpatients and 18 demographically matched community participants. Social functioning in the community was assessed with the Social Functioning Scale. Planning, mental flexibility, inhibition, and abstraction were assessed with subtests from the Delis-Kaplan Executive Function System and the Neuropsychological Assessment Battery. Theory of mind was assessed with two measures: Reading the Mind in the Eyes Test-Revised and the Joke Comprehension Test. Performance on the Reading the Mind in the Eyes Test requires the ability to make cognitive mental state attributions from facial cues. The Joke Comprehension Test provides situational content information, and participants make specific attributions about the content of a character's intention or false belief. Trend level differences between groups were found on inhibition, abstraction, and the Reading the Mind in the Eyes theory of mind task. The measures of theory of mind were not significantly related. Performance on the Reading the Mind in the Eyes Test was significantly and moderately related to mental flexibility, inhibition, and abstraction, while performance on the Joke Comprehension Test was unrelated to the executive functions. Theory of mind, as assessed by performance on the Reading the Mind in the Eyes Test, was the only cognitive function assessed in this study to be significantly related to patients' social functioning in the community. This finding suggests that impairment in the ability to infer complex thinking and feeling states may lead to impaired social functioning. The failure to find other significant relationships between cognition and social functioning may be due, in part, to the relatively preserved nature of cognition in this patient sample. The results suggest that there may be a threshold at which cognitive impairment adversely impacts social functioning.

CONCURRENT VALIDITY OF A COMPUTERIZED NEUROCOGNITIVE ASSESSMENT SYSTEM ENCOMPASSING CATIE AND MATRICS™ BATTERIES FOR USE IN CLINICAL TRIALS OF ANTIPSYCHOTIC MEDICATIONS

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Neurocognitive assessment is an integral component of controlled clinical trials of candidate antipsychotic treatments, as well as a wide range of research protocols. However, manual administration of large neurocognitive batteries is often inefficient, error prone, and frequently inconsistent across multiple sites. As such, the Computerized Multiphasic Interactive Neurocognitive Diagnostics System (CMINDS®) was developed, with funding from the National Institute of Mental Health (NIMH), to provide a unique dual-monitor platform for comprehensive administration of various protocols utilizing contemporary multi-media capabilities for automated presentation of instructions, electronic data capture and report generation. Purpose: To conduct a preliminary comparison of traditional administration of a representative battery of neurocognitive assessments, such as those selected by the NIMH-sponsored CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) consortia, with computerized administration of the same battery on CMINDS, in a sample of patients diagnosed with schizophrenia and normal control subjects. Method: 32 stable, medicated outpatients provided informed consent to participate at the Schizophrenia Outpatient Clinic of the University of Southern California. An additional sample of 56 unmedicated subjects with no current or prior psychiatric diagnoses consented to participate at NeuroComp Systems. All participants received both the CMINDS and standard paper-pencil (PP) batteries at each of two visits, approximately 30 days apart, with the order of administration counterbalanced across participants. Results: Intraclass Correlation Coefficient and General Linear Model comparisons of all individual tests on the CMINDS and PP batteries yielded highly significant levels of absolute agreement, with no significant mean differences. (Additional results will also be reported from identical studies currently being conducted at the Mt. Sinai School of Medicine, University of California, San Diego, and University of California, Irvine.) Conclusions: These results indicate that computerized administration of a neurocognitive battery on CMINDS exhibits substantial equivalence with paper-based forms of the assessment instruments from the CATIE and MATRICS initiatives and highlight its potential for utilization in clinical trials of putative antipsychotic medications.

SAFETY OF LURASIDONE IN SCHIZOPHRENIA: RESULTS OF A PHASE 2, PLACEBO-CONTROLLED, STUDY

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Objectives: This analysis evaluated the tolerability and safety for the starting dose of once daily 80 mg lurasidone without a titration schedule after a washout period (minimum 3 days, maximum 7 days). Methods: This clinical study was conducted as a randomized, double-blind, placebo-controlled, fixed-dose study with a total of 180 patients at 22 centers in the US. The study will consist of a 3- to 7-day single-blind placebo washout period, followed by up to 6 weeks of double-blind treatment with placebo or 80 mg lurasidone. Patients were hospitalized during the single-blind placebo washout period and the first 4 weeks of the double-blind treatment period. At the discretion of the investigator, the hospitalization would be extended an additional 2 weeks during double-blind treatment. Results: Discontinuations because of AEs occurred more frequently with lurasidone (6.7% vs. 1.1% with placebo). There was no clear pattern of adverse events leading to discontinuation in either group. Nausea was reported by more subjects in the lurasidone group (16.7% vs. 3.3% with placebo, p=0.0050). All cases of nausea reported with lurasidone were mild to moderate in intensity, and only one patient discontinued treatment because of this adverse event. No difference was seen in prolactin levels in the males from 6-week completers of two groups. There were no notable effects on lipid profile or glucose regulation or clinically significant weight gain (≥7% increase of body weight: 7.8% with placebo and 6.7% with lurasidone), suggesting lurasidone may have a favorable safety profile regarding cardiovascular events and diabetes. Overall, the tolerability of lurasidone appears quite favorable. Conclusions: The results suggest that lurasidone 80 mg, as a starting dose, was safe and well-tolerated in chronic schizophrenic patients experiencing an acute exacerbation.

THE GENETIC DECONSTRUCTION OF PSYCHOSIS?

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A number of lines of evidence suggest that schizophrenia and bipolar disorder share overlapping etiological and pathogenic processes. Evidence from genetic epidemiology has traditionally been interpreted to support the canonical view that the two disorders are discrete disease entities, although recently emerging, as well as classical, data do not fit well with this model. Moreover, the pattern of findings emerging from molecular genetic studies shows increasing evidence for an overlap in genetic susceptibility across the traditional classification categories-including association findings at DAOA(G72), DTNBP1 (dysbindin), COMT, BDNF, DISC1, and NRG1. The emerging evidence suggests the possibility of relatively specific relationships between genotype and psychopathology. For example, DISC1 and NRG1 appear to confer predisposition to illness in individuals either side of the Kraepelinian divide and the effects of both genes are felt most strongly in disorders with features of both schizophrenia and bipolar disorder. In contrast DAOA appears to confer risk to bipolar disorder and only to schizophrenia where episodes of mood disorder have also occurred. The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research rather than continuing to rely heavily on the traditional Kraepelinian dichotomy.

THE MELBOURNE FIRST-EPISODE MEDIUM TERM FOLLOW-UP STUDY: DECLINE IN ATTENTIONAL SET-SHIFTING BUT NOT SPATIAL WORKING MEMORY AFTER THE ONSET OF PSYCHOSIS

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Available evidence of neuropsychological functioning (including working memory) in first-episode psychosis has generally found stable deficits from illness onset. However, cross-sectional studies would suggest a decline in attentional set-shifting ability after illness onset. However, there are no reported longitudinal studies investigating this ability in first-episode psychosis. In this study we examined change over time in visuospatial memory and executive functioning in a first-episode psychosis sample. The measures used were the Spatial Working Memory, Pattern Recognition Memory, and the Intra-/Extra-Dimensional Set-Shifting tests from the CANTAB. The study cohort was first tested from 1996 to 2001, and re-assessment began in 2002. Our preliminary data from 32 patients and 20 controls (mean time between assessments = 86.4 months, range = 63.5 – 120.9 months) showed no significant decline in the patient group on any of Spatial Working Memory Total Between-search Errors (repeated-measures (RM) ANCOVA; Time x Group interaction F[1,48]=0.27, p=0.61), Spatial Working Memory Strategy (RM ANCOVA; Time x Group interaction F[1,48]=1.21, p=0.28), Pattern Recognition Total Correct (RM ANCOVA; Time x Group interaction F[1,38]=0.89, p=0.35), and Set Shifting Total Errors (RM ANCOVA; Time x Group interaction F[1,48]=0.33, p=0.57). Further analysis of the Set-Shifting data revealed no differences between patients and controls in the percentage passing each stage at Time 1. At Time 2 the patients were significantly more likely than controls to fail the final extra dimensional shift reversal stage (Chi-square(1)=4.62, p=0.03), with the finding restricted to the non-remitted group. These data support previous studies of stable working memory in schizophrenia that are present from illness onset. In contrast, attentional set-shifting ability, which is not impaired at the onset of illness, deteriorates with progression of illness. These findings may be understood in relation to the progressive brain structural changes affecting prefrontal cortex in the first few years following onset of psychosis.

PRENATAL INFECTION AND EXECUTIVE FUNCTION DEFICITS IN ADULT SCHIZOPHRENIA

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We aimed to assess whether prospectively documented in utero infection is associated with executive function abnormalities in schizophrenia. Neuropsychological abnormalities, including executive function deficits, have been consistently demonstrated in schizophrenia. Early developmental insults, including prenatal infection, are associated with schizophrenia. In a previous study, obstetric complications (OC) were associated with mental set-shifting errors in schizophrenia. That study was limited, however, by use of a summary measure of OC. We therefore sought to investigate whether a particular class of in utero teratogens—prenatal infection—was associated with a specific executive function disturbance—mental set shifting— in schizophrenia. The subjects were derived from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, which includes prospectively collected data on serologically documented prenatal exposure to influenza and toxoplasmosis, both of which have been associated with an increased risk of schizophrenia in this cohort. We administered several tests of executive function from a standard neuropsychological battery in 26 schizophrenia cases from this cohort. We found that schizophrenia cases who had been exposed to prenatal infection, compared to unexposed cases, had significantly greater total errors on the Wisconsin Card Sort Test [exposed: mean (SD)=21.00 (15.72); unexposed: mean (SD)=12.28 (8.48), t=2.10, p=.047], and required a significantly longer time (secs.) to complete the Trails B Test [exposed: mean (S.D.)=142.71 (66.55); unexposed: mean=87.63 (25.41), t=3.12, p=.005]. There were no significant differences between the exposed and unexposed schizophrenia groups in performance on letter number sequencing, digit symbol, and the auditory N-back tests, which also require executive function and working memory ability but not set shifting, or on tests of psychomotor or processing speed, including the Trails A test. To our knowledge, these are the first findings to identify an association between prenatal infection and a specific neurocognitive disturbance in schizophrenia. These results provide further support for the neurodevelopmental hypothesis of schizophrenia, and yield additional evidence that prenatal infection contributes to risk of this disorder.

EFFICACY OF LURASIDONE IN SCHIZOPHRENIA: RESULTS OF A PHASE 2, PLACEBO-CONTROLLED, STUDY

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Objectives: To evaluate the efficacy of fixed-dose lurasidone, compared with placebo in acutely exacerbated schizophrenia patients. Methods: A 6-week, double-blind, randomized, parallel-group study (Study 196) was conducted to evaluate the efficacy of once-daily 80mg lurasidone versus placebo in the treatment of patients with schizophrenia experiencing an acute exacerbation of symptoms (diagnosed by DSM-IV criteria) as measured by reductions from baseline in the scores of the BPRS derived from PANSS, PANSS total and subscale, CGI-S and MADRS. This was a study with a total of 180 patients at 22 centers in the US. Enrolled patients entered a 3 to 7-day single-blind placebo washout, followed by up to 6 weeks of double-blind treatment with placebo or 80 mg lurasidone. Patients were hospitalized during the single-blind placebo washout period and the first 4 weeks of the double-blind treatment period. At the discretion of the investigator, the hospitalization would be extended an additional 2 weeks during double-blind treatment. Results: 1)Acute efficacy Lurasidone, at once daily doses of 80 mg after a placebo washout period, was significantly superior to placebo on PANSS total score and CGI-S score, with significant effects first appearing three days after the initiation of treatment

(p=0.0096 and p=0.0280, respectively), and this effect was maintained throughout the study. 2)Endpoint analysis Statistically significant differences (p<0.05) favoring lurasidone were also demonstrated for mean change from baseline in the scores of PANSS Total, PANSS Positive, PANSS Negative, PANSS Cognitive Component, PANSS Depression, BPRS Total, MADRS and CGI-S, using an LOCF ITT analysis. Conclusion: The results suggest that lurasidone, at once daily doses of 80 mg, is an effective treatment for the rapid improvement of acute psychosis and across a broad range of symptomatology in chronic schizophrenic patients experiencing an acute exacerbation.

ABNORMAL CORTICO-AMYGDALA ACTIVITY DURING EMOTION COGNITION: DISTINGUISHING BIPOLAR DISORDER, UNIPOLAR DEPRESSION AND SCHIZOPHRENIA

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Background: We have aimed to identify potential biomarkers of bipolar disorder, type I (BPI) by examining BPI-specific abnormalities in neural systems underlying emotion processing and cognition. Methods: Using functional neuroimaging, we have measured neural activity to positive and negative emotional stimuli in remitted and depressed adults with BPI, depressed adults with unipolar depression, adults with schizophrenia and age-matched healthy individuals. Here, we have employed different experimental paradigms including: 1. emotion processing: gender labeling of displays of standardized facial expressions of happiness, sadness and fear; 2. executive control: a working memory task (digit sorting); and 3. the ability to regulate emotion processing during cognitive task performance: presentation of emotional words embedded in a working memory task. Results: To date, our findings indicate patterns of increased amygdala and decreased dorsolateral prefrontal cortical activity predominantly to positive facial expressions and to positive emotion words during subsequent digit sorting that distinguish all BPI from either unipolar depressed or schizophrenic individuals. By contrast, unipolar depressed individuals show increased amygdala and ventral striatal activity only to negative emotional stimuli, while schizophrenic individuals show increased parahippocampal activity to neutral but not emotional stimuli. Our findings also indicate that relative increases rather than decreases in dorsolateral prefrontal cortical activity during digit sorting may also distinguish BPI from unipolar depression. Conclusions: Our findings indicate first that patterns of abnormally increased amygdala and decreased dorsolateral prefrontal cortical activity predominantly to positive emotional stimuli may be specific to BPI rather than common to individuals with unipolar depression or those with schizophrenia. Second, they indicate that patterns of dorsolateral prefrontal cortical activity during digit sorting may distinguish bipolar from unipolar depression. Thirdly, our findings indicate persistent rather than episodic patterns of abnormally increased amygdala activity to positive emotional relative to neutral stimuli in BPI - a potential focus for future studies examining biomarkers of bipolar disorder.

FACIAL EMOTION PROCESSING IN SCHIZOPHRENIA AND ASPERGER'S SYNDROME: NO DEFICIT IN INTELLECTUALLY INTACT PATIENTS WITH EITHER DISORDER

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Many studies have found that patients with schizophrenia show poor performance on tests requiring judgements about facial emotion. What is less clear is the specificity of the deficit, ie whether it simply reflects the general intellectual impairment seen in the disorder, or is greater than impairment on non-emotional face processing tasks. In autism, it has been proposed that the inability to recognize emotions from facial expressions may form one of the bases for the impaired development of theory of mind abilities in the disorder. Method: 22 intellectually preserved patients with schizophrenia (WAIS-R IQ 85+), 18 high functioning adults with Asperger syndrome (WAIS-R IQ 85+) and 20 matched normal controls were given three tasks designed to test different aspects of face processing: emotional face processing (Eckman faces), structural encoding of the facial percept (Benton Facial Recognition Test), and recognition of famous faces. Results: The schizophrenic patients were not impaired compared to the normal controls on the facial emotion test (64.7±12.8 vs 65.5 ±9.7, NS) or on structural encoding of the facial percept (31.3±8.3 vs 37.2±6.5, NS). However, they showed impairment on the famous faces test (22.9±8.3 vs 29.5 ±7.6, P<0.05). The Asperger patients showed an essentially similar pattern of performance to the schizophrenic patients. Conclusions Poor performance on facial emotion processing tasks is not seen in relatively intellectually preserved patients and shows no evidence of neuropsychologically specificity – in contrast, there was evidence of a specific deficit in the semantic aspects of face processing. High functioning adult autism spectrum patients also failed to show a facial emotion processing impairment in this study. The finding of a semantic face processing deficit in the latter patients was unexpected, but has support from at least one other recent study.

ILLNESS CHRONICITY AND FACIAL AFFECT MISATTRIBUTION IN SCHIZOPHRENIA

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Patients with schizophrenia show an impaired ability to identify facial emotions. This perceptual-cognitive impairment is generally not related to the experience of positive and negative clinical symptoms and is found to co-vary with cognitive impairment. To further investigate the nature of the relationship between emotion perception and psychopathology in people with schizophrenia, we examined performance on a computerised Emotion Attribution Test of 71 patients diagnosed with schizophrenia or schizoaffective disorder and 30 healthy individuals. The task consisted of male and female faces showing happy, neutral, fearful or angry expressions. The patients were also rated on the Positive and Negative Syndrome Scale (PANSS, Kay et al, 1987; Schizophr Bull). Following the five-factor structure of the PANSS, there were few correlations between the number of emotion misperceptions and positive symptoms (neutral as angry and hallucinatory behaviour, r = 0.26, p = 0.03) and

negative symptoms (neutral as fear and emotional withdrawal, r = -0.29, p = 0.01). Instead, most emotion misattribution correlations were with items from the cognitive construct. A longer duration of illness, controlling for current age, was associated with misattribution of facial expressions of fear as neutral (r = 0.25, p = 0.04) and, at a trend level, of fear as anger (r = 0.22, p = 0.06). The observed negative effects of illness chronicity in facial affect attribution, which involves prefrontal-based cognitive processes, may be associated with a preferential decline in the prefrontal cortex as a function of illness duration (Premkumar et al., 2006, J Psychiat Res). At a psychosocial level, the greater likelihood of misattribution of facial expressions of fear as neutral or angry as the duration of illness increases may reflect an attunement to facial expressions of fear displayed by others when they interact with people with schizophrenia. Acknowledgement: Supported by funds from the Wellcome Trust.

WITHIN-GROUP DIFFERENCES IN COGNITIVE CHANGE AND RESPONSE TO COGNITIVE REMEDIATION THERAPY (CRT)

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Little is known about within-group differences in change in cognition over time and response to CRT. People with similar cognitive profiles may also show similar patterns of cognitive improvement or response to treatment. 85 people with schizophrenia and cognitive inefficiency were assessed on three executive/working memory factors, (i) 'verbal working memory', (ii) 'response inhibition' and (iii) 'schema generation'; two composite verbal and visuo-spatial long-term memory measures; estimated premorbid IQ; the PANSS and the Social Behaviour Schedule. They were then randomised to receive 40 sessions of individual CRT or treatment-as-usual and re-assessed immediately post-therapy. Cluster analyses using the 6 cognitive variables identified two internally and externally valid clusters showing 'moderate' or 'severe' cognitive impairment. The 'severe' group showed significantly worse social functioning and disorganised and negative symptoms than the 'moderate' group (there was also a trend for higher levels of positive symptoms). There were no significant differences between the clusters in terms of age, gender or chronicity. Results from the RCT showed greater cognitive improvements in those who received CRT. In addition, the 'moderate' cluster showed greater cognitive improvements than the 'severe' cluster in terms of 'verbal working memory', 'response inhibition' and 'verbal long-term memory'. However, there were no differences between the two clusters in response to CRT. This suggests that whilst people with severe cognitive impairment generally do appear to show a relatively intractable course of cognitive functioning, they may still respond well to cognitive remediation.

ASSOCIATION BETWEEN COGNITION AND CLINICAL SYMPTOMS ON FIRST-EPISODE PSICOSIS

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Introduction. Cognitive dysfunctions have frequently been related to symptomatology on chronic and first episode patients, giving support to neurobiological theories of this disease. Specific relationships have been stablished between negative and disorganized symptoms and disturbances on executive functions, memory, attention and motor functioning, however inconsistencies reported in the literature remain to be ellucidated. Method 125 First Episode patients with schizophrenia spectrum disorders subserved a comprehensive neuropsychological test battery. Clinical evaluations with SANS-SAPS scales were performed six weeks after treatment implementation. Correlational and regression analysis were used to study relationships between cognitive and clinical variables Results Negative symptoms assessed at six weeks related to Executive Functions-Speed of Processing and to Motor Coordination cognitive factors. These factors explained respectively 11.2% and 16.2% of variance of negative symptoms. Within Executive Functions-Speed of Processing factor those test with a heavier load on speed of processing accounted most for observed relationships. Conclusion Is confirmed the existence of relationships between negative symptoms and measures of executive functions and motor coordination. It seems that the relationship with executive functions might be mediated by the effect of speed of processing. Research Grants: Instituto de Salud Carlos III, FIS 00/3095, 01/3129, G0332, PI020499, Plan Nacional de Drogas SCO/3246/2004 and SENY Fundació Research Grant CI 2005-0308007.

COMPARISON BETWEEN THE EFFECT OF TYPICAL AND ATYPICAL ANTIPSYCHOTICS ON COGNITION: A THREE-MONTH FOLLOW-UP IN FIRST EPISODES OF PSYCHOSIS

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The cognitive déficits in patients with psicosis is one of the most relevant issues in terms of functional outcome. These deficits have been described as independent of psychotic symptoms. Typical and atypical antipsychotics have proven efficacy in the reduction of clinical symptoms. However, there is controversy regarding their effect on cognitive abilites. The use of typical antipsychotics has been related to extrapyramidal symptoms, as well as to psychomotor deficits. This is one of the reasons that favoured the utilization of atypical antipsychotics. The aim of this study is to analize the relationship between the kind of antipsychotic medication and changes observed in several cognitive domains in patients with first episodes of psicosis. 131 patients (diagnosis of schizophrenia) were randomly assigned to one of three treatment groups (haloperidol, olanzapine and risperidone). A first cognitive assessment was conducted after iniciation of pharmacological treatment once clinical stability was reached. Three months after the first cognitive assessment, a second follow up evaluation was completed. Statistical analysis included paired-t tests to assess differences between both sets of measures. In those variables that did show change, a repeated measures ANOVA was used in order to determine which treatment group displayed significant changes and to examine between-group differences. The three groups showed changes in several factors between both assessments. No statistically significant differences between the three experimental groups was found at any time point. The results suggest that the specific antipsychotic used in the pharmacological treatment of first episodes of psicosis may not have differential effects on the cognitive performance during the first three months.

FRONTOSTRIATAL DYSFUNCTION IN SCHIZOPHRENIA: A STUDY OF EXECUTIVE FUNCTION IN PATIENTS WITH AND WITHOUT MOTOR DISORDER

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The prefrontal cortex has been implicated in schizophrenia by functional imaging findings and several other lines of evidence. Other evidence implicates the basal ganglia, including particularly the finding of extrapyramidal symptoms (EPSEs) in some patients unrelated to drug treatment. These findings have led to the formulation of the 'fronto-striatal' hypothesis of schizophrenia, but this, however, has received little direct investigation. We tested a prediction of the hypothesis that, in chronic schizophrenic patients, executive test impairment would associated with motor disorder, including EPSEs and catatonic symptoms. Method: Matched groups of 27 schizophrenic patients with motor disorder (predominantly tardive dyskinesia), 27 with no motor disorder and 27 healthy volunteers were administered a battery of executive tests (BADS) and memory tests (WMS III). Patients above were selected for having relatively intact overall intellectual functioning (WAIS III IQ of 85+) Motor disorder was rated using the Modified Rogers Scale. This rates both EPSEs and catatonic symptoms, and also allows a score for the latter, defined conservatively, to be extracted. Video records were made and two independent ratters scored movements blinded to diagnostic status and neuropsychological test scores. Results: The schizophrenic patients as a group performed significantly more poorly than the normal controls on both the executive (BADS profile score 11.80 vs 17.07, P< 0.0001), working memory (Letter number-sequency profile score 6.43 vs 9.46, P< 0.0001) and the other subtests of WMS III. Posthoc analysis showed no differences between the patients with and without motor disorder on either the executive or memory measures. There were also no differences between groups in psychopathology, illness severity and treatment. Conclusions: Schizophrenic patients have a frontal/dysexecutive system that is not more dysfunctional in patients with motor disorder than in those without.

TRAINING OF MNEMONIC STRATEGIES IN SCHIZOPHRENIA GUDRUN SARTORY (UNIVERSITY OF WUPPERTAL, GERMANY) AND BERNHARD MüLLER (UNIVERSITY OF DUISBURG-ESSEN)

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Patients with schizophrenia were found to show different neural activity during encoding of word lists compared to healthy controls (Heinze et al., 2006). Whereas the latter recalled words that were associated with parietal activation during learning, patients with schizophrenia recalled words whose encoding was accompanied by occipital activation, indicative of a visualizing strategy. The present study aimed at comparing the success of training a visualization strategy with that of rehearsal. Thirty-three patients with chronic schizophrenia of a mean duration of 11 years were randomly allocated to either the visualization or the rehearsal group. All patients were clinically stabilized and on medication during training. During training patients were presented with 7 lists of words. Patients of the visualization group were asked to imagine the words and consider the colours, size and context of the named objects. The rehearsal group was asked to silently repeat the words. Each list was recalled immediately. A final test list was presented after a rest period. Neuropsychological tests were given the day before training and the test list was to be recalled again the day after. Visualization conferred a marginal benefit during recall of the training lists not, however, during recall of the test list. The day after, patients recalled either none or one of the words of the test list. The results suggest either that a brief training such as the present one is insufficient or that visualization does not improve memory performance in schizophrenia. Heinze, S., Sartory, G., Müller, B. et al. (2006) Neural activation during successful verbal learning in schizophrenia. Schizophrenia Res. 83, 121-130.

NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA

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Neurological soft signs (NSS) refer to subtle neurological abnormalities comprising deficits in sensory integration, motor coordination, and sequencing of complex motor acts. It is generally accepted that NSS are more prevalent in schizophrenia patients including first-episode cases compared to healthy subjects. Moreover, NSS have been consistently demonstrated in neuroleptic-naïve first-episode patients prior to medication exposure, thus they are thought to be an intrinsic feature of schizophrenia. This notion is underlined by the increased NSS scores in high-risk subjects, such as relatives of schizophrenic patients, or in the unaffected co-twins of monozygotic twin-pairs discordant for schizophrenia. However, recent studies clearly demonstrate that NSS are not a static feature of the disease but vary in the clinical course of the disorder. This variation with psychopathological symptoms was first established in the short term course with remission of acute symptoms under neuroleptic treatment but also applied for the long-term course over a follow-up period of up to 5 years. This effect was more pronounced in patients with a favorable than with a chronic course and was mainly accounted for by motor signs. In addition, NSS scores at remission and compliance with treatment could be identified as predictors. NSS in general and their variability in particular may represent the "process activity" as hypothesized by Huber. At the same time, NSS can be also interpreted as an expression of the genetic liability towards the disease – "schizotaxia" (Meehl) - where among others dysdiadochokinesia constitutes a trait-like marker of a baseline defect ("hypokrisia"). From a clinical standpoint, their fluctuations demonstrate that NSS are not merely a consequence of neuroleptic therapy. Although NSS are intrinsic to schizophrenia, their level varies with the clinical course. In conclusion, NSS correspond to both genetic liability and the activity of the disease process and be considered as potential predictors of outcome.

PRELIMINARY RESULTS OF SPANISH VALIDATION OF BRIEF ASSESSMENT IN COGNITION IN SCHIZOPHRENIA, BACS

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Cognitive impairment in schizophrenia is a core feature of the illness and very important to be assessed for clinicians and researchers.

The Brief Assessment in Cognition in Schizophrenia BACS, assess the main cognitive domains which are impaired in patients with schizophrenia: verbal memory, working memory, motor speed, attention, executive functions and verbal fluency. Also, the BACS has the advantage that takes less than 35 minutes to be completed and it is as sensitive to cognitive impairment as a standard battery of tests that required over 2 hours to be completed (Keefe et al., 2004). The Schizophrenia Clinic Program from the Hospital Clinic of Barcelona, Spain, in coordination with the University of Duke, USA (Dr. Keefe), completed the Spanish Adaptation of the BACS. The Spanish Adaptation is suitable to use it in patients with schizophrenia with Spanish as mother tongue. The total number of subjects until now are 100. They are divided into two groups: 75 DSM-IV-TR criteria schizophrenia patients (50 stable, 25 acute) and 25 healthy controls. To assess the cognitive status we have used the Spanish Adaptation of the BACS (randomly assigned to a sequence of versions A and B) and a standard cognitive battery. All the subjects were tested in three separate days with no more than two weeks between assessment. On the first test session, subjects received one version of the BACS (A or B); on the second session they received the standard battery and in the third session the other version of the BACS. As a preliminary results, we have found significant correlations for all cognitive domains in all the samples (patients and healthy controls) between both versions of the BACS and the standard cognitive battery. Sensitivity to between-group impairment on all measures was determined with independent t-tests and all tests (BACS and standard battery) have demonstrated significant differences between controls and patients with schizophrenia. These results suggest that the Spanish BACS is a good neuropsychological tool with stable and acute patients with schizophrenia.

IS PREMORBID ADJUSTMENT A PREDICTOR OF COGNITION IN SCHIZOPHRENIA AND DISCORDANT SIBLINGS?

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This study investigates the relationship between premorbid function and cognition in a large cohort of patients with schizophrenia and their siblings. The current study investigated 237 schizophrenic probands, 185 siblings free of any schizophrenia spectrum diagnoses, and 225 healthy controls. Wechsler Adult Intelligence Scale (WAIS), Wide Range Achievement Test (WRAT), Premorbid Adjustment Scale (PAS), Four Factor Index of Social Status (SES) and years of education scores were obtained for each participant. WRAT, WAIS, WAIS-WRAT (a measure of cognitive decline), and PAS scores were the main outcome variables. All covariates were reduced to categorical variables (5 levels for SES, 4 for years of education, 3 for age, 2 for gender), in order to have enough subjects/cell. Variables of interest were then adjusted to correct for the covariates that were found to be significant using an ANOVA model (gender did not require a correction). After these adjustments, the three diagnostic groups were significantly different on WAIS (107.14 ± 8.49, 105.77 ± 9.18, 97.92 ± 10.46 for controls, siblings, and probands respectively), PAS childhood (.150 ± .103, .181 ± .110, .233 ± .152), and PAS early adolescence (.170 ± .095, .201 ± .091, .269 ± .144), but not on premorbid IQ (107.60 ± 8.00, 107.57 ± 7.10, 106.93 ± 8.52). Siblings were significantly less well adjusted in childhood and early adolescence than controls. Despite patterns of poor premorbid adjustment, siblings of patients with schizophrenia did not show marked cognitive decline (WAIS-WRAT: -0.501 ± 9.01), nor did they show significant current cognitive dysfunction. When looking across all groups, PAS scores in childhood and early adolescence predicted current cognitive ability as measured by IQ ($r = -.2496$, $p<.001$, $r = -.2758$, $p<.001$, respectively). PAS scores in early adolescence ($r = -.2059$, $p<.001$) and in childhood ($r = -.1294$, $p=.002$) predicted measures of cognitive decline. Results suggest that heritable mechanisms affect premorbid adjustment of non-psychotic siblings of probands in childhood and adolescence. This is associated with their general cognitive abilities and, to a much lesser extent, with cognitive decline. This data set can be used to identify, in more detail, which genes contribute to cognitive decline and to social functioning in childhood.

METHODOLOGY FOR CLINICAL RESEARCH AND SERVICE PROVISION FOR RURAL YOUTHS EXPERIENCING EARLY PSYCHOSIS: AN AUSTRALIAN STUDY

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Introduction: Clinical research on psychotic disorders in rural and remote communities (RARC) has been substantially understudied compared to urban areas. Barriers to research in RARC bear similarity to those for clinical service provision – vast distances, scattered and migrating populations, lack of specialist mental health services and reliance on primary health care workers. Consequently rural service delivery models often tend to be poorly designed adaptations of urban models. It is critical that research methodology in RARC be tailored to the specific characteristics of the communities so that a sound empirical base can be established to inform service delivery models. While telepsychiatry has been utilised for clinical assessment there is currently a lack of evidence for its reliability with neuropsychological assessment. Telepsychiatry provides an opportunity for specialist assessment without the high costs of flying specialists to remote locations. Hence telepsychiatry has the potential to reduce research and clinical costs while providing greater access to services for youths in RARC. Objectives: The paper will address (i) characteristics of rural youths in Australia with early psychosis (EP), and (ii) reliability of neuropsychological assessment by telepsychiatry. Method: Routine clinical data will provide demographic and clinical information on EP rural youths in Australian. The reliability of telepsychiatry for neuropsychological assessment will be examined by a comparison of face to face and telepsychiatry methods. Youth will be recruited through health services across the central western region of rural New South Wales, Australia. Measures will assess the domains of symptoms, social functioning, cognition and substance use. Results: EP in RARC is characterised by a substantial proportion of aboriginal youths in some areas, high levels of drug/alcohol problems and vast distances to access services. Assessment by telepsychiatry achieved reduced costs but maintained reliability compared to face to face. Discussion: The utility and reliability of neuropsychological assessment by telepsychiatry provides a platform to facilitate early psychosis research in RARC. Such research will assist in the development of empirically based intervention models for rural youth experiencing and at risk of developing psychosis. Hence the paper provides the opportunity to further explore the specific needs of rural youths in providing early intervention services.

INSIGHT INTO ILLNESS IN THE EARLY AND CHRONIC PHASES OF SCHIZOPHRENIA: RELATIONSHIP TO BASIC SCIENCE MEASURES OF ATTENTION, MEMORY, SOCIAL COGNITION, AND EMOTION REACTIVITY

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Poor insight is associated with less treatment adherence, and in turn, poorer symptomatic and functional outcome in schizophrenia. However, the determinants of poor insight are not understood. We examined the associations between insight and measures of dual-task processing, episodic memory, social cognition, and emotion reactivity. These measures were part of the UCLA Center for Neurocognition and Emotion in Schizophrenia (www.schizophrenia.ucla.edu) (P.I.: KHN). Clinical and basic behavioral scientists collaborated to translate advances in basic behavioral research to schizophrenia research. Among first episode patients, overall unawareness of having a mental disorder, unawareness of medication benefits, and unawareness of the social consequences of illness were significant correlated with poorer social cognition, in particular theory of mind. Inability to relabel unusual thoughts as a symptom of the disorder (relabeling) was associated with greater response interference in a dual task attention paradigm. Poorer awareness of hallucinations was associated with poorer episodic memory and slower processing speed. Less awareness of deficits in memory, attention, and work functioning was associated with the poor episodic memory and central dual-task interference. Among chronic schizophrenia patients, overall unawareness of having a mental disorder was associated with poorer episodic memory, whereas the unawareness of social consequences of the disorder was associated with measures of social cognition and emotion reactivity. Failure to correctly attribute impairment in work, attention, memory, and processing speed to the schizophrenic disorder was related to poorer social cognition. These findings suggest that the awareness of having a mental disorder shares some characteristics with understanding what other people are thinking and the reasons for their behaviors. This study extended prior findings to measures of dual-task processing and episodic memory paradigms. Impairment in memory and attention resulted in difficulty being aware of one's own problems in these domains, a situation also seen in dementia. Our previous work suggested that insight of schizophrenia patients improved over time, which might explain the attenuated relationships seen among the chronic schizophrenia patients.

RELATIONSHIP BETWEEN COGNITIVE PERFORMANCE AND PSYCHOTIC/SCHIZOTYPAL DIMENSIONS

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INTRODUCTION Based on previous published data we hypothesized specific correlations between psychotic dimensions (negative [NEG], positive [POS] and disorganisation [DIS]) and cognitive performances in schizophrenic patients. We expected significant correlations between NEG and results on tasks involving initiation and maintenance of an action, between DIS and tasks measuring distractibility and between the POS and measures of source monitoring. We also hypothesized similar correlations between schizotypal dimensions in relatives of patients and in normal controls. METHODS Cognitive performances were assessed in schizophrenic subjects (N=54), their first degree unaffected relatives (N=36) and controls (N=39) using a semantic Verbal Fluency task (VF), the Stroop test and a Source Monitoring Task. Scores of NEG, POS and DIS were derived from the SSPI in schizophrenic patients and from the SPQ in relatives and controls. We assessed the influence of symptomatic and demographic variables on cognitive variables using a stepwise backward regression. We calculated partial correlations for the clinical dimensions that had significant influence on cognitive variables. All analyses were done separately for schizophrenic subjects and healthy subjects (i.e. relatives and controls). RESULTS In schizophrenic subjects NEG correlated with performances on all cognitive tests. The only other significant correlation was between DIS and total number of items in the interference condition of the Stroop. In healthy subjects, all significant correlations involved variables derived from the VF task. Total number of words and number of clustered words were positively correlated with DIS score although number of switches was inversely and mean cluster size positively correlated with the NEG score. DISCUSSION The data did not verify our hypotheses. In particular, we failed to find any significant correlation with POS and did not found similar correlations in the two different groups (schizophrenic and healthy subjects). In patients, the fact that DIS and POS dimensions are not stable could be an explanation for the paucity of significant correlations with the (more stable) cognitive variables. In healthy subjects the positive correlations involving variables from the VF suggest that NEG dimension is related to difficulties in shifting attention, i.e. deficient cognitive flexibility although DIS could be linked to excessive, and probably superficial, associations.

DO PEOPLE WITH SCHIZOPHRENIA HAVE BETTER INSIGHT INTO THEIR PSYCHOTIC OR NEUROCOGNITIVE SYMPTOMS?

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Impaired insight into psychotic symptoms is a hallmark of schizophrenia, and psych-education is often used to improve patients' insight into illness. Most psycho-education focuses on psychotic symptoms but if insight into neuro-cognitive deficits is poor, psycho-education may need to be broader in focus. The purpose of this study was to directly compare whether insight into psychotic symptoms is better or worse than insight into neuro-cognitive symptoms. In this study, 75 people with schizophrenia who were all active participants in treatment programs, were administered the SUMD and IS to assess insight into psychotic symptoms, as well as a newly developed measure of insight into cognitive status called the MIC. The MIC has two forms, a clinician rated version (MIC-CR) which allows clinicians to rate patient's insight into neuro-cognitive status, and a self-report version (MIC-SR) which allows the patient to rate the frequency of problems with attention, memory and various aspects of executive functioning. The MIC-CR was modeled after the SUMD, and uses a similar 5 point scale to assess both awareness and attribution of symptoms. Results indicated that patients had more

insight into having a mental disorder than a neuropsychological disorder, t(74)=10.20, p<0.001. Whereas 45% of the subjects had no insight and 35% had full insight into their neuropsychological deficits, 10% had no insight and 77% had full insight into their mental disorder. In this sample, patients enrolled in treatment programs had more insight into their psychotic symptoms than their cognitive symptoms. Given the poor insight into the neuro-cognitive deficits associated with illness, psycho-education may need to be broader in focus so patients can gain a better understanding of their cognitive symptoms.

REMEMBERING TO REMEMBER: PROSPECTIVE MEMORY IMPAIRMENT IN SCHIZOPHRENIA

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Individuals with schizophrenia may have impairments in prospective memory (ProM), encompassing the ability to form, maintain, and execute future intentions. ProM is a domain of neuropsychological performance that remains poorly understood, despite its implications for everyday functioning. We administered the Memory for Intentions Screening Test (MIST) and other neuropsychological and clinical tests to 41 outpatients with schizophrenia or schizoaffective disorder (66% male, 66% Caucasian, mean age = 48, mean years of education = 13) and 41 demographically similar healthy comparison subjects. The MIST requires responses to be performed in reaction to time-based and event-based cues, following 2- or 15-minute delays. Mean Z-scores were calculated across neuropsychological tests to create domain-wide Z-scores and a global neuropsychological Z-score. The data were analyzed with Wilcoxon rank sums tests, Pearson correlations, and multiple linear regression techniques. Compared with healthy subjects, the schizophrenia patients performed worse on all MIST components, with most errors being failures to respond to the ProM cue. However, the groups did not differ on a post-test multiple-choice recognition trial. In the patients, MIST summary scores were not associated with self-ratings of ProM difficulties or any demographic or disease burden variables. Better MIST performance was significantly associated with better performance on tests of processing speed, attention, working memory, language, learning, and executive functioning (all correlations .31-.51), global neuropsychological performance (r = .65), and less severe negative symptoms (r = -.48), but not delayed recall performance (r = .22). In a multiple regression, global neuropsychological functioning predicted MIST scores, but negative symptom severity did not. The ProM deficit in schizophrenia appears to be related to impairments in self-directed monitoring and retrieval, rather than encoding or retention. ProM functioning was associated with neuropsychological domains commonly impaired in schizophrenia and appears to rely on multiple cognitive substrates.

VIRTUAL REALITY AND PARANOID IDEATIONS IN PEOPLE WITH AN AT RISK MENTAL STATE FOR PSYCHOSIS

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Introduction: Appraisal of anomalous experiences plays a central role in the cognitive model of psychosis (Garety et al 2001). Virtual reality provides a useful tool to manipulate a life-like environment while observing spontaneous responses to different stimuli. Pilot data has confirmed that virtual characters can elicit unfounded paranoid thoughts in healthy controls (Freeman at al., 2003; 2005). This paper describes the results a study to examine: whether individuals with an at risk mental state (ARMS) have persecutory thoughts about virtual reality characters; and to explore which emotional and cognitive processes are associated with paranoid thoughts. Methods: Twenty-one ARMS participants entered a virtual underground train populated by computer-generated people. The participants completed dimensional assessments of items related to psychiatric symptoms (Paranoia Scale; Persecutory Thoughts Scale; Launay Slade Hallucination Scale; Depression, Anxiety, Stress Scale; Interpersonal sensitivity scale); of their thoughts about the virtual characters (VR-Paranoia); and the Beads task and Wisconsin Card Sorting Test. Results: The results show that individuals attribute mental states to virtual reality characters. The majority of participants (57%) endorsed at least one persecutory item. Individuals who had persecutory thoughts about the virtual characters had significantly higher levels of anxiety (rho=.57, p<.01), perceived stress (rho=.50, p<.05), and a fragile inner self (rho=.46, p<.05). Jumping to conclusions (beads task) did not correlate with persecutory ideations. Conclusion: VR methodology can be used with a clinical group, it is realistic, not distressing and non-intrusive. The virtual environment triggers persecutory ideations which are associated with emotional and cognitive processes predicted by a cognitive model.

A COMPARISON OF INSIGHT AND NEUROPSYCHOLOGICAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR I DISORDER

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Background: There is substantial evidence for reduced insight and neurocognitive deficits in schizophrenia. However, the diagnostic specificity of insight variables and their correlates are not known. Methods: To assess specificity, awareness of illness (using the Scale to Assess Unawareness of Mental Disorder; SUMD), level of psychopathology and neuropsychological function was investigated in 32 DSM-IV patients with schizophrenia, 37 patients with bipolar I disorder, and 31 healthy comparison subjects matched for age and gender. Results: There was no sognificant difference between the two diagnostic groups on general illness awareness. However, bipolar patients had better awareness of their symptoms and their pathological nature than patients with schizophrenia. General unawareness was associated with clinical severity, especially of the affective type, and working memory deficits (WAIS Digit Span) in both diagnostic groups. The contribution of other cognitive deficits to insight differed across the groups. Misattribution differed from the other aspects of insight in its relative independence of clinical and neurocognitive correlates. Both patient groups were neurocognitively impaired compared to normal control subjects, with the schizophrenia group performing significantly worse than the bipolar group on conceptual ability, verbal learning, visuospatial processing and motor speed. Conclusion: The results suggest that differences in general insight between diagnostic groups may be explained by symptom severity and working memory function rather than the specific diagnosis per se. The findings necessitates a differentiation between insight measures and point to a diagnostic specificity of the underlying cognitive

and emotional processes involved. Keywords: Insight; Unawareness; Schizophrenia; Bipolar disorder; Neuropsychology

NEUROPSYCHOLOGICAL DEFICITS IN HIGH NAILFOLD PLEXUS VISIBILITY SCHIZOPHRENIA PATIENTS

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Nailfold Plexus Visibility is a putative marker for a distinct subtype of schizophrenia. The purpose of the current study is to further characterize this phenotype. We compared schizophrenia patients with high nailfold plexus visibility to other schizophrenia patients and to normal controls in performance on a neuropsychological battery. Based on the literature we hypothesized a specific deficit in tasks tapping frontal lobe function in the high nailfold plexus visibility subjects. Patients were also rated on clinical scales, and all subjects underwent structural and diffusion tensor imaging in a 3 Tesla magnetic resonance imaging scanner. At this time we have completed study on 21 subjects with 16 others in process. Recruitment is ongoing. In this preliminary analysis we have confirmed a high rate (38%) of high plexus visibility among our schizophrenia subjects. In general high plexus visibility patients show more impairment on frontal lobe tasks including Category Fluency, Trails B and the Tower of London. This group difference is significant at this time only for the CalCap Sequential Reaction Time 2 variable (F= 6.48,p=.03), a measure of attention and working memory. The high plexus visibility subjects are also tending to show greater impairments of a similar magnitude relative to other schizophrenia subjects on control tasks of verbal (Hamilton Verbal Learning Test) and visual (Benton Visual Retention) memory. The high and low plexus visibility patients are not showing differences in clinical symptoms or in a structural brain imaging measure of ventriculomegaly. Diffusion Tensor Imaging measures of cerebral white matter integrity are still being processed and will be analyzed at a later time. Results to this point confirm a high rate of elevated nailfold plexus visibility among patients with schizophrenia, and suggest more impaired neuropsychological functioning in this subgroup of patients. Some of these data were gathered as part of the MIND Clinical Imaging Consortium

CLINICAL AND NEUROCOGNITIVE STATUS IN ADOLESCENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS: A LONGITUDINAL STUDY EXAMINING THE FIRST YEAR OF ILLNESS

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Background: Adults with schizophrenia consistently show significant deficits in IQ, attention, memory, executive functioning, and processing speed. Neurocognitive status is considered a potentially important indicator because of its relationship to clinical variables such as negative symptoms, adaptive functioning, employment status, and others. In contrast to the large number of adult studies, relatively few studies have examined neurocognitive functioning in adolescents with schizophrenia-spectrum conditions. As a result, little is known about the levels of deficits in young patients, the longitudinal course of these deficits, and the relationship to clinical symptomology. Methods: The patients included 37 adolescents, ages 12 to 17, with DSM-IV diagnoses of Schizophrenia (14), Schizoaffective Disorder (7), Schizophreniform Disorder (6), and Psychosis – Not Otherwise Specified (10). Diagnoses were made with K-SADS structured interviews. Patients were administered a neuropsychological battery after stabilization of symptoms; 13 have been evaluated again at one year, thus far. PANSS ratings were also collected at both time points. Most patients were inpatients and all were on atypical antipsychotics at the time of testing. Results: At baseline, patients showed impairment relative to normative data (approx. one standard deviation impairment on average) on measures of verbal memory, processing speed, fluency, and executive functioning. Baseline IQ was correlated with negative symptoms at baseline and at one year. Several baseline neurocognitive measures predicted positive and negative symptoms at one year. The strongest correlations were with negative symptoms. Better baseline cognitive performance predicted better symptom outcome. A MANOVA revealed a significant effect for time (improvement) in both positive and negative symptoms for the group of patients over one year. A second MANOVA showed no significant main effects for time (improvement or decline) on any of the neurocognitive measures over the year. Conclusions: Near the time of first symptom-onset, adolescents with schizophrenia-spectrum disorders showed neurocognitive deficits similar to those seen in adults. Over the first year, while symptoms fluctuated, cognition was stable. In general, lower IQ and neurocognitive deficits predicted worse symptom outcome at one year.

NEGATIVE SYMPTOMS AND THE FRONTAL LOBE SYNDROME: DIFFERENT OR THE SAME?

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BACKGROUND: A leading theory of the negative symptoms of schizophrenia is that they are due to frontal lobe dysfunction. While many studies have investigated this proposal neuropsychologically, ie by examining executive function in patients with and without negative symptoms, there have been no studies to date comparing negative symptom schizophrenia and the frontal lobe syndrome from the behavioural point of view. METHOD: 13 DSM IV schizophrenic patients with prominent negative symptoms and 12 neurological patients with the frontal lobe syndrome (frontal dementia N=11, anterior communicating artery aneurysm N=1) were rated on a negative symptom scale (SANS). Relatives or carers also filled in questionnaires for frontal lobe behaviours (DEX and FrSBE). Both groups were also tested on a range of executive tests, including the Hotel Test, an 'ecologically valid' task which mimics the kinds of executive skills necessary in daily life. RESULTS: The schizophrenic patients scored significantly higher on negative symptoms than the frontal lobe patients (SANS summary score 9.23± 3.39 vs 3.81 ±4.44, P=0.01). In contrast, the frontal lobe patients had significantly higher carer ratings of frontal problems in daily life than the schizophrenic patients. However there was no evidence of a differential pattern of scoring on carer ratings of apathy, disinhibition and executive failures in the two groups. Both groups showed a broadly similar pattern of performance on executive tests, with failures being least common in verbal fluency (3/13 vs 5/12) and most frequent on an ecologically valid test, the Hotel Test (8/13 vs 9/12). An exception was the Hayling Test (which requires inhibition of prepotent responses): 0/13 of the schizophrenic patients failed this compared to 7/12 of the frontal patients. An unexpected finding was rateable poverty of content of

speech in 3 of the frontal lobe patients. CONCLUSIONS: The negative schizophrenic syndrome and the frontal lobe syndrome resemble each other in important respects, although there are some differences.

PREDICTORS OF VOCATIONAL SUPPORT INTENSITY FOR PEOPLE WITH SCHIZOPHRENIA IN SUPPORTED EMPLOYMENT

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This study examined predictors of intensity of vocational specialist support for clients with schizophrenia or schizoaffective disorder in a supported employment program. Sixty-nine outpatients with schizophrenia or schizoaffective disorder were recruited from a community mental health center for 12 months of vocational and cognitive rehabilitation. Client characteristics associated with work outcome including neuropsychological test scores, symptom ratings, lifetime severity of illness, and employment hx. were used to predict intensity of vocational specialist support, expressed as hours receiving direct coaching in ratio to total hours worked for each client over 12-months.Weekly work hours were inversely correlated with intensity of vocational support (r= -.55, p<.0001). ANOVA results comparing work participation quartiles on vocational specialist support were significant (p<.0001). The upper 50% averaging 10 to 40 hours of work per week received significantly lower proportions of on-site job coaching than the lowest quartile averaging between 2 and 5 hours of work per week. Vocational support reached 100% for only the lowest quartile. Regressions predicting to vocational support intensity from neuropsychological composite scores,educational/vocational, and hospitalization hx. were not significant. Significant regressions utilized PANSS component scores (p<01), R2 = .17; SANS subscales(p<.05), R2=.07; and SAPS subscales (p<.05), R2=.07. Individual PANSS, SANS and SAPS items responsible for explained variance were isolated. A final regression using SANS social inattention, PANSS poor attention and active avoidance, and SAPS agitated/aggressive behavior was significant (p<.001), R2= .23, with SANS social inattention (p<.005), and PANSS active avoidance (p<.005),predicting 12 and 11 percent of the variance respectively in support intensity. A one-way ANOVA comparing work participation quartiles on these symptoms showed a significant effect for SANS social inattention (p<.05) and PANSS active avoidance (p<.01). Post-Hoc comparisons showed significantly higher levels of active avoidance and social inattention for participants working less than ten hours per week. A profile emerged of the high intensity client as a socially inattentive or avoidant individual requiring a limited work schedule. Results suggest that these clients require more specialist contact because of failure to adequately engage natural supports at work.

22. Functional and Psychosocial Outcome

IMPAIRED POSITIVE EMOTIONAL EXPERIENCE IN DEFICIT SYNDROME SCHIZOPHRENIA

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It has long been noted that individuals with schizophrenia experience emotion abnormally. However, debate exists as to whether the failure to express emotion signifies an inability to experience emotion. Previous reports suggest that most individuals with schizophrenia evidence a disjunctive relationship between experience and expression, although this relationship has been found to differ in patients with deficit syndrome schizophrenia, who display an impaired ability both to express and experience positive emotion. The current study attempted to determine whether the deficit syndrome is associated with an inability to experience multiple types of positive emotion, and whether this impairment is consistent across both frequency and intensity of experience. Participants included 15 patients with deficit syndrome schizophrenia, 24 patients with non-deficit schizophrenia, and 25 healthy controls. Self-report questionnaires were administered to examine frequency of discrete emotional experience (Differential Emotions Scale), as well as the intensity of state and trait positive and negative emotions (Positive and Negative Affect Scale). Results indicated that deficit syndrome patients experienced joy, interest, and surprise significantly less frequently than non-deficit patients; however, patients did not differ in relation to frequency of negative emotional experience. Deficit patients also reported significantly lower intensity of positive, but not negative emotional experience in comparison to non-deficit patients. Findings suggest that the deficit syndrome is associated with an impaired ability to experience positive emotion that extends across multiple types of positive emotions and to both intensity and frequency of experience.

IMPAIRED SOCIAL PERCEPTION IN PATIENTS WITH SCHIZOPHRENIA

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To determine the nature of the impairment of the social perception in schizophrnia, we investigated the simple factual perception and emotional contextual perception ability of 20 patients. Social perception scale was composed of simple factual perception and emotional contextual perception. All 6 stimuli were black and white photographs depicting social situations such as a man hit by several angry women, two lovers, an elderly woman desperately trying to sell the fishes. Patients showed more marked impairment of emotional contextual perception than that of factual perception, although patients did poor performances in both perception. These findings suggested that patients with schizophrenia showed impaired social perception ability, which might be derived from not only dysfunction in the simple factual perception but, more importantly, impaired emotional contextual perception.

Social perception in patients with schizophrenia (n=20) and normal controls (n=20)

	Patients with schizophrenia	Normal controls	t/F (p)
Simple factual perception (A)	11.3 (1.2)	12.0 (0.0)	(A) -2.78 (0.012) (B) -3.09 (0.004) (A)x(B) 5.5 (0.024)
Emotional contextual perception (B)	8.4 (2.7)	10.5 (1.5)	

Values indicate mean (SD).

EMOTIONAL EXPERIENCES IN SCHIZOPHRENIA: TOWARDS MORE CLARITY?

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The evaluation of positive and negative emotions involves two independent but interacting emotional systems. These systems differently impact higher-order behaviors such as mood, personality and functional competence. For example, frequent experiences of positive affect lead to better social outcomes. Emotion clarity (which can be defined as the ability to identify, distinguish and describe specific emotions) reflects one form of emotion regulation, which is particularly important for the regulation of negative emotions, and it has been associated with the experience of negative mood and negative well-being. Although individuals with schizophrenia (IWS) show significant functional deficits during the course of the illness, the relation between basic emotion processes and social deficits has rarely been studied in schizophrenia. Thirty-nine individuals with a SCID diagnosis of schizophrenia and 17 nonpatient control subjects (NCS) completed the revised Physical Anhedonia Scale (PAS), the revised Social Anhedonia Scale (SAS), the revised Toronto Alexithymia Scale, and the General Temperament Survey. Clarity was measured by summing the scores of two subscales of the Toronto Alexithymia scale: Difficulty Identifying Feelings and Difficulty Describing Feelings. Psychopathology was measured with the Positive and Negative Symptom Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS). Social perception was measured with a facial and an acoustic emotion recognition test. Social competence was measured with the University of San Diego Performance Based Skills Assessment (UPSA). Compared to NCS, IWS reported a significantly higher degree of physical and social anhedonia, and alexithymia. Among IWS, PAS and SAS (measures of the positive emotion systems) were correlated with negative symptoms (0.59 and 0.30 respectively), with the UPSA total scores (-0.34 and –0.43 respectively), and with social perception (-0.20 and –0.34 respectively). Clarity (measure linked to the negative emotion system) was correlated with Negative Temperament (-0.64) and with positive symptoms (-0.28), but not with Positive Temperament nor negative symptoms. Our results confirmed that positive and negative emotion processing are two independent evaluative systems, they correlate differently to the psychopathology and social deficits observed in schizophrenia; and they have causality potential. This should lead to new psychosocial interventions and new therapeutic approaches.

CRIMINAL JUSTICE SYSTEM INVOLVEMENT AND COSTS FOR PATIENTS TREATED FOR SCHIZOPHRENIA

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To assess criminal justice system (CJS) involvement and its costs for individuals treated for schizophrenia and related disorders over a 1

year period. This post-hoc analysis used data from a 1-year, multisite, randomized open-label cost-effectiveness study of antipsychotics in the treatment of schizophrenia and related disorders. The study (HGGD) was conducted in the U.S. between 5/1998 and 9/2002, using broad inclusion criteria and enrolling patients treated in usual care settings. Patients' resource utilization (medical record-based psychiatric and medical resources) was used to calculate total direct treatment costs per patient per year. Patients were also interviewed about involvement with the CJS and about specific types of involvement, including arrests (e.g., for arson, assault), and encounters not involving arrest. This information was used to calculate direct per patient cost of involvement with the CJS, using previously reported costs per type of encounter (Clark RE et al, Psychiatr Serv1999). Patients with and without CJS involvement were compared on baseline characteristics and direct annual treatment costs. During the 1-year study, 46% (298/651) of the participants reported at least one involvement with the CJS. The most prevalent type of involvement was being a victim of a crime (31%), followed by being on parole or probation (12%), arrest for assault (6%), and being charged without arrest with a major driving violation (5%, e.g., reckless driving). Patients with and without CJS involvement did not significantly differ on direct annual treatment cost ($22,357 vs. $20,168, respectively, p>.05). The mean cost of CJS involvement was $2,565 (range $38 - $25,402), thus increasing by 11.5%, on the average, the direct total cost. Patients with and without CJS involvement significantly differed on various demographic, clinical and functional variables. Patients with CJS involvement had greater likelihood of substance use disorders and poorer adherence to antipsychotic regimens. In this 1-year study, almost one-half of the participants reported involvement with the criminal justice system, incurring additional costs that often go unaccounted for in cost studies of schizophrenia. Findings highlight the need to improve understanding of the interface between the mental health and the criminal justice systems for patients with schizophrenia and their related costs, in economic, personal and societal terms. Funded by Eli Lilly and Company

NEUROCOGNITIVE FUNCTIONING, THEORY OF MIND, AND SOCIAL FUNCTIONING IN SCHIZOPHRENIC DISORDERS

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Schizophrenic disorders are characterized by positive and negative symptoms (i.e. hallucinations, affective withdrawal) as well as deficits in social functioning. Moreover neurocognitive impairments are frequently reported as well as Theory of Mind (ToM) impairments. However, the type and the magnitude of these deficits and the relationship between them are still not well understood. The aim of the present study is twofold: 1) To compare neurocognitive-, social-functioning, and ToM in patients with schizophrenic disorders and healthy controls. 2) To investigate whether the psychiatric symptoms severity is related to the impairments in the various domains. Sixteen out-patients with schizophrenia diagnosis according to DSM-IV and 16 matched healthy controls participated in the study. All participants signed an informed consent form. They were aged from 18 to 60 years. Duration of the illness was more than two years. Participants were administered neuropsychological battery assessing verbal (RAVLT) and non verbal memory (ROCF), executive functions (Verbal Fluency, WCST) attention (D2) and global intellectual functioning (PM38). ToM capabilities were measured with six stories and Social Functioning was assessed with questionnaires (QFS, ERA) and a video-test (AIPSS). In addition, psychopathology was assessed with BPRS. Results show that patients and controls differ on most neurocognitives variables (verbal and non-memory, attention, and executive functions). They also differ on one ToM factor (2nd order ToM) and on two social measures (QFS frequency index and ERA pleasure factor), these two last measures being only related with manic-hostility and negative symptoms subscores of BPRS. These findings do not support the hypothesis of other authors (e.g. Green 1996, 2000) that there is causal link between neurocognitive impairments and social dysfunctioning in patients with schizophrenia. Alternative associations between ToM-, social- neurocognitive impairments and clinical symptoms are proposed.

VERBAL FLUENCY IS A STRONG PREDICTOR OF SHORT-TERM OUTCOME IN FIRST EPISODE PSYCHOSIS

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Objective: Neurocognitive dysfunction is associated with poorer functional outcome in patients with schizophrenia and bipolar disorder, and is an important target for treatment and rehabilitation efforts (Green, 2006). The following study aimed to determine the ability of a comprehensive array of neurocognitive measures to predict short-term functional outcome in a sample of patients with a first episode of psychosis. Methods: Eighty four patients (M/F = 57/27; mean age = 33.15 s.d. = 11), participants in the Northern Ireland First Episode Psychosis Study, were included in the analysis. All patients underwent neurocognitive testing at illness onset and subsequently agreed to a clinical assessment examining levels of functioning at one year follow-up. The following neurocognitive variables were included in the regression model: IQ, attention, working memory, verbal and visual memory, executive functioning, verbal fluency, language and callosal function. Age of onset, positive and negative symptoms at onset, preliminary diagnosis, handedness and gender were subsequently assessed as possible additional predictor variables. Outcome was measured using the Global Assessment of Functioning Scale (GAF). Results: Three factors accounted for approximately 34% of the variance in GAF at one-year follow-up: verbal fluency ($\beta = 0.5$, $p<0.001$), positive symptoms ($\beta = -0.25$, $p<0.01$) and gender ($\beta = 0.19$, $p<0.05$). Conclusions: Reduced verbal fluency, greater severity of positive symptoms and male gender independently predict poorer short-term functional outcome in patients with a first episode of psychosis. Notably, previous profiling of neurocognitive functions in this sample indicated that verbal fluency was relatively unimpaired at illness onset as compared to other neurocognitive indices. Mild deficits were however present in those patients with a preliminary diagnosis of schizophrenia. It is suggested that both verbal fluency and duration of untreated psychosis (McCaul et al. 2007; ICOSR poster presentation) are strong independent indicators of prognosis in first episode psychosis. References: Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry. 2006;67 Suppl 9:3-8. McCaul et al., (2007) Duration of untreated psychosis in first episode patients: relationship to functioning and symptomatology at one year. Poster presentation at the ICOSR.

SUBSTANCE MISUSE AS A CAUSAL FACTOR FOR LATER ONSET OF PSYCHOTIC SYMPTOMS: IS THERE AN ASSOCIATION?

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Background: Substance abuse is increasingly prevalent in persons with psychosis and related disorders. Up to 50% of schizophrenia patients present with comorbid substance disorder. To further elucidate whether substance use may be a risk factor for the onset of psychotic symptoms, an assessment of first-episode psychosis patients was performed. Method: A representative first-episode sample of 73 patients, who fulfilled the criteria for psychosis, was enrolled in a long-term study of psychosis. Rates of substance misuse were conducted using the Substance Misuse portion of the Structured Clinical Interview for DSM-IV (SCID). Age at onset of psychotic symptoms was also recorded. Results: Fifty of the 73 subjects (69%) had a lifetime pattern of cannabis abuse, of which 80% consumed cannabis before the onset of psychosis. In only 16% of subjects did the onset of psychosis pre-date cannabis consumption. Only two patients (4%) had consumed cannabis concurrently with the onset of psychotic symptoms. Similar patterns existed for other illicit drug use. In a large proportion (70%) of polysubstance users, consumption of drugs pre-dated the onset of psychotic symptoms. Of this sub-group, only 21% of subjects experienced their first onset of psychotic symptoms prior to their substance misuse, with 9% experiencing symptoms concurrently. Mean age for onset of cannabis consumption was 15 years and 18 years for other illicit drug use respectively. The mean scores for onset of psychotic symptoms was 18 years. Conclusions: Early onset of cannabis consumption has been associated with increased risk of experiencing psychotic symptoms. This study lends supportive evidence to the notion that consumption of cannabis and/or other illicit drugs in early adolescence increases the risk for developing psychosis.

SOCIAL FUNCTIONING AND COGNITION IN FIRST EPISODE AND MULTI-EPISODE SCHIZOPHRENIA

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Individuals with schizophrenia have demonstrated impairments in both social and cognitive functioning (Addington & Addington, 1999; 2000). It has been suggested that poor cognition has a significant impact on social functioning (Addington et al 2005, Green, 2000). The aim of this study was to test the hypothesis that deficits in cognitive functioning impact on social functioning in both patients and in control groups and that this association is stable longitudinally. This was a one year longitudinal cohort study comparing three groups: 50 first-episode psychosis patients (FE), 53 multi-episode schizophrenia patients (ME) and 55 non-psychiatric controls (NPC). Subjects were assessed on a wide range of cognitive tests and three measures of social functioning. Results of ANOVA demonstrated that both the FE and ME subjects were clearly impaired (significance ranged from 0.01 – 0.0001) relative to NPCs in both cognition and social functioning. Cognition and social functioning were generally stable over time in all three groups. The one exception was that the FE subjects demonstrated an improvement on social functioning from baseline (which, for this group, was their admission to an outpatient program for first treatment) to the one year follow-up. There were significant associations among cognition and social functioning in all three groups (significant r ranged from 0.28 to 0.44 with p values ranging from 0.001 to 0.0001). However, significant associations depended on which measure of social functioning was used. This study demonstrates that deficits in cognition may impact social functioning in first episode psychosis and multi-episode schizophrenia patients, and in normal controls. **References:** Addington J. & Addington D. 1999 Neurocognitive and social functioning in schizophrenia. Schiz Bull 25:173-182; Addington, J. & Addington D. 2000 Neurocognitive and social functioning in schizophrenia, a 2.5 year follow-up. Schiz Res 44: 47-56; Addington, J. et al., 2005. The course of cognitive functioning in first episode psychosis: Changes over time and impact on outcome. Schiz. Res. 78, 35-43; Green, M.F. et al., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the right stuff? Schiz. Bull. 26,119-136.

A LONGITUDINAL NATURALISTIC STUDY OF COGNITION AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA: DO SPECIFIC NEUROCOGNITIVE DIMENSIONS ARE LINKED WITH SPECIFIC DOMAINS OF COMMUNITY FUNCTION?

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Neurocognitive deficits are a core feature of schizophrenia that is robustly related to functional disability independently of clinical symptoms. However, targeting these deficits with new treatment approaches (pharmacology, rehabilitation programs…) will only yield functional improvements if those cognitive operations that are responsible for different dimensions of functional recovery can be identified. We have conducted a longitudinal naturalistic study among French schizophrenic patients for 12 months to assess the evolution of the neurocognitive profile using the BACS. Then we have studied if the evolution of the global score and of each subscore of the BACS could be associated with variables linked with the functioning outcome.A sample of 34 French stable schizophrenic patients (diagnosed according DSM IV-TR criteria, 27 men, 7 women; mean age = 40, 2 years, SD = 12, 1; 17 hospitalized, 17 ambulatory) was assessed at baseline (T1) with the French validated version of the BACS and with clinical variables (sociodemographics, therapeutics, daily activities, residences). Cognitive and clinical assessments were carried out again at 12 months (T2). We performed follow-up t-tests on global and on each subscore of the BACS, then Anova analysis. The level of significancy was $\alpha < 0.05$. 27(79,41 %) patients completed the second assessment (T2). The t-tests showed a significative improvement for 2 subscores: digit sequencing ($t = -2, 19$; $df = 26$; $p < 0.03$) and token motor ($t = 2, 30$; $df = 26$; $p < 0.03$), but not for the others subscores as well as the global score. Then performing Anova analysis on this improvement with clinical variables, we found significative associations between digit sequencing and level of education ($F = 13, 36$; $df = 1$; $p < 0.0006$), increase in daily activities ($F = 7, 11$; $df = 1$; $p < 0.01$) and improvement in residence ($F = 4, 71$; $df = 1$; $p < 0.03$). Regarding token motor task there is a significative association with level of education ($F = 6, 79$; $df = 1$; $p < 0.01$). These preliminary results in a naturalistic longitudinal study show an improvement of 2

specific key cognitive domains, working memory and motor speed. This improvement is associated with the level of education, and also with work and residence for working memory. Further studies must be conducted (large sample, statistical analysis models) to confirm these results in order to target adequately new treatment approaches.

A BRIEF COGNITIVE ASSESSMENT TOOL FOR SCHIZOPHRENIA (B-CATS): SCALE CONSTRUCTION

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Cognitive impairment in schizophrenia is severe and enduring, and it contributes more to chronic disability and unemployment than do the classically rated symptoms. But the ability of clinicians to assess cognition is limited by a lack of instruments that can be administered and interpreted easily in a clinical setting. To meet this need, we are developing a very brief battery (~10 minutes) of existing cognitive tests that will generate a summary score representing global cognitive function, and that will require minimal training in both administration and interpretation. This tool will allow clinicians to measure global cognitive function, monitor cognitive change, and make better informed treatment decisions. It will also serve researchers who want an estimate of global cognitive function without requiring a full neuropsychological battery. The battery is composed of three tests extracted from the larger neuropsychological batteries of four NIMH-sponsored studies. We have performed a series of regression analyses to determine which tests account for the largest proportion of variance in global cognitive ability while minimizing administration time. These analyses have explicitly considered such factors as part-whole correlation and possible redundancy of measurement in the estimation of different functional domain constructs. The available sample sizes (ranging from ~100 to ~1000) offer good precision in estimating both correlations and regression parameters; in general, even considering use of multiple "predictors" (3 to 4 variables), the sample sizes enable detection of increments to R2 between ~1% (for N = 1000) and ~10% (for N = 100), and actual precision will be higher as we replicate across the different studies. Preliminary analyses in two of the four datasets suggest that three tests with a total administration time of approximately 10 minutes (Digit Symbol, list learning, verbal fluency and/or letter-number sequencing), capture >80% of the variance in global scores obtained from neuropsychological batteries taking 6 to 20 hours of administration time. Similar findings emerged from analysis of the CATIE dataset (Keefe RSE, et al; Neuropsychopharmacology 2006; p1-14), and further analysis of the CATIE and MATRICS-PASS data sets are planned for presentation.

HOW NEUROCOGNITIVE AND PSYCHOPHYSIOLOGICAL FACTORS IMPACT FUNCTIONAL REHABILITATIVE CHANGE IN SCHIZOPHRENIA

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While there is literature on how psychophysiological variables impact functional outcome in schizophrenia, there is no research on how these variables interact with neurocognition to influence functional change. The purpose of this study was to examine the way in which psychophysiological variables and neurocognition combine to influence the rates of rehabilitative change for schizophrenic individuals who are in intensive community-based psychosocial rehabilitation. The sample consisted of 145 individuals diagnosed with schizophrenia who were followed for 12 months after entering intensive community-based psychosocial rehabilitation. Neurocognition was measured at baseline as a standardized sum of measures that reflected verbal fluency, immediate memory, secondary memory, sustained attention, and mental flexibility. The psychophysiological variables were measured at baseline and consisted of skin conductance arousal at rest (resting arousal), and skin conductance measured in response to a stressor (stress reactivity). Psychosocial functioning was measured at baseline, 6 and 12 months using a composite of work, social and independent living domains that came from face-to-face interviews. Three multivariate models were tested using longitudinal structural equation modeling with latent variables. One was a direct effects model, the second was a moderator model which posited that higher levels of psychophysiological arousal would interfere with the influence of neurocognition on functional outcome, and the third, based on non-clinical literature in psychophysiology, posited that psychophysiological arousal would have no direct effect on functional change but that higher arousal would be related to better neurocognition and would facilitate the influence of neurocognition on functional outcome. Using parameter significance and model fit indices as criteria, there was support for the third model (chi-square=46.3, df=43, p=.34; all parameters significant at $p < .05$; RMSEA =.02). Specifically, higher resting arousal and greater stress reactivity were interpreted as providing a readiness to engage with environmental stimuli that activated or facilitated the impact of neurocognition on functional rehabilitative change. These findings have implications for understanding the biosocial factors that contribute to functional change during rehabilitation, and for devising novel clinical strategies for enhancing functional change for individuals with schizophrenia.

VARIANCE COMPONENTS MODEL PREDICTING OUTCOME IN A MULTI-SITE, MULTILEVEL STUDY OF EARLY PSYCHOSIS TREATMENT

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Established clinical guidelines for the treatment of Early Psychosis (EP) recommend activity at a number of levels: mental health service activities, clinician characteristics, and clinical activity. This study examined the relative contribution of each of these levels of activity to clinical outcome. A multi-site prospective cohort study was conducted across 19 different EP teams following the first six months of treatment of 456 EP patients. The project was approved as a quality assurance activity, meaning that patient consent was not required, ensuring a more accurate representation of real world clinical practice than is usually possible. Routine measures of outcome and clinical activity were introduced in all participating services. Additionally, surveys were conducted of clinician, and mental health service characteristics. As seen in Table 1, the bulk of influence in patient outcome is associated with factors that vary over time. Examples of such factors would include: elements of treatment, as well as extra-therapeutic change factors such as change in employment status or living arrangements. Enduring patient characteristics also seem to

play an important role in the prediction of outcome. Potential explanatory variables at this level would include duration of untreated psychosis, diagnosis, age and sex. These data strongly suggest that outcomes in EP treatment are influenced principally by the pre-morbid characteristics of the patients, and what occurs to the patient over the course of treatment. Clinicians clearly have a role in influencing what happens to patients over treatment, however it would appear that the characteristics of the clinician themselves play very little role in patient outcome. These results would suggest that future policy development in EP treatment should focus more on the implementation of clinical practice guidelines, and less on reform of service models. When fully analyzed, the data from this project should provide important insights into which aspects of treatment are supported in a real world environment, and should consequently be a major part of future guideline development.

Table 1. Variance Components Model predicting improvement in SOFAS

Level	Potential Variance Explained	significance
4. Mental Health Service	0.0%	p = 1.00
3. Clinician	8.6%	p = 0.02
2. Patient	28.4%	p = 0.00
1. Observation over time	63.0%	p = 0.00

CROSS-SECTIONAL EPIDEMIOLOGICAL STUDY EVALUATING SYMPTOMATIC REMISSION AND SOCIO/VOCATIONAL FUNCTIONING IN OUTPATIENTS WITH SCHIZOPHRENIA

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To describe, in a sample of patients with schizophrenia, their distribution across the different levels of symptomatic remission and social/vocational functioning, identifying factors that could be associated with such clinical outcome. Outpatients with schizophrenia (DSM IV-TR) attending to Public Health Mental Centers were enrolled. In a single visit sociodemographic and clinical relevant information were registered. Remission of symptoms was defined by Andreasen et al severity criteria based on SANS and SAPS Scales; Adequate social/vocational functioning was defined as a score ≧ 81 in the Global Functioning Scale (GAF). Other clinical scales and questionnaires implemented included Drug Attitude Inventory (DAI-10), Montgomery & Asberg Depression Rating Scale (MADRS), Premorbid Adjustment Scale (PAS), SF-12 Questionnaire and GEOPTE Scale of Social Cognition for Psychosis. A logistic regression model was fitted in order to evaluate associations between symptomatic remission and clinical and sociodemographic variables. 1010 valuable patients were recruited. The mean age (±SD) is 38.8±10.7 years, 66.3% are male, 75% single, 26.9% employed, 71.1% have a diagnosis of paranoid schizophrenia and the mean age for first episode is 23.9 (±6.4) years. 452 (45%) patients fulfill Andreasen severity criteria for symptomatic remission 103 (22.7%) of whom met also criteria for adequate social/vocational functioning. Factors associated with good levels of symptomatic remission were good premorbid adjustment (OR 4.01), current formal psychotherapy (OR 2.23), absence of substance abuse/dependence (OR 1.88), current better cognitive functioning (OR 1.07) and younger age (OR 0.90). Symptomatic remission seems to be a realistic clinical outcome although these results evidence a notable gap between it and an adequate social/vocational functioning. Supported by unrestricted funding from Ely Lilly and company.

SOCIAL COGNITION AND INTERACTION TRAINING (SCIT) FOR SCHIZOPHRENIA

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Individuals with schizophrenia exhibit consistent deficits in social cognition such as emotion perception, attributional style, and theory of mind. Recently, there has been increased attention to interventions that attempt to remediate the social cognitive deficits found in schizophrenia. Previous interventions are limited in that they have typically focused on only one aspect of social cognition, imbedded social cognition in broader cognitive remediation training, and have not assessed generalization of treatment to improvements in social functioning. Social Cognition and Interaction Training (SCIT) is a new group based treatment developed to improve social cognition and social functioning in schizophrenia. The purpose of this presentation will be three fold. First, we will provide a description of SCIT in terms of its theoretical foundation in the social cognition literature. Second, we will describe SCIT in terms of its goals, procedures, and treatment components. SCIT is centered around three primary phases of treatment: emotion training, figuring out situations, and integration, and we will discuss how these components lead to improved social cognition. Third, we will review previous studies on SCIT and present new data on the effectiveness of SCIT in a clinical sample. In our recent study, eighteen inpatients completed SCIT and were compared with 10 inpatients who completed a coping skills group in a quasi-experimental design. Participants were assessed at pre-test and post-test by blinded researchers on measures of emotion perception, theory of mind, attributional style (e.g., blame, hostility, and aggression), cognitive flexibility, and tolerance for ambiguity. To examine the effect of SCIT on social functioning, we also administered the Social Functioning Scale and recorded the frequency of aggressive incidents on the treatment ward. The results showed that compared to the control group, SCIT participants improved on all measures of social cognition and cognitive flexibility and showed better social functioning and fewer aggressive incidents on the treatment unit at post-test. More importantly, these changes were independent from changes in clinical symptoms (PANSS) over time and support the unique role of SCIT in remediating social cognitive deficits in schizophrenia. The symposium will provide information on the theoretical, clinical, and empirical foundations of SCIT relevant to clinical settings.

NEUROCOGNITION AND THERAPEUTIC ALLIANCE OVER TWO MONTHS OF INDIVIDUAL PSYCHOTHERAPY IN SCHIZOPHRENIA

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It has long been noted that forming therapeutic alliances with persons with schizophrenia can present multiple challenges. One possibility is that these are linked to neurocognitive impairments which are associated with the condition. To explore this possibility we obtained therapist and client ratings of therapeutic alliance using the Working Alliance Inventory short form (WAI)in the first and second month of psychotherapy. Participants were 49 adults in a post acute phase of a schizophrenia spectrum disorder enrolled in a randomized trial of cognitive behavior therapy and work outcome and were

receiving both individual psychotherapy and a work placement. The WAI-S ratings from the first and second month were each correlated with select subtests of the Weschler Adult Intelligence Scale (WAIS III), the Bell Lysaker Emotion Recognition Test (BLERT), the Conners Continuous Performance Test (CPT 2) and the Wisconsin Card Sorting Test (WCST). Pearson Correlation revealed neurocognitive test performance was generally unrelated to client or therapist perception of therapeutic alliance in the first month of therapy. In the second month of therapy, therapist perception of alliance was positive correlated with performance on the WCST, BLERT, and the Block Design and Arithmetic Subtests of the WAIS III. Client perception of alliance was positive correlated with performance on the CPT, BLERT, and the Vocabulary and Digit Symbol Subtests of the WAIS III. Results suggest that neurocognitive impairments while not an initial barrier to therapeutic alliance may prove an impediment as treatment develops. Implications for treatment are discussed.

RISK FACTORS FOR MEDICATION NON-ADHERENCE IN PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA AND RELATED DISORDERS; A PROSPECTIVE FOUR YEAR FOLLOW-UP

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Medication non-adherence remains an important problem in the care for patients with schizophrenia. We conducted a study to assess, prospectively, the relative contribution of baseline variables to long-term medication adherence in patients with a first episode of schizophrenia. 119 Consecutively admitted and consenting patients suffering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder were investigated. Subjective experience, attitudes towards treatment, insight, interaction with members of staff, involuntary admission, substance abuse, and severity of psychopathology were independently assessed at first admission (=baseline) and related to medication adherence during four year follow up. Correlation analysis and standard multiple regression analysis were used. Decreased level of adherence during 4 year follow-up was associated with more hostility and uncooperativeness, involuntary admission and cannabis abuse or dependence. Standard multiple regression analysis revealed that hostility and uncooperativeness ($p = 0.007$) and involuntary admission ($p = 0.02$) assessed at baseline were associated with level of adherence during 4 year follow-up after admission (controlling for other baseline variables). We propose that patients who are involuntary admitted in their first psychotic episode require more intensive follow-up intervention during the succeeding years of their illness.

CHILDHOOD NEGATIVE EXPERIENCES AND NON-CLINICAL PSYCHOSIS IN ADOLESCENCE: A LONGITUDINAL GENERAL POPULATION STUDY

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Background Increasing evidence suggests that trauma during childhood is associated with increased risk to develop clinical and subclinical psychosis in adults. A recent study of our group extended these findings to adolescence thus reporting a strong and independent dose-response association between experiences of victimisation and subclinical psychotic symptoms in healthy youngsters. However, the cross-sectional nature of that study made it impossible to establish causal relationships. The current study aims to investigate the association between negative life experiences at baseline and the development of subclinical psychotic symptoms over a two-year period. Method Data were derived from the standard health screenings of the Youth Health Care Divisions in the south of the Netherlands. A total of 1129 adolescents attending second grade of secondary school (age 13/14 years) were questioned at the beginning of the study and 2 years later in third grade (age 15/16 years). They filled out a self-report questionnaire assessing psychotic experiences, as well as experiences of being bullied, sexual trauma, and negative life events. Results Logistic regression analyses revealed that sexual abuse, being bullied and the experience of negative life events at baseline were all strongly associated wit subclinical psychotic experiences two years later. The effect of life events and sexual abuse remained after controlling for baseline psychotic experiences. In order to investigate reverse causality, baseline reported subclinical psychotic experiences were regressed on the negative life experiences two years later. No significant associations were found, except for negative life events. Conclusion The results provide further evidence for an association between childhood trauma and psychosis in the crucial developmental period of early adolescence. The experience of sexual abuse and negative life events increase the risk to develop psychotic experiences two years later, whereas the experience of bullying contributes to the persistence of psychotic experiences. The association is not the result of reversed causality, except for the experience of negative life events, since subclinical psychotic symptoms in early adolescence make exposure to future negative life events more likely.

ENVIRONMENTAL SUPPORTS AND OUTCOMES IN SCHIZOPHRENIA

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Cognitive Adaptation Training (CAT) uses environmental supports such as signs, checklists, and alarms to cue and sequence appropriate behavior in the home environment. In an NIHM funded trial, 120 outpatients with schizophrenia (SCID-DSMIV) received baseline assessments and then were randomized into one of 3 treatment groups; 1) Full-CAT (CAT treatment customized to an individual's needs with supports set up by trainers in the home on weekly visits), 2) Generic Environmental Supports (GES) (Environmental supports given to subjects at routine clinic visits, established in the home by the subject, and replaced monthly as needed) or 3) treatment as usual. Functional outcomes and symptomatology were assessed each 3 months. Treatment lasted 9 months. Group differences over time by treatment were examined using repeated measures analyses of covariance for mixed models with baseline scores used as covariates. Results indicated significant main effects for group for Social and Occupational Functioning $F(2, 106)=23.15$ $p<.0001$). All groups differed significantly from one another with those in CAT doing better than those in GES, and those in GES doing better than those in Treatment as usual. On a more detailed measure of functional outcome, the Multnomah Community Ability Scale, only CAT was found to be superior to treatment as usual ($p<.01$). No significant differences were found with respect to symptomatology as rated from

the Brief Psychiatric Rating Scale or the Negative Symptom Assessment. Results confirm that environmental supports improve functional outcomes in patients with schizophrenia. This is the first study to establish evidence of functional improvement for patients with schizophrenia with relatively inexpensive, generic supports. Individualized supports established in the home lead to more robust and consistent gains in functioning than generic supports offered at clinic visits and set up by the patients themselves. While previous studies found symptom improvement for CAT relative to controls, this was not confirmed by the present large-scale randomized trial. It may be that greater involvement in functional roles increases stress for those in CAT. The increase in stress may wash out any benefits CAT may have on medication adherence. Environmental supports may be important tools in the rehabilitation of individuals with schizophrenia. Even simple supports may help to improve role functioning.

INTERNALIZED STIGMA AND DISCRIMINATION AMONG INDIVIDUALS WITH SERIOUS MENTAL ILLNESS

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Individuals with schizophrenia and other serious mental illnesses (SMI) are subject to negative treatment stemming from discrimination and stigma. Recent work has only begun to examine the impact of internalized stigma, the incorporation of these negative beliefs into one's personal identity. Internalized stigma has been associated with decreased morale and poorer recovery outcomes (Ritsher & Phelan, 2004). Our study was designed to expand upon this prior work by (a) characterizing experiences of discrimination and internalized stigma among persons with SMI and (b) identifying demographic and clinical factors associated with internalized stigma. Forty-two participants diagnosed with serious mental illness receiving outpatient treatment at a VA Medical Center were administered questionnaires assessing demographic characteristics, discrimination experiences, psychiatric symptoms (Brief Symptom Inventory; BSI), and internalized stigma (Internalized Stigma of Mental Illness Scale; ISMI). The ISMI includes subscales that assess alienation, stereotype endorsement, discrimination experiences, social withdrawal, and stigma resistance. Seventy-one percent of participants reported a prior experience of discrimination in at least one area (i.e. work, housing, medical/mental health care, relationships, and legal domains). Most prevalent was discrimination in an interpersonal context, with almost half of the participants reporting discrimination associated with a family member's (48%) or friend's (45%) knowledge of their mental illness. When applying cut points previously used with the ISMI, few participants (14%) reported high levels of internalized stigma overall or strongly endorsed negative stereotypes (2%). In contrast, 88% reported high levels of stigma resistance, the ability to resist or reject internalized stigma. Increased symptoms of paranoia were associated with greater perceived discrimination and social withdrawal. These results highlight the prevalence of discrimination experienced by individuals with SMI, particularly in their interpersonal relationships. Compared to reports from other studies our sample evidenced lower rates of internalized stigma and stereotype endorsement and greater stigma resistance, suggesting significant hetereogeneity in the impact of stigma among individuals with SMI. These results support the need for further work to better understand who experiences internalized stigma and what factors may account for these differences.

CHOICE OF OUTCOME IN CBT FOR PSYCHOSES (CHOICE): THE DEVELOPMENT OF A SERVICE-USER LED OUTCOME MEASURE OF CBT FOR PSYCHOSIS

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Outcome measures of Cognitive Behaviour Therapy (CBT) for psychosis have derived from pharmacological outcome studies and have focused on presence and severity of symptoms rather than CBT relevant outcomes such as distress and functioning. Service users have also emphasised other priorities such as exclusion, stigma, empowerment and fulfilment (May 2000; Perkins 2001). This study aimed to derive a new CBT outcome measure, which reflected the aims of CBT for psychosis and the priorities of service users. Service users (n=12) who had received CBT for psychosis were convened in focus groups to discuss their outcome priorities. The discussion guide was prepared by consensus from experienced CBT for psychosis therapists. A qualitative thematic analysis was applied to the transcribed data by three independent researchers (including a service user) who reached a consensus on themes. Two follow-up interviews with each group member validated the outcomes and language, and confirmed that these were deemed achievable through CBT. The questionnaire was further piloted with service users who had not received CBT, stratified by service (inpatient, community team, specialist service), ethnicity, and first language (n=15). This procedure ensured that the measure was user-friendly and applicable prior to CBT. Test–retest reliability (n=30) and construct (convergent and divergent) validity (n=60) against standard measures were explored. The final measure consists of 28-item. Each item incorporates problem severity as well as the relative importance and satisfaction with the current state. Items include outcomes that are specific to CBT goals (e.g. "The ability to question the way I look at things"; "Knowing I am not the only person who has unusual experiences") and that are related to service users' expectations of recovery more generally (e.g. "Understanding myself and my past"; "A positive purpose and direction in life"). The measure is both reliable and valid. Factor structure (n=150) and sensitivity to change will be explored. This measure is original in incorporating the outcome priorities of service users and those outcomes that are specifically targeted by CBT. It evaluates both problem severity and the relative health implication (importance and satisfaction) of the problem. The outcomes also include important elements of recovery in general, thus warranting a broader appeal as a service-user led outcome measure for treatment trials.

CLINICAL CORRELATES OF EVERYDAY FUNCTIONING IN OLDER ADULTS WITH SEVERE MENTAL ILLNESS

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This cross-sectional correlational study investigated the strength of relationships between cognitive function, psychiatric symptoms, everyday functioning, and community living in a sample of independent living older adults with severe mental illness (SMI). Forty-eight participants (64.5% affective disorder, 33.3% schizophrenia spectrum, 2.1% other) completed a diagnostic interview, symptom ratings, a brief cognitive screen, and the UCSD Performance-based

Skills Assessment (UPSA), a laboratory measure of real-world functioning. Primary clinicians provided ratings of daily functioning (Pfeffer Outpatient Disability Scale and Lawton-Powell Physical Self-Maintenance Scale) and community living (HAPI-A). It was hypothesized that global cognitive ability, followed by negative symptoms, would have the strongest associations with UPSA performance, while the UPSA, relative to clinician-rated functional assessments, would have the strongest association with ratings of community living ability. Global cognitive function was found to have the strongest association with UPSA performance, as compared to psychiatric symptoms. Although negative symptoms were found to correlate with UPSA performance, the strength of this association was not greater than that of other symptom domains. As expected, performance on the laboratory measure of real-world functioning, the UPSA, was positively and more strongly associated with community living than clinician-rated functional assessments, global cognitive function, and negative symptoms. The importance of cognitive ability in successfully completing everyday tasks is highlighted in this study of independent living older adults with SMI. Interventions based on compensatory strategies may help older adults with SMI overcome cognitive limitations in order to maintain independence in the community.

A 20-YEAR MULTIFOLLOWUP STUDY OF SEX DIFFERENCES IN SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

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Objective: Although a number of studies have provided data indicating that women with schizophrenia have better clinical courses than their male counterparts, little research has been devoted to sex differences in other psychotic disorders. To address this issue, we are currently presenting prospective longitudinal followup data from the Chicago Follow-up Study. The current study provides data about potential sex differences in posthospital functioning, based on 20 years of followups. Method: We assessed a large sample of patients, (69 with schizophrenia and 56 with other psychotic disorders). Patients were evaluated prospectively at index hospitalization and then followed-up six times over the next 20 years. They were assessed on standardized research instruments evaluating symptom, psychosocial functioning, treatment, and global outcome. Multiple followups on the same cohort over 20 years have not been available in the past. Results: 1) Female schizophrenia patients had significantly better overall outcomes, with more periods of recovery than men. 2) Female schizophrenia patients also had significantly more psychosis-free interims over the 20-year period. 3) Patterns of sex differences were not as strong or consistent for patients with other psychotic disorders. 4) When premorbid functioning was controlled, sex differences in outcome for the schizophrenia patients diminished. 5) For schizophrenia patients of both sexes, and for women with other psychotic disorders, psychosis was significantly related to anxiety. Conclusions: The results emphasize that women with schizophrenia have a more favorable long-term course than their male counterparts. They showed more frequent periods of recovery and fewer psychotic symptoms. For patients with other psychotic disorders, women with other psychotic disorders show better courses and outcome than men, but the differences are not as robust in some areas. The data indicate that gender differences in clinical course and outcome are influenced by a number of factors, including premorbid functioning, different societal demands, and treatment differences.

RECEPTIVE AND EXPRESSIVE DEFICITS OF SOCIAL COGNITION IN SCHIZOPHRENIA

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Deficits in social functioning represent a cardinal feature of schizophrenia, yet little is understood regarding their origin, their relationship to cognitive dysfunction or whether they reflect specific deficits in social cognitive functions. Using a battery of laboratory measures of social cognition, the current study aimed to evaluate specific deficits in social cognitive functioning and their relationship to current social adjustment, taking into account non-social cognitive processing abilities. Methods: 22 individuals with DSM-IV schizophrenia and 27 healthy control subjects were evaluated on a newly developed behavioral battery of social cognition measures, reflecting two broad domains of social cognition (receptive and expressive), along with conventional measures of Theory of Mind (ToM), and a battery of non-social cognitive functions, including measures of executive abilities (Wisconsin Card Sorting Test, the Tower of London), selective attention (Continuous Performance Task), motor speed, information processing speed, working memory (finger tapping, trails A and B and digit recall) and IQ. Results: Individuals with schizophrenia performed worse than controls on both receptive and expressive measures, showing behavioral deficits in third-person interpretation of key dimensions of social reasoning (thoughts, affects, motives and affective changes) within an interpersonal context ($p<.04$), as well as deficits on a measure of verbal communication that engages on-line metacognitive processing during an interactive task with a research assistant. Sensitivity to changes in the affective state of another individual, along with ability to grasp the 'gist' of a social exchange were deficient among individuals with schizophrenia as compared with healthy controls ($p<.04$). These specific indices of an individual's ability to interpret social behavior within an interpersonal context correlated with indices of current social adjustment ($p<.02$), as did a behavioral measure that reflected the ability to monitor and adapt behavior to the verbal communication of another individual ($p<.05$). Behavioral indices of social cognition accounted for variance in 'real world' social functioning independent of IQ and non-social cognitive functions. Conclusions: Results of this study point to specific dimensions of social cognition that appear to be deficient among individuals with schizophrenia and correlate with deficits in 'real world' social functioning.

EARLY DETECTION AND OPTIMAL TREATMENT MAY IMPROVE OUTCOME IN EARLY-ONSET SCHIZOPHRENIA: EVIDENCE FROM THE EPPIC MEDIUM-TERM FOLLOW-UP STUDY OF FIRST EPISODE PSYCHOSIS

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Previous research has suggested that poor outcome is typical in early-onset schizophrenia (EOS) which manifests before the age of 18 years. However, no study to date has compared the medium-term outcome of EOS vs. adult-onset schizophrenia (AOS) attending the same, specialized treatment program. The purpose of this analysis is to examine the medium-term clinical and functional outcome of EOS

vs. AOS within the Early Psychosis Prevention and Intervention Centre (EPPIC) medium-term follow-up study of first episode psychosis. This is a naturalistic, prospective follow-up of a large epidemiologically representative sample of 765 first-episode psychosis patients, followed up on average 7.4-years after initial presentation to a specialist early psychosis service (EPPIC) in Melbourne, Australia. Standardised assessments were used at the follow-up to assess participants' demographic characteristics, axis I diagnosis, psychopathology and level of work and social functioning. Follow-up interviews were conducted on 511 participants; 133 refused; 39 were deceased and 82 were un-contactable. No participant bias due to study attrition was found. This study focuses on the 290 individuals diagnosed at baseline with schizophrenia-spectrum disorders. Independent samples t-tests were used to compare EOS and AOS groups on psychopathology and outcome measures at medium-term follow-up. Statistical tests were two-tailed. P values of 0.05 or less were considered statistically significant. EOS was found in 31 (10.7%), AOS in 259 (89.3%) of individuals in the sample. T-tests indicated no significant group differences on BPRS total, BPRS psychotic subscale, SANS total, and SOFAS mean scores. In contrast to an expected poorer outcome, individuals with EOS were characterized by significantly better functioning (GAF and SOFAS) and higher quality of life (QLS) at 7.4 year follow-up as compared to individuals with AOS. The present findings emphasize a much more optimistic view on the medium-term outcome of EOS which may be related to early detection and the specialized treatment program provided by EPPIC. These results also suggest that younger patients might stand to profit more from the treatment approach offered by such a service, particularly in terms of enhancement of their functioning and quality of life several years subsequent to treatment entry.

A RANDOMIZED WAITLIST CONTROLLED TRIAL OF COMPUTER ASSISTED COGNITIVE REMEDIATION IN FIRST EPISODE AND CHRONIC SCHIZOPHRENIA

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This study assessed the effectiveness of computer assisted cognitive remediation in the treatment of cognitive deficits in people with both recent onset and chronic schizophrenia. A randomized waitlist control study was conducted over 8 sites using Medalia's Neuropsychological Approach to Remediation (NEAR). All subjects (n=67) were diagnosed with schizophrenia or schizoaffective disorder and were recruited from a range of community and inpatient facilities. Subjects were randomized between an immediate treatment and a waitlist group, the later being treated after 15 weeks. Subjects were assessed at (1) baseline, (2) after at least 20 sessions of NEAR and (3) 15 weeks after the completion of treatment, on measures of symptomatology, function and neurocognition. Minimal differences were observed between waitlist and immediate treatment groups at baseline. However subjects with chronic schizophrenia were rated significantly higher for positive and total symptoms on the Positive and Negative Syndrome Scale (PANSS). After treatment, significant improvements were observed for sustained attention, processing speed and verbal memory. This was accompanied by an improvement in social and occupational functioning particularly for subjects with recent onset disease. There was few change in levels of symptomatology, self esteem or quality of life. This study supports the effectiveness of computer assisted cognitive remediation in both recent onset and chronic schizophrenia in treating the cognitive deficits of schizophrenia. This appeared to have a social and occupational impact for young people with recent onset disease.

RECOVERY IN SCHIZOPHRENIA - WHAT FACTORS ARE RESPONSIBLE?: A 26-YEAR FOLLOWUP

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Purpose: While schizophrenia has traditionally been viewed as a poor outcome disorder, there is increasing evidence that in modern times some or many patients with schizophrenia experience periods or intervals of recovery. Still unknown is how many experience periods of recovery. Even more important, still unknown is what factors contribute to their periods of recovery. The present research studied these issues using a 26-year multi-followup, longitudinal sample. Method: 137 patients with schizophrenia and other psychotic and nonpsychotic disorders from the Chicago Followup Study were assessed prospectively at index hospitalization and then followed up 7 times over the next 26 years. Using standardized research instruments patients were assessed at each followup for positive and negative symptoms, psychosocial adjustment, rehospitalization, global outcome, and medication treatment. The operational definition of recovery required adequate work and social functioning, no rehospitalization and the absence of major symptoms for one or more years. Results: 1. After the 2-year assessment, at each subsequent followup, from 19% - 27% of the patients with schizophrenia were in a period of recovery. 2. Although still a relatively poor outcome disorder, at some point over the 26 years, over 40% of the schizophrenia patients showed the potential for periods or intervals of recovery, select ones lasting over 10 years. 3. Over 70% of the patients with good prognostic factors showed one or more periods of recovery. 4. Fitting in with reports by consumers, patients with favorable personality and attitudinal characteristics (e.g., good self-esteem, internal locus of control, more interest in social interaction, less trait anxiety) were more likely to show periods of recovery ($p < .05$). Conclusions: Contrary to earlier views, the data indicate that during the 26-year followup period over 40% of modern-day schizophrenia patients experienced one or more intervals or periods of complete recovery. A combination of different types of factors associated with less vulnerability and greater resiliency contributed to recovery, rather than one factor alone. These include internal characteristics, treatment, and attitudinal and personality characteristics. The strongest influences were internal characteristics of the patients, including favorable prognostic factors and good premorbid developmental achievements.

PSYCHOSIS REACTIVITY TO CANNABIS IN DAILY LIFE: AN EXPERIENCE SAMPLING STUDY

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Cannabis use increases the risk to develop psychotic symptoms and aggravates symptoms in existing psychotic illness. An interaction

between exposure to delta-9-tetrahydrocannabinol and pre-existing liability to psychosis may underlie this association. The purpose of the current study was to compare groups with different levels of pre-existing psychosis liability in their reactivity to cannabis exposure in the flow of daily life. A structured time-sampling technique (Experience Sampling) was used to collect data on cannabis use and occurrence of symptoms in daily life in patients with a psychotic disorder (n=42) and healthy controls (n=38). Models of positive and negative affect and positive psychotic symptoms were examined to assess i) main effects of cannabis and group and ii) interactions between cannabis and group. Use of cannabis in daily life was weakly predicted by positive affect (OR=1.09, 95% CI: 1.00, 1.19, p= 0.046), but not by intensity of psychotic symptoms or by negative affect. Cannabis use was associated with subsequent increases in positive affect (β=0.21, 95% CI: 0.13, 0.28, p< 0.001) and, only in patients, decreases in negative effect (β=-0.11, 95% CI: -0.18, -0.04, p= 0.002). In patients but not in controls, cannabis use was associated with increased levels of hallucinatory experiences (β= 0.08, 95% CI: 0.03, 0.13, p= 0.002), but not with increases in delusional ideation. The mood-enhancing properties of cannabis were acute, whereas its psychosis-inducing effects were sub-acute. The results show that psychosis liability is associated with differential sensitivity to both the psychosis-inducing and mood-enhancing effects of cannabis and does not give rise to the hypothesized phenomenon of self-medication in the flow of daily life. The temporal dissociation between acute rewarding effects and sub-acute toxic influences may be instrumental in explaining the vicious circle of deleterious use in patients with psychotic illness.

THE EPPIC LONG TERM FOLLOW-UP STUDY OF FIRST EPISODE PSYCHOSIS: CLINICAL AND FUNCTIONAL OUTCOMES AT 7.5 YEARS

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The purpose of this study is to examine the long-term clinical and functional outcome of first-episode psychosis (FEP). The study was a naturalistic, prospective follow-up of a large epidemiologically representative sample of 765 FEP patients, mean 7.4-years after initial presentation to a specialist early psychosis service (EPPIC) in Melbourne, Australia. Standardised assessments were used at the follow-up to assess participants' demographic characteristics, axis I diagnosis, psychopathology and level of work and social functioning. Follow-up interviews were conducted on 511 participants; 133 refused; 39 were deceased and 82 were un-contactable. No participant bias due to study attrition was found. Some 230 (45.0%) of the interviewed group, met DSM-IV criteria of a current psychotic disorder; 281 (55.0%) individuals received a lifetime diagnosis of psychotic disorder. Numbers of individuals diagnosed with schizophrenia, schizoaffective disorder, affective psychosis and other psychosis, were 306 (59.6%), 48 (9.4%), 110 (21.5%) and 47 (9.2%), respectively. Comparisons between the diagnostic groups found the schizophrenia group to have significantly higher BPRS (total, psychotic subscale) and SANS (total) mean scores and significantly lower GAF, SOFAS and QLS mean scores than the other diagnostic groups at follow-up. The prevalence of current psychotic disorder was significantly higher in the schizophrenia group (60.1%) as compared to the other diagnostic groups (χ2=78.4, df=3, p<0.001). Considering the course of the psychotic disorder over the most recent two years, the majority (49.1%) reported that they have never been actively psychotic, 31.6% reported a continuous course, 17.1% reported an episodic course and 2.2% individuals neither episodic nor continuous course of illness. In contrast to previous medium and longer term follow-up studies of first episode schizophrenia where 19-37% were reported to be occupationally engaged,(and 10-15% of those with established schizophrenia in Australia) the proportion of individuals observed in this study with some level of employment in the last two years was substantially higher (schizophrenia, 52%; affective psychosis, 74.5%; schizoaffective, 60.4%; and other psychotic group, 72.3%). Findings from the EPPIC long term follow-up study emphasis that a specialised early intervention service program might result in better functional outcomes in contrast to previous assumptions, especially for those with schizophrenia.

DYSFUNCTIONAL BELIEFS AND POOR SLEEP IN SCHIZOPHRENIA

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Persons with schizophrenia experience insomnia which may increase their risk for poor outcomes. Because primary insomnia in persons without psychosis has been linked to dysfunctional beliefs about sleep we chose to evaluate dysfunctional beliefs and attitudes about sleep in persons with schizophrenia and schizoaffective disorder. To examine the relationships between dysfunctional beliefs about sleep and sleep quality, and between sleep disturbance and positive/negative symptoms, we recruited thirty-one males in a post-acute phase of either schizophrenia or schizoaffective disorder receiving ongoing outpatient care. We also sought to determine whether there were differences in beliefs about sleep between patients with good and with poor sleep. Participants completed the following assessments: the Dysfunctional Beliefs and Attitudes about Sleep Scale, a self report of sleep-related beliefs and attitudes; the Pittsburgh Sleep Quality Index, a sleep quality self assessment; the Positive and Negative Syndrome Scale, a symptom rating scale completed by clinically-trained research staff; and the State-Trait Anxiety Inventory, a measure of anxiety in adults. Data analyses included univariate correlations between beliefs about sleep, sleep quality, symptoms and anxiety measures, and t-tests between patients with good and with poor sleep. The Dysfunctional Beliefs and Attitudes about Sleep Scale had acceptable internal consistency (Cronbach's alpha of 0.70). The Pittsburgh Sleep Quality Index also had moderate internal consistency with a Cronbach's alpha of 0.65. High dysfunctional belief scores correlated with poor global sleep quality. Dysfunctional beliefs and attitudes about sleep were not related to overall symptom level, positive symptoms or negative symptoms, but correlated instead with measures of depression, emotional distress, and trait anxiety. Sleep quality was also related to anxiety. Patients with poor sleep had beliefs that anticipated dysfunctional sleep practices. Poor sleepers were taking higher levels of medication on average than good sleepers and had almost three times as many lifetime psychiatric hospitalizations as those reporting good sleep. One possible implication of these findings is that Cognitive Behavioral Therapy designed to address dysfunctional beliefs about sleep and poor sleep practices may improve the sleep and quality of life in patients with schizophrenia.

SOCIAL COGNITION AS A MEDIATOR OF NEUROCOGNITION AND FUNCTIONAL OUTCOME AMONG DEAF PEOPLE WITH SCHIZOPHRENIA

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The purpose of this study is to replicate and extend research in the area of cognition and outcome among people with schizophrenia (PWS) by analyzing differences between deaf and hearing PWS. Sixty-five subjects (34 deaf, 31 hearing) were recruited from a large, community based psychosocial rehabilitation agency in Chicago, Illinois. Participants were assessed using measures of neurocognition (verbal and visual memory, attention, visual processing), social-cognition (facial affect processing and theory of mind) and functional outcome. Regression analyses were employed to test two hypotheses. The 1st hypothesis tested if cognition predicted functional outcome in a similar fashion across deaf and hearing subjects. The 2nd hypothesis tested if social-cognition served to mediate the relationship between neurocognition and functional outcome. Both hypotheses were supported: 1) For all subjects, higher levels of neurocognitive ability were significantly associated with higher levels of functional outcome, and the strongest predictors of outcome were verbal memory and visual-spatial memory. However, the deaf and hearing groups showed different patterns of relationships between the predictors and outcome; 2) Social cognition mediated the relationship between neurocognition and functional outcome for both groups, however the ability to infer another person's intentions (i.e., theory of mind) served as a potent mediator of the relationship for hearing subjects only. For deaf subjects, facial affect processing served as the most potent mediator of the relationship between neurocognition and outcome. These findings suggest that the development of interdisciplinary rehabilitation strategies for PWS should include interventions targeting not only specific neurocognitive abilities such as attention and memory, but also interventions for social-cognitive domains including facial affect processing and theory of mind. Further, deaf and hearing subjects may benefit from interventions that address different aspects of cognition.

COGNITIVE FUNCTIONING IN PSYCHOSIS: RELATIONSHIP TO OBJECTIVE AND SUBJECTIVE MEASURES OF OUTCOME

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Previous research has emphasized the role of neurocognitive functioning as a predictor of outcome in psychosis. Outcome, however, is not a unitary concept and different domains of outcome may differ in their predictors. In the current study we aimed to clarify the relationship between neurocognitive functioning and outcome by investigating the predictive value of premorbid and current cognition on various measures of objective and subjective outcome at baseline and at 2 year follow up, taking into account the role of symptomatology. Data for the present study were drawn from the baseline and 2-year follow-up assessment of the UK700 Case Management Trial, in which 708 subjects with a diagnosis of psychotic illness were investigated. At baseline, premorbid and current cognitive functioning was measured using the NART and TMTB. At baseline and at follow-up objective outcome was measured on the domains of work, independent living, and hospitalization. Subjective outcome was measured by the Lancashire Quality of Life Profile (QoL), the Camberwell Assessment of Need (CAN) and the WHO Disability Assessment Schedule (DAS). Symptomatology was measured using the CPRS. Multiple linear regressions, a priori adjusted for demographic characteristics, were applied to investigate relationships between cognition and outcome. A cross-sectional association was found between TMTB and months of employment (Beta=-0.12, p=0.02). This association was reduced but did not disappear after adjustment for current symptomatology (Beta=-0.08, p=0.16). A similar pattern of associations was found for the measures of independent living and number of hospitalizations. For subjective outcome, associations were found with NART as well as with TMTB (QoL: NART Beta=-0.11, p=0.04, CAN: TMTB Beta=0.14, p=0.01, DAS: NART Beta=-0.11, p=0.02), although some of these associations were reduced after adjustment for symptomatology. Longitudinally, TMTB was associated with subjective (DAS and CAN) but not objective outcome. NART was not associated with any of the outcome measures at follow-up. Both objective and subjective outcome were associated with cognitive functioning, but prospectively an association was found for subjective outcome only. Only part of the association is due to the overlap with symptoms.

IS ADVANCES IN PSYCHOPHARMACOLOGY HELP IN SOCIAL REHABILITATION IN PATIENTS WITH SCHIZOPHRENIA

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INTRODUCTION: I want to inform you regarding the some of challenges coming across my practice with the person with the psychiatric disorder diagnosis as schizophrenia in social rehabilitation like education and training, work and employment, family, groups, social, sexual, environmental and regional, coordination with the other health group and care giver, insurance problems, medical, physical, occipital vocational, languages problems mostly how to give opportunities with in the society to help in social rehabilitation and many more to be come in future. HYPOTHESIS: About 100 patients diagnosis as schizophrenia all sub types on ICD- 10 only 39 having employment, which is permanent rest, are wondering on the street with without support and some are just without any support because no one want to help them not at all on any level. METHOD: I keep the records with me since I join the medical college and my during practice but these are really challenging to calm down for question with their relatives and care givers working with this patients. RESULTS: It is always to see the experience of the other people including self help groups in this regards and most challenging with near by perfect action and required more interaction with the rehabilitation groups because some are social problems in psychiatric disorder. CONCLUSIONS: There is big challenge in the for social rehabilitation for the persons diagnosis with Schizophrenia as multifactor involvements are there in this groups with early intervention and long term rehabilitation so that we can produced many working individuals with in the society among the person with Schizophrenia in psychiatric disorder the more interaction among the society and care giver working in this field as well as Psychiatrist working in this field so that we will able to achieve almost complete social rehabilitation more in favors in the theraputic community where they can work and live to gather with social support as till today we are not able to achieve social rehabilitation up to 40% till now.

EFFECT OF BOARD GAME THERAPY ON COGNITIVE REHABILITATION IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

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Objectives: In order to explore the effect of board-game therapy for cognitive rehabilitation in patients with schizophrenia, we investigated the change of executive cognitive functions over a 2-month period of board-game therapy in patients with schizophrenia. Methods: Two groups of chronic schizophrenic inpatients were participated in this study. One group (n=21) were treated with board-game therapy for 2 months and the other control group (n=19) were not treated. For the evaluation of the executive cognitive function, a Wisconsin Card Sorting Test (WCST) was administered before and after the introduction of the board-game therapy. PANSS score change was also evaluated. Result: At the beginning of this study, there was no significant difference in performance of cognitive function tests, demographical data or clinical severity between both patient groups. After 2 months of treatment with the board-game therapy, the board-game therapy group showed significant improvements of executive cognitive function without any significant change of their schizophrenic symptoms. On the contrary, there was no change in control group. Conclusion: This study showed that a board-game therapy is effective for the enhancement of executive cognitive function in patients with chronic schizophrenia. A board-game therapy could be introduced with ease into psychiatric fields, such as inpatients' or outpatients' clinic wards and day hospital. Our result indicates that the board-game therapy is a promising tool for the enhancement of cognitive function, especially executive cognitive function and helpful for cognitive rehabilitation for schizophrenic patients.

DISCLOSURE OF SEVERE MENTAL ILLNESS IN THE WORKPLACE

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Despite the development of supported employment as an evidence-based practice for helping people with severe mental illnesses (SMI) find jobs, these workers often have trouble keeping their jobs; workers' well-documented struggles with disclosure of SMI at work might help explain some of the factors that contribute to premature job terminations. However, disclosures also give workers the opportunity to obtain support and accommodations they might need to be successful in the workplace. Based on the available literature, we developed a conceptual map of disclosure highlighting the phenomenon's many characteristics (e.g., disclosure frequency, identity of disclosers and disclosure recipients, selectivity of disclosure recipients, etc.) as well as the contexts in which it occurs (e.g., characteristics of the workers who are the subjects of the disclosures, characteristics of any vocational programs used by the workers, etc.). We also developed a literature-based conceptual model of disclosure's outcomes in the workplace, including its link with workplace relationship characteristics and other long-term job outcomes. We then used the new map and new model to guide correlational analyses of data from 101 individuals with SMI who held competitive jobs as part of a larger NIMH-funded study. Few background variables were associated with disclosure, although we found a negative correlation between participants' level of education and disclosure to supervisors. Although the analyses of disclosure's outcomes suggested disclosure to supervisors had no significant correlations with supervisor-worker relationship variables or other long-term outcome variables, these results did reveal positive correlations between disclosure to coworkers and both coworkers' emotional support and workers' satisfaction with their relationships with coworkers. These results suggest that disclosure might play a role in determining the quality of workplace relationships for these workers; these relationships could be key to improving other vocational outcomes like job satisfaction and job tenure for workers with SMI. To enhance the quality of workers' relationships at work and therefore increase the chances of improved overall vocational outcomes for these workers, employment specialists should help workers with SMI develop and use effective disclosure strategies that include plans for what, when, how, and to whom to disclose. Some potential strategies are discussed.

IS THE EFFECT OF DUP ON SOCIAL FUNCTION MEDIATED VIA NEGATIVE SYMPTOMS? A ONE-YEAR FOLLOW-UP STUDY OF FIRST- EPISODE PSYCHOSIS

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Studies in first-episode schizophrenia suggest that the longer the period of unchecked psychosis before treatment is initiated, the poorer the clinical and social outcomes. To understand the possible impact of intervening to reduce the duration of untreated psychosis (DUP), it would be helpful to establish the extent to which the relationship between longer DUP and poor social function might be indirectly mediated via greater severity of symptoms. This association was examined in 136 patients, recruited at the time of first presentation to psychiatric services into the prospective West London First Episode Schizophrenia Study and receiving baseline clinical and neuropsychological assessment. Ninety-eight of the study participants were followed up at one year (median 383 days). Assessments included measures of mental state (SAPS and SANS), social function (SFS), and cognitive function (CANTAB). The sample was split into short and long DUP groups around the median (20 weeks). There were no significant clinical differences between these subgroups at baseline, and no significant differences on measures considered possible predictors of outcome in addition to or instead of DUP, such as age at onset, premorbid IQ, gender or length of follow-up period. When the DUP subgroups were compared at follow-up, there were no significant differences in global IQ or performance on a range of cognitive tests, but longer DUP was significantly associated with greater severity of positive and negative symptoms and poorer social function. We conducted path analyses to examine the nature of the relationship between DUP and social function, positive symptoms and negative symptoms at follow up, using either overall negative syndrome score or core negative symptom score, the latter to minimise any confound related to a possible overlap in the domains covered by the negative symptom and social function scales. The path analyses revealed that the poor social function in those with a longer DUP was mediated via greater severity of negative symptoms. In summary, the findings suggest that longer DUP may have some predictive value for poorer response to treatment in first-episode schizophrenia in respect of persistent

symptoms and social re-integration that is independent of age and age of onset of psychosis. However, there was no effect of DUP on cognition, and the poor social function observed with longer DUP appeared to be partly a consequence of more severe negative symptoms.

EVALUATION OF THE PERSONAL AND SOCIAL PERFORMANCE SCALE (PSP) IN ACUTELY ILL AND CHRONIC PATIENTS WITH SCHIZOPHRENIA

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Outcome measures of successful treatment of schizophrenia is traditionally defined in terms of improved positive and negative symptomatology. In contrast, "remission" and "recovery" not only refer to the absence or reduction of psychopathological symptoms, but also to successful psychosocial reintegration, e.g. living at home with partner or family, being able to care for oneself, working on a regular basis, etc.. For standardized assessment of psychosocial functioning the Global Assessment of Functioning Scale (GAF) and the Social and occupational functioning Assessment Scale (SOFAS) are widely used. However, the validity and reliability of these scales are limited due to a lack of operationalized criteria. Accordingly, the Personal and Social Performance Scale (PSP) was developed (Morosini et al. 2000) covering four main areas of socially useful activities such as personal and social relationships, self care, and disturbing and aggressive behaviors. Pilot studies have shown that the PSP has good reliability and validity. An evaluation in sufficiently large cohorts of patients with chronic schizophrenia and acutely ill patients in a naturalistic design is, however, warranted. In order to replicate inter- and intrarater-reliability, test-retest reliability, validity and sensitivity of the PSP, the scale was translated in to German. We investigated 150 acutely ill patients with schizophrenia in several psychiatric hospitals in Westphalia in Northwestern Germany, as well as 150 chronic patients with schizophrenia from several nursing homes. We compared the PSP with GAF and SOFAS ratings. Severity if illness was assessed by CGI. Ratings using the PSP were comparable with previous studies in Italian and US samples. Test-retest reliability was sufficient with $r > 0.75$, inter- and intra-reliability was $r > 0.80$. The PSP was able to differentiate between patients in severe psychopathological states and those with mild symptoms, including differences in psychosocial functioning. The PSP was less correlated with CGI scores than to GAF and SOFAS scores. Using a naturalistic approach, we were able to demonstrate that the PSP is a reliable and valid instrument to assess psychosocial functioning in patients with schizophrenia in various stages of the disease. Thus, the PSP is well suited to monitor changes of psychosocial functioning under different treatment regimes.

RESULTS OF THE FIRST AUSTRALIAN RANDOMISED CONTROLLED TRIAL OF INDIVIDUAL PLACEMENT AND SUPPORT IN FIRST EPISODE PSYCHOSIS

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Surveys consistently show that the top priority of people with mental illness is participation in the open labour market. Despite this finding, the employment outcome for people with psychotic illnesses is not good. At the onset of illness unemployment rates of 40-50% are commonly found. For those who develop schizophrenia unemployment rises to 70-95%. These figures are troubling to consumers, clinicians, and politicians. Individual Placement and Support (IPS) is a vocational intervention which has been developed and trialled successfully in populations with chronic serious mental illness in The United States of America. To date there has been no published randomised trial of IPS in first episode psychosis. This study aimed to examine the efficacy of IPS in a RCT with people with first episode psychosis. Clients of the Early Psychosis Prevention and Intervention Centre (EPPIC) at ORYGEN Youth Health in Melbourne, Australia who wished to find work were randomised to treatment as usual (TAU) (n=20) or TAU + IPS (n=20). Participants were assessed at baseline and after six months with a range of symptomatic, demographic and functional measures. Raters were blind to group allocation. In TAU case managers could refer to external vocational agencies funded by the federal government. The IPS condition involved working with an employment consultant who was integrated with the mental health team. Her role involved rapid job searching with clients and provision of support once they had obtained employment. At the time of writing the trial is nearing completion. Clients randomised to the IPS group have achieved greater employment outcomes than those in the TAU-only group (14 out of 18 vs 4 out of 14 thus far ($p < .005$)). Results examining symptomatic and functioning factors will also be available for the presentation. There is an increasing recognition that the rehabilitation of people with mental illness needs to take into account functional as well as symptomatic domains. One of the key functional domains is work, because among other important things such as a meaningful role, work provides access to the means to participate in society. Addressing vocational issues in the phase of life in which psychosis typically has onset is attractive because it is congruent with normal developmental processes. This project shows that an evidence based employment intervention in this population produces good vocational outcomes.

RELATIONSHIP BETWEEN SOCIAL RECOGNITION AND QUALITY OF LIFE IN REMITTED SCHIZOPHRENIA

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Objectives : A remission from schizophrenia gives one many of the skills that mentally healthy individuals have, but there are still impaired quality of life that may continue to persist. The purpose of the present study was to evaluate the relationship between quality of life and social recognition in remitted schizophrenic patients. METHOD: Remitted 40 schizophrenic outpatients meeting PANSS 7-items remission criteria were included. They completed FEEST (facial recognition test) and self-reported quality of life scale (SQLS-R4). Corrlation between facial recognition errors and quality of life was analyzed. Also, subjects completed rating scales for psychotic symptoms, mood and extrapyramidal side effects, as well as standardized neuropsychological measures. RESULTS: There was a significant correlation between quality of life and facial recognition errors. CONCLUSIONS: This result support the importance of social recognition in remitted schizophrenic patients. Further research and treatment toward improving social recognition in remitted schizophrenia might be needed.

SCHIZOPHRENIA AND SOMATIC COMORBIDITY: A LIFE-SPAN PERSPECTIVE

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Introduction: Substantial rates of medical morbidity and mortality is associated with schizophrenia. Hypothesis: An updated review of the prevalence and risk factors for cardiovascular diseases and sudden death in schizophrenia may have a positive effect on the detection and treatment of the common risk factors. Methods: The PubMed database was searched and relevant literature from 1966 up to 2006 was reviewed. Results: In schizophrenia patients respiratory diseases have previously been the most important causes of death. However, nowadays the cardiovascular diseases, such as coronary heart disease, are increasingly important consisting of 40 to 45 per cent of all natural deaths. Patients with schizophrenia have been reported to be three times as likely to experience sudden unexpected death as individuals from the general population. Conclusions: Part of the high death rates may be explained by long-lasting negative health habits and metabolic disorders. The antipsychotic medications may also increase the risk as some antipsychotics may cause prolongation of QT-time, serious ventricular arrhythmias and predispose to sudden death. A structured follow-up system for the risk factors and negative health habits is needed.

DEVELOPMENT AND INITIAL VALIDATION OF THE DETERMINANTS OF SMOKING SCALE - PSYCHOSIS VERSION (DSS-PV)

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Introduction: Compared to the general population the prevalence of smoking is high among patients with Schizophrenia (SCZ). It has been suggested that high prevalence rates are because smoking improves negative symptoms, negative affect, and cognitive deficits among these patients. Support for this notion can be found in a recent qualitative study in which SCZ patients' reported reasons for smoking included attempts to self-medicate, decrease medication side effects, protect oneself from stigma, increase one's sense of identity, and increase one's sense of control. This and other research suggests that a unique set of factors underlie smoking in persons with SCZ; yet to date, there are no measurement tools designed to examine these determinants. Therefore, the current project aimed to develop a scale measuring both the standard (i.e., those that overlap with determinants in the general population) and unique (i.e., those inherent to psychotic illness) reasons for smoking in patients with SCZ. **Hypotheses:** The determinants of smoking scale will demonstrate adequate construct validity (i.e., principle component's analyses will demonstrate dimensions corresponding to standard and unique factors). It will also demonstrate high reliability when administered to smokers with SCZ. **Methods:** A panel of SCZ and addictions researchers generated items tapping unique reasons for smoking among persons with SCZ. These items were combined with standard items (i.e., reasons for smoking in the general population). An independent panel of 3 specialists (expertise in either schizophrenia, psychometrics, or nicotine addiction) then evaluated all items for content validity. Analysis of their responses resulted in the creation of an initial questionnaire consisting of 153 items, which was administered to smokers with SCZ. **Results:** Principal component's analysis was completed, and the number of components retained was determined using parallel analysis criterion. Of the seven components retained, only one (Improvement of Cognition) appeared to be unique to SCZ. Interestingly, this component accounted for the greatest proportion of variance in the item responses. The remaining six components appeared to reflect standard reasons for smoking (e.g., Relaxation, Somatosensory Stimulation, Physical Addiction, etc.). Analysis further revealed high internal consistency of the entire scale, as well as the individual components (all Cronbach's Alpha's > .76).

NEUROCOGNITION, SOCIAL COGNITION AND FUNCTIONAL OUTCOMES OF SCHIZOPHRENIA PATIENTS

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Schizophrenia patients exhibit a variety of functional outcomes due to the heterogeneous pathogenesis. The ability to predict the functional outcomes in these patients when beginning treatment would enable them to be managed with better-planned and more-sophisticated treatment modalities. This preliminary study was designed to investigate the factors that predict the functional outcome of schizophrenia patients by measuring neurocognition and social cognition. Fourteen patients with schizophrenia (10 males and 4 females) were recruited for this study. We assessed neurocognitive function using the Continuous Performance Test (CPT), Verbal Learning Test (VLT), Wisconsin Card-Sorting Test (WCST), and Trail-Making Test A. Social cognition was assessed using the Theory of Mind Test (ToM), Facial-Affect Identification Test (FAIT), and Social Behavioral Sequencing Task (SBST). The functional outcomes were measured on the Social Skill Scale (SSS), Social Adjustment Scale, and Role Functioning Scale (RFS). The severity of symptom did not correlate with scores of functional outcome scales. But the number of hospitalization (NoH) was significantly correlated with RFS score. The recognition of fearful and angry facial expressions in FAIT was significantly correlated with the SBST score, but there were no significant correlations between the results of neurocognitive and social cognitive function tests. Linear regression showed that SSS can be predicted by VLT-delay and VLT-total scores. Among four domains of RFT, the work productivity was significantly predicted by SBST, independent living by NoH, SBST and WCST-perseverative error, family network by NoH, and social network by dosage of medication. These findings suggest that the ability to identify fearful and angry faces is important to successful social functioning. Furthermore, the abilities of verbal learning, social behavioral sequencing, and executive functioning are valuable in predicting functional outcomes in patients with schizophrenia. A long-term follow-up will be conducted with this cohort.

ASSOCIATION BETWEEN CHANGES ON THE NEGATIVE SYMPTOM ASSESSMENT SCALE AND MEASURES OF FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

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We sought to correlate changes in negative symptoms of schizophrenia, assessed by scores on the 16-item Negative Symptom Assessment scale (NSA-16), with changes in scores on various func-

tional outcome scales. Of 166 stable outpatients with schizophrenia or schizoaffective disorder participating in 1 of 3 medication or psychosocial intervention studies, 99 had data at baseline and 9 months and were included in the analysis. The rating instruments used were the NSA-16, Brief Psychiatric Rating Scale, and several functional outcome rating scales: Quality of Life Scale (QLS), Multnomah Community Ability Scale (MCAS), Global Assessment of Functioning (GAF), Social and Occupational Functioning Assessment Scale (SOFAS), Frontal Systems Behavioral Scale (FrSBe), Functional Needs Assessment (FNA), and Life Skills Profile (LSP). The association between change scores was assessed using Pearson's correlation coefficients. Changes in negative symptoms showed moderate to fairly strong correlations with changes recorded on all functional outcome rating scales. The associations were statistically significant for all functional outcome measures, including structured assessments (QLS: $r = -0.423$, $P<0.0001$; MCAS: $r = -0.338$, $P=0.0008$), global assessments (GAF: $r = -0.521$, $P<0.0001$; SOFAS: $r = -0.497$, $P<0.0001$), performance-based assessments (FrSBe: $r = =0.414$, $P=0.0003$; FNA: $r = -0.231$, $P=0.0247$); and observational assessment (LSP: $r = -0.367$, $P=0.0003$). This pattern of association between reductions in negative symptoms and improvements in functional outcome ratings was evident even after controlling for the effects of treatment-related improvements in positive symptoms. Reductions in negative symptoms, as rated with the NSA-16, are associated with improvements in clinician- and patient-assessed functional outcomes measures. This association is particularly strong when functional outcome is measured on the QLS, GAF, and SOFAS. These findings suggest that treatments that decrease negative symptoms may reduce the considerable functional disability associated with schizophrenia.

COGNITIVE, CLINICAL, AND FUNCTIONAL CORRELATES OF MMN DEFICITS IN SCHIZOPHRENIA PATIENTS

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Schizophrenia patients have widespread deficits ranging from abnormalities in sensory processing to impairments in cognition and daily living. Mismatch Negativity (MMN) is an EEG waveform that is passively elicited by infrequent stimuli that occur during the presentation of more frequent stimuli. MMN is a probe of the earliest stages of cognition and can be elicited in the absence of directed attention. The aim of the present study was to determine if MMN deficits in schizophrenia patients are associated with cognitive, clinical and functional impairments in a large sample of schizophrenia patients. Schizophrenia Patients (n=150) and normal subjects (n=108) underwent MMN and cognitive, clinical, and functional assessments. Schizophrenia patients had significantly reduced MMN ($p<0.001$) that was associated with impaired performance on tests of working memory ($p<0.01$) and verbal recall ($p<0.01$). MMN deficits were also associated with more severe negative symptoms ($p<0.01$), reduced performance ($p<0.05$) on a comprehensive functional skills assessment battery (e.g., ability to perform basic financial tasks), and significantly ($p<0.001$) lower ratings on several measures of functional status (e.g., independence in living situation, managing finances, Scale of Functioning, Global Assessment of Functioning Scale). In contrast, MMN deficits were not associated with performance on other cognitive measures or positive symptoms. MMN deficits reflect neural dysfunction associated with the core cognitive, clinical, and functional deficits of schizophrenia patients. MMN deficits may have multiple applications including use as a biomarker in drug development and as an endophenotype in genetic studies of schizophrenia.

TRANSLATING EVIDENCE-BASED PRACTICES INTO COMMUNITY TREATMENT SETTINGS

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Evidenced-based "best practices" to address symptom management and psychosocial needs have been developed for patients with schizophrenia. Implementation of these practices in community settings has often been slow and erratic. Outcomes with translation into the community have not always been as robust as hoped. We examined implementation of two practices, medication management recommendations from the Texas Medication Algorithm Project (TMAP) and Cognitive Adaptation Training (CAT) in a community agency, the Center for Health Care Services (CHCS). In the case of medication management, the agency is required by the state to implement the Texas Implementation of Medication Algorithms program, derived from TMAP, and the intervention was to provide a Medication Management Coordinator (MMC) to facilitate transition from psychiatric hospital to the community and to assist the prescribing physician in following algorithm guidelines. One hundred seventy eight individuals have been enrolled in the MMC program and 79 have been enrolled in CAT (home visits to establish environmental supports to improve functional outcomes) run by CHCS staff. Barriers to implementation were identified, including location specific funding streams, poor communication between inpatient and outpatient facilities leading to problems in coordinating follow-up care, regulations mandating frequency of visits, level of staff training, training time reducing billable hours and consumer refusal of home visits. We examined patients participating in evidence-based practices versus controls within the same system. We also examined individuals prior to and during participation in MMC and CAT programs. Preliminary results suggested that patients in the MMC program experienced a significant decline in symptomatology over time and were more likely than a group of control subjects to adhere to medication based upon prescription records. As in randomized, controlled trials, CAT significantly improved scores on the Social and Occupational Functioning Scale over time. Individuals in CAT had significantly better medication adherence than historical controls. These preliminary data suggest that evidence-based practices can successfully be implemented into community agencies. Development of specialized training programs and time for training reducing billable hours are important hurdles that must be overcome.

DEVELOPING A PATIENT INTERVIEW TO ASSESS REASONS FOR ANTIPSYCHOTIC DISCONTINUATION OR CONTINUATION IN THE TREATMENT OF SCHIZOPHRENIA

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Objectives: Time to treatment discontinuation (TTD) is commonly used as a global index for evaluating effectiveness of antipsychotic medication. TTD inherently incorporates all factors that contribute to decisions regarding whether treatment with a particular drug

should be continued. However, TTD does not provide information regarding reasons for discontinuation, and limited options are available for assessing these reasons. The purpose of this study was to develop a patient interview to assess reasons for discontinuation or continuation of antipsychotics for the treatment of schizophrenia. Methods: A preliminary Reasons for Antipsychotic Discontinuation/Continuation Interview (RAD-I) was constructed based on literature review, patient interviews, and expert working group input. Patients with schizophrenia completed the RAD-I and structured cognitive debriefing interviews assessing the RAD-I's comprehensibility, clarity, and comprehensiveness. The RAD-I was revised based on feedback from patients and interviewers. Results: The RAD-I was developed to be administered in 3-steps: (1) interviewers ask patients open-ended questions about reasons for discontinuation; (2) interviewers record patients' initial responses on scoring sheets divided into three categories; and (3) interviewers ask follow-up questions regarding the importance of each reason on a 3-point Likert scale. Items on the scoring sheets assess insufficient benefits in five domains (positive symptoms; negative symptoms; mood; cognition; functional status), adverse events, and reasons other than direct effects of the medication (e.g., cost, difficulty negotiating the healthcare system, inadequate social support). For patients continuing their current treatment regimen, a parallel interview assesses reasons for continuing an antipsychotic. In cognitive debriefings, patients indicated that the interview was clear, easy to complete, and comprehensive. Conclusions: This study is the first step in developing a patient interview to assess reasons for antipsychotic discontinuation and continuation. Results of cognitive debriefing interviews indicate that the RAD-I has good ease-of-use and comprehensibility. The next step in this research is psychometric validation of this measure in a broad sample of patients with schizophrenia and schizoaffective disorder.

DURATION OF UNTREATED PSYCHOSIS IN FIRST EPISODE PATIENTS:RELATIONSHIP TO FUNTIONING AND SYMPTOMATOLOGY AT ONE YEAR

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Background: A Longer duration of untreated psychosis (DUP) confers a poor prognosis in psychosis(1).These effects appear to persist for years after first onset(2).A number of studies have reported evidence of a relationship in first episode patients between DUP and poorer outcome at 1 year while others have failed to find such evidence(3). Patients' DUP may be related to both the severity of symptomatology and their functional disability. The following analysis examined the relationship between DUP and two measures of outcome: symptomatology and levels of assessed disability at on year follow-up. Methods: DUP was estimated from structured patient/family interviews. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and patients functioning were assessed using the Global Assessment of Functioning Scale (GAF). Correlations were examined using Spearman's Rho. The analysis included 158 patients (Median age = 30.8yrs; m/f = 103/55). Median DUP was 6 months (IQR = 1-12). Results: DUP significantly correlated with the PANSS Positive Scores (Rho = .358, p<.001) and the GAF Symptoms Score (Rho=-.403, p<.001) and the GAF Disability Score (Rho=-.455, p<.001).No significant relationships were observed between DUP and PANSS Negative Scale. Conclusions: Our results confirm that a longer DUP is related to poorer levels of functioning and higher levels of positive symptoms at 1 year in first episodes psychosis, thus providing support for the necessity of early intervention. References: 1:R.M.G.Norman, & A. K.Malla, (2001) Duration of untreated psychosis: A critical examination of the concept and its importance. Psychological Medicine, 31, 381 –400.[2:R.M.G. NORMAN, S. W. LEWIS, and M. MARSHALL Duration of untreated psychosis and its relationship to clinical outcome Br. J. Psychiatry, August 1, 2005; 187(48): s19 - s23. 3:M.Marshall, S. Lewis, A. Lockwood, R. Drake, P. Jones, and T. Croudace Association Between Duration of Untreated Psychosis and Outcome in Cohorts of First-Episode Patients: A Systematic Review Arch Gen Psychiatry, September 1, 2005; 62(9): 975 - 983. Funded by the R&D OFFICE

EVALUATING A GROUP INTERVENTION TO REDUCE ENGULFMENT AND SELF-STIGMATIZATION IN FIRST EPISODE SCHIZOPHRENIA: PRELIMINARY FINDINGS

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Background: Young people coping with a first episode of schizophrenia may be predisposed to the phenomenon of illness engulfment. Psychosocial interventions are needed to preserve an identity distinct from illness, promote hopefulness and minimize the impact of stigma to enable young adults to embrace a healthy sense of self and an optimistic future. Aims: The purpose of the present study is to evaluate a group intervention designed to promote healthy self-concepts by reducing self-stigmatization and engulfment for young adults recovering from first episode schizophrenia. Method: Participants at two first episode psychosis clinics in Toronto and Ottawa were assigned to the group intervention plus treatment as usual or to the comparison group which involved treatment-as-usual. Results: Following the 3 month intervention, the treatment group demonstrated significant unique improvement when compared to the comparison group on measures of engulfment, identity, quality of life, negative symptoms, hope, self-esteem and global functioning. Some general improvements in symptoms and self-concept thought to be related to treatment as usual were noted in the comparison group. Conclusion: Intervening early in the course of the illness to address engulfment may allow young people to acquire positive attitudes toward themselves and the future. Future longitudinal data will determine whether this intervention will prevent the development of chronicity and demoralization overtime.

FUNCTIONAL CAPACITY IN SCHIZOTYPAL PERSONALITY DISORDER: EVIDENCE OF IMPAIRED PERFORMANCE ACROSS THE SCHIZOPHRENIA SPECTRUM

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Schizophrenia patients demonstrate broad social and occupational impairment. The relationship between functional capacity and real-

world functioning, however, is complex and multi-determined, particularly for individuals with this disorder. Individuals with schizotypal personality disorder (SPD), although largely free from psychosis, share many common features of schizophrenic illness: they exhibit a similar profile of cognitive impairment and also demonstrate impairment in social and occupational functioning. However, to date there has been no systematic evaluation of the functional competence of individuals with SPD. In an ongoing program of research, we have administered the UCSD Performance Based Skills Assessment (UPSA; Patterson et al., 2001), a well-validated measure of skills competence modified for use in individuals with schizophrenia, to 13 individuals with DSM-IV SPD. Mean UPSA total scores for this sample were 83.7 (SD = 7.2); 54% of participants scored below the normative mean for healthy individuals and 23% scored more than 1 SD below the normative mean. In addition, 46% of the sample scored more than 1 SD below the normative mean in the finance domain and 23% scored more than 1 SD below the normative mean in the communication domain. Thus, individuals with SPD appear to demonstrate impaired overall functional capacity, with specific deficits in the areas of finance and communication. This suggests that the functional incapacity seen in schizophrenia may extend to individuals with other schizophrenia spectrum illnesses. In addition, the examination of the relationship between functional capacity and functional outcome in SPD could allow a better understanding of this extremely complex relationship in schizophrenia.

SCHIZOTYPY AND WORK

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Research documents the functional impairments of schizophrenia, but less attention has been paid to the functional correlates of SPD. A robust relationship has been shown between schizophrenia and poor work functioning, mainly in clinical samples. Considering that most people with SPD are not in treatment, it is unclear whether SPD is related to worse employment in community samples. This study examined the relationship between SPD and work in a large sample of subjects recruited from the community. Subjects were recruited through advertisements and referrals from local clinics. Exclusion criteria were: current (past 6 months) substance abuse or dependence, a positive urine toxicology screen at assessment, lifetime diagnosis of a psychotic disorder or bipolar I, and history of head trauma. The study sample included 174 subjects, of whom 69% were male and 56% were Caucasian, with a mean age of 38.4 years and 14.9 years of education. All subjects were assessed with the SCID-I and SCID-II, and completed comprehensive interviews, including work history. Review of associations between different personality disorders indicated a significant correlation (phi = .34, p = .000) between SPD and paranoid personality disorder (PPD). Therefore, the present analyses compared work outcomes between 4 different groups: No PPD/SPD (N = 82), SPD Only (N = 38), PPD Only (N = 17), and SPD + PPD (N = 37). Logistic regressions predicting current work status (yes/no) indicated that compared to the No PPD/SPD group, subjects in all 3 other groups were less likely to be employed: SPD Only (p = 036), PPD Only (p = .009), and SPD + PPD (p = .013). Similar analyses predicting job history (defined as 1 year or more of continuous full-time work) indicated that compared to the No PPD/SPD group, subjects with PPD (p = .036) and SPD + PPD (p = .002) were less likely to have a work history, whereas subjects with SPD Only did not differ. T-tests were computed comparing the No PPD/SPD group with the other 3 groups on social contact, cognitive complexity, and Hollingshead SES for current job, and Hollingshead Educational Index (HEI). These tests indicated that the SPD Only subjects had jobs with less social contact (p = .029), the PPD Only subjects had jobs with lower cognitive complexity (p = .024) and SES (p = .028), and the SPD + PPD subjects had lower HIE (p = .021). The findings suggest that both SPD and PPD are associated with impaired vocational functioning in a community sample.

EARLY DETECTION IMPROVES OUTCOME: A TWO YEAR FOLLOW-UP STUDY

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Objective: Previous result from this study show that it is possible to reduce the duration of untreated psychosis in one catchment area through and early detection (ED) program. It also shows that the reduction in DUP is followed by decreased symptomatology across all domains including baseline, with a remaining effect on negative symptoms after one year in treatment. The objective here is to study if the ED program/reduction of DUP has an impact on two-year outcome. Method: A total of 231 patients (82% of original sample) participated in a personal follow-up two years after start of first treatment. Five patients were dead, three by suicide and two by accidental overdose. Five could not be found while the remaining either did not want to participate or did not show up for the personal follow-up. Results:There were no differences between patients from the early detection area (ED) and patients from the area without any early detection (No-ED), in neither PANSS positive symptoms nor GAF symptoms. ED patients had significantly lower PANSS negative symptoms (mean (SD) NoED 15.9 (7.6) ED 11.9(5.5)**), general symptoms mean (SD) NoED 27.1(8.8) ED 23.8(7.1)**)and significantly better GAF function (NoED 50.8 (14.8)ED 53.8(17.3)*) (*p<0.05, **p<0.001). The effect sizes were generally moderate (Cohen's d 0.5-0.6) but increasing from the one-year follow-up (Cohen's d 0.3-0.4). The tree patients dead by suicide were all from the No-ED group. Conclusion: The positive effect of the ED program is present also after two years of treatment.

SF-36: A MEASURE OF RECOVERY IN THE FIRST SIX MONTHS OF TREATMENT FOR SCHIZOPHRENIA

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We have explored data from the widely used SF-36 health status self report as a measure of recovery in a prospective, ongoing clinical sample receiving care in an Early Psychosis program. Patients entering care had less than 6 months prior exposure to antipsychotic medication and met diagnostic criteria for a schizophrenia spectrum disorder. Clinical assessment including PANSS, GAF, SOFAS and SF-36 self-report was conducted at treatment initiation and 6 months of treatment. Norm based SF-36 values were calculated yielding scores such that 50 corresponds to the mean of a large normative sample and 10 represented the standard deviation. Summary mental (MC) component scores were calculated. Symptom remission at 6 months was determined using 8 PANSS items (Andreasen et al, Am

J Psychiatry 162:441-9:2005). ANOVA, paired t and Pearson correlations were used in the statistical analysis. The first 15 patients with complete 6 month SF-36 were studied. Mean MC was 39.9 (+/-10.3). The distribution of MC was: 50-59=2, 40-49=5, 30-39=6, 20-29=1, and 10-19=1. Among the 6 month ratings, MC was negatively correlated with Total PANSS (r=-.861, p=.001) and positively correlated with GAF (r=.722, p=.012) and SOFAS (r=.899, p=.001). 11 subjects had complete PANSS data at 6 months. 5 of the 11 met symptom remission criteria. There was a trend (p=.063) for remitted subjects to have higher MC. 8 subjects had complete SF-36 data at treatment initiation and 6 months. For these subjects the mean MC at 6 months, 38.4+/-13, was higher than at treatment initiation, 30.4+/-12 (p=.031). Recovery, as opposed to symptom remission, does not yet have accepted standardized measures and criteria. SF-36 data provides a self report reflecting the subjects' view of their own mental health. Norm based calculation allows a direct comparison with a large normative sample. In this sample at 6 months 87% rated themselves below the norm and 53% more than one standard deviation below the norm. MC at 6 months was strongly correlated with clinician rated symptom and function measures. Subjects with complete SF-36 data at treatment initiation and 6 months showed statistically significant improvement in MC. Thus the SF-36 appears sensitive to clinical change. Larger samples and longer follow up will allow more complete evaluation of the SF-36 as a measure of recovery in this population.

PREDICTORS OF FUNCTIONAL OUTCOME IN SCHIZOPHRENIA: A STRUCTURAL EQUATION MODELING DESIGN

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Little is known about the mediating factors between cognitive functioning, symptom presentation, and functional outcome in schizophrenia. Research in the area can help identify potential factors to be targeted in rehabilitation of patients towards independent living in the community. The present study aimed to examine the relationship between demographic variables, memory, current cognitive functioning, estimates of premorbid levels of intellectual functioning, symptom presentation, and measures of basic living skills and functional outcome in 118 patients with schizophrenia. Structural equation modeling was used to allow for complex relationships between the variables in comparing their relative contribution to functional outcome. Initial analysis of covariance and structural equation modeling revealed a mixed pattern of results. To achieve a model that best fit the data, a number of weak indicators had to be eliminated from each of the above hypothesized predictive domains. Preliminary analysis and results suggested that verbal memory, estimates of premorbid cognitive functioning, specific aspects of current cognitive functioning and levels of general symptomatology all contributed indirectly to both measures of basic living skills and functional outcome (consisting of items covering the domains of independent living and work). However, only verbal memory, estimates of premorbid cognitive functioning and severity of negative symptoms showed consistent and/or significant direct relationship with functional outcome measures, regardless of the model design. The characteristics of revealed competing models and the implications of our findings for improving functional outcomes in schizophrenia are discussed in detail.

STIGMATIC BELIEFS AND ATTITUDES TOWARDS SCHIZOPHRENIA BEARERS BY TEENAGERS STUDENTS AT INTERMEDIATE DEGREE OF SECONDARY SCHOOL: ASSESSMENT AND INTERVENTION

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The objective of this study was to identify the presence of stigmatic beliefs and attitudes of teenagers towards schizophrenia bearers and check the efficacy of an intervention by improving these items for this population. This approach was performed in 415 subjects, students of two Secondary Schools in São Paulo, Brazil. 302 of these students studied at a private school and 113 of them at a public school. The subjects were allocated in control group (n=195) and intervention group (n=220). All of them were asked to complete a questionnaire about stigmatic beliefs and attitudes towards schizophrenia bearers. One week later the intervention group was submitted to an intervention which consisted of supplying information and contact with the bearer. On month after the intervention both control and intervention groups answered the same initial questionnaire. In order to analyse them such answers were split in positive answers (referring to positive beliefs and attitudes towards schizophrenia bearers) and neuter answers (comprehending answers which did not presented positive beliefs and attitudes towards schizophrenia bearers and "I don't know" answers as well). The questionnaire was submitted to a factor analysis identifying three factors. One of these factors was put apart in this study. The two left ones were called social distance and stereotype. The female students showed a higher rate of positive answers not only in the whole scale, but also in the sub-scale of social distance. The private school presented more positive answers in the whole scale and also in the stereotype scale. Students who had a previous knowledge about schizophrenia showed more positive answers both in the whole scale and in the two sub-scales. There were more students in the private school than students in the public school who had a previous knowledge about schizophrenia. Students who had been in contact with a schizophrenia bearer prior to the study showed more positive answers both in the whole scale and social distance sub-scale. After the intervention, the intervention group exhibited more positive answers than the control group in whole scale and both sub-scales. Variables like sex, access to information and previous contact with the bearer had an influence as to positive answers in stigmatic beliefs and attitudes towards schizophrenia bearers. Students who were submitted to the intervention displayed more positive beliefs and attitudes towards schizophrenia.

INVESTIGATION OF FELT STIGMA AND ITS RELATIONSHIP TO SYMPTOM PRESENTATION IN PATIENTS WITH SCHIZOPHRENIA AS SEEN AT BUTABIKA NATIONAL REFERRAL MENTAL HOSPITAL, KAMPALA,UGANDA

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Stigma has been defined as a mark of shame or disgrace that sets a person apart from others and often leads to discrimination, prejudice, rejection and isolation in various sectors of society. Felt stigma is reported to be the most disruptive form of stigma for patients with

mental illness. Schizophrenia is probably the most stigmatized of all mental disorders. Though stigma of mental illness is considered to be very high in Uganda, there is no documentation of its prevalence and how it impacts on the lives of the mentally ill, especially those with Schizophrenia. The study investigated the frequency and extent of felt stigma in patients with Schizophrenia in Butabika Hospital and how this related to their symptoms. One hundred and fifty six patients with Schizophrenia were studied in a cross sectional descriptive study. Study participants included Forty inpatients and One hundred and sixteen out patients on treatment for Schizophrenia. Psychiatric diagnosis was confirmed using the MINI-DSM 1V.Patients' symptoms were identified and categorized using the PANSS and the extent of felt stigma was evaluated using the Internalised Stigma of Mental illness (ISMI) scale. Associations were sought between high levels of felt stigma and patients demographic and illness characteristics. High levels of felt stigma occurred in 34.6% of all respondents, 42.5% of inpatients and 31.9% outpatients had high levels of felt stigma though this difference was not statistically significant (p= 0.224). High levels of felt stigma were significantly associated with a bad relationship with sibling, more severe symptoms and particular positive, negative and general psychopathology symptoms in these patients. Difficulty in abstract thinking and Disorientation were the patient symptoms which predicted high levels of felt stigma after multiple logistic regression. High levels of felt stigma were found to be present in a substantial portion of the study population. These were associated with patient characteristics. Management of felt stigma should be part of routine care of patients with Schizophrenia and management of patients with Schizophrenia should target particular patient symptoms and socio-demographic characteristics. This study was carried with help of a research grantof $2700 from The Support to the Health Sector Strategic Plan Project (SHSSPP) of the Ministry Of Health-Uganda

EXAMINING MEDIATOR AND MODERATOR EFFECTS BETWEEN NEUROCOGNITION, INTRINSIC MOTIVATION, AND PSYCHOSOCIAL FUNCTIONING AMONG INDIVIDUALS WITH SCHIZOPHRENIA

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Despite the long-standing recognition of motivational difficulties experienced by persons with schizophrenia, there is little understanding of the nature and mechanisms of intrinsic motivation in schizophrenia and how it relates to neurocognition and functional outcome. The aim of this study was to explore whether intrinsic motivation mediated the relationship between neurocognition and psychosocial functioning, and to examine if neurocognition moderated the relationship between intrinsic motivation and psychosocial functioning outcomes. The sample consisted of 120 individuals diagnosed with schizophrenia involved in community-based psychosocial rehabilitation programs. Subjects completed baseline measures of neurocognition, motivation, psychosocial functioning, and symptoms. Five measures were used to assess neurocognition including verbal fluency, immediate memory, secondary memory, sustained attention, and mental flexibility. Intrinsic motivation was measured by the sum of three items from the intrapsychic deficits sub-scale of the Quality of Life Scale: purpose, drive, and curiosity. The psychosocial measure assessed work, independent living, and social functioning. Psychosocial functioning data were gathered within two weeks of neurocognitive testing. Trained research interviewers who conducted the semi-structured psychosocial interviews were blind to the neuropsychological results. Structural equation modeling with latent variables was used to test the mediator and moderator models. There were significant bivariate correlations between all three variables (Pearson r ranged from .28 - .5). Controlling for symptoms, the mediator model demonstrated very good fit to the data, ($\chi 2$ (48, N = 120) =58.19, p > .10; CFI = .97; RMSEA = .04, CI: .00, .08), with a significant degradation in the path between neurocognition and psychosocial functioning as expected. The results suggest that intrinsic motivation is a process through which neurocognition influences psychosocial functioning outcomes. There was no support for the moderator model. Outcomes from this study indicate that intrinsic motivation is an important concept for understanding the mechanisms of how neurocognition influences functional outcome. The findings also suggest that developing interventions to improve intrinsic motivation could contribute to better functional outcomes in schizophrenia.

POSITIVE, DISORGANIZATION AND DEPRESSIVE SYMPTOMS (NOT ONLY NEGATIVE ONES) ARE CORRELATED TO GLOBAL FUNCTIONING IN SCHIZOPHRENIA

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It is generally stated that negative symptoms are, among symptoms in patients with schizophrenia (SZ), the major sources of disturbances in global functioning (GF). This has fed a tendency of downplaying the role of other types of symptoms (e.g., depressive and positive ones) as sources of disability in SZ. To address this issue, the relationship between severity of symptoms and GF was examined in a cohort of chronic SZ patients. The following methodological features, which may increase the power to detect important correlations between the severity of symptoms and GF, were used: i) rating lifetime severity of symptoms, not only cross-sectional severity; ii) gathering a sample representing the full spectrum of severity, i.e., including not only stabilized outpatients but also inpatients living on long-term wards; iii) rating severity for both acute episodes and stabilized stage. We randomly sampled 114 DSM-IV SZ subjects from 2 strata defined according to level of functioning. The lower functioning stratum included patients living on long-term psychiatric wards or in highly structured group housing facilities. The higher functioning stratum included patients living in the community without supervision. Subjects were assessed for lifetime severity of positive, disorganized, negative and depressive symptoms, both during acute psychotic episodes and during the stabilized stage, and for premorbid adjustment, age of onset and level of functioning. We observed strong significant correlations between poorer GF and more severe positive and disorganization symptoms assessed during the stabilized stage. Also, better GF in the stabilized stage was significantly correlated to more severe depressive symptoms only during acute episodes. The results challenge the commonly held position that only negative symptoms affect GF and support distinguishing the two states of illness since depressive symptoms measured during acute episode, not during the stabilized stage, were specifically predictive of better GF.

DURATION OF UNTREATED PSYCHOSIS AND RELAPSE AFTER FIRST EPISODE SCHIZOPHRENIA

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Early intervention strategies in schizophrenia management claim better outcomes if the time to starting treatment is reduced. We re-analysed data from one study frequently quoted in support of early intervention (the Northwick Park First Episodes Study : NPHFE) addressing multiple factors that may relate to poorer outcome independent of time to treatment. NPHFE study was a placebo controlled RCT of maintenance antipsychotic following a first schizophrenic illness. Patients were consecutive admissions to various hospitals in south east England over a 2 year period. In addition to demographic and historical data, all patients had a Present State Examination (PSE) performed, usually within 2 weeks of entry and before drug treatment was started. Follow-up was for 2 years or to point of relapse, whichever came first. For this re-analysis, we used PSE symptom scales derived by Owens et al and hypothesised that those with a longer duration of illness prior to admission would show a) greater psychotic symptom severity on admission; b) longer in-patient stays and c) increased likelihood of bizarre behavioural disturbance evidencing greater deterioration. Full data were available on 101 subjects. They were divided into DUP > 1 year (28)/< 44 days (29)/intermediate (44). Those with DUP > 1 year had, as previously reported, significant higher relapse rates ($p<0.004$). They also had higher scores for 'tension' on PSE-derived scales ($p<0.01$). No differences emerged in severity of illness using the PSE Index of Definition, or duration of hospitalisation. Long DUP was associated with more threatening ($p<0.5$) and bizarre ($p<0.005$) behaviour and with single status ($p=0.005$), living alone ($p=0.03$), being unemployed ($p=0.001$) and experiencing major prior life events ($p<0.05$) but not with substance misuse, genetic liability, ethnic origin of English as a second language. Logistic regression produced a best fit model comprising 'tension' (less tension = greater relapse), bizarre behaviour and being unemployed on discharge, as well as being in the placebo trial arm. Time to initial hospitalisation did not enter the model once these variables were considered. Thus, while a protracted time to initiation of treatment in schizophrenic patients does appear to disadvantage in terms of subsequent relapse, this may not simply be a consequence of delay but might also reflect characteristics of the illness itself.

A NATURALISTIC STUDY OF TIME-TO-RELAPSE IN FIRST EPISODE PSYCHOSIS PATIENTS WHO DISCONTINUED MEDICATION

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The purpose of this study is to determine how long it takes to relapse when FEP patients stop taking medication. Although it is reported that ~90% of patients with chronic schizophrenia relapse within 2 years of medication withdrawal there is no such clear information in FEP patients. In particular there is no information on time-to- relapse in FEP patients who discontinue the newer antipsychotic medications abruptly through non-compliance. Also many patients with FEP are eager to know how long the duration of prophylaxis for relapse prevention is. Unfortunately ethic currently forbids a definitive study of withholding medication from stabilized FEP patients in order to provide precise evidenced-based answer. Clinic patients who discontinued medication and refused to resume treatment until they relapsed were closely followed up and monitored with psychosocial supports from the programme. Relapse is determined by return of symptoms with visit to a physician, clinic, ER or an hospitalization. Patients in our programme are regularly rated on the PANSS,BPRS, CGI among others. The patients scores on these items confirmed the relapse. A total of 20 patients,11 males 9 females, were included in the study.Thirteen of them, (65%)relapsed. The time to relapse ranged from 61 to 1095 days (mean =270.5days., median= 182days. Fifty five percent of the population relapsed within the first year. The only available placebo controlled trial in this population was by Crow et al in 1986 with patients on the classical antipsychotic medications. Sixty-two percent of their patients on placebo relapsed, a figure similar to our current finding. Ours is the first report on the time to relapse in FEP patients on the atypical antipsychotic medications who discontinued medication. We conclude that Psychosocial treatment alone does not prevent relapse of FEP, and that pharmacotherapy is essential. The increased efficacy of atypical agents in psychosis does not protect patients any longer from relapse than the classical antipsychotics did; if they discontinued treatment. Relapse prevention in Psychosis at any stage of illness requires compliance with adequate pharmacotherapy.

SELF-REPORTED AND PERFORMANCE-BASED FUNCTIONING IN MIDDLE-AGED AND OLDER OUTPATIENTS WITH SCHIZOPHRENIA

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The number of older patients with schizophrenia and their demand on the healthcare system are growing. Treatment of the disorder is expanding from symptom reduction to improvement of everyday functioning, but functioning is a complex construct and little is known about the validity of its assessment methods in middle-aged and older patients with schizophrenia. Performance-based measures test the ability to demonstrate functional skills such as financial management and shopping in a laboratory setting and have been proposed as an alternative to self-reports, which may be more susceptible to confounds such as cognitive impairment, depression, or poor insight. The purpose of this study was to evaluate the relationship between these measures and determine how well they correspond to indicators of "real-world" functioning in a group of 77 middle-aged and older outpatients with chronic schizophrenia. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) and Hamilton Rating Scale for Depression. A composite neuropsychological (NP) ability score was calculated from a group of tests that measured executive functioning, verbal memory, processing speed, and attention. Insight was measured with the Birchwood Insight Scale and self-reported and performance-based functioning were measured with the Independent Living Skills Survey (ILSS) and UCSD Performance-Based Skills Assessment (UPSA), respectively. An index score consisting of living situation, driving status, employment, and marital status was created as a measure of "real-world" functional outcome. Path analyses revealed that NP ability significantly predicted both self-reported (β=.35, p<.05) and performance-based (β=.60, p<.01) functioning and indirectly predicted real-world functional outcome through its effect on performance-based functioning. The self-report and performance-based measures were weakly correlated (r=.08, ns). The relationship between self-reported functioning and real-world outcome was weak (r=.06, ns) and not confounded by NP ability, depression, or insight. The results suggest that performance-based

functioning is strongly determined by NP ability and that it is a better predictor of functional outcome than self-reported functioning in middle-aged and older patients with schizophrenia. Additional research is needed to clarify the construct of functioning and to develop more valid measures for it in this population.

A RANDOMISED CONTROLLED TRIAL (RCT) OF COGNITIVE BEHAVIOUR THERAPY (CBT) FOR PSYCHOSIS IN A ROUTINE CLINICAL SERVICE: LOOKING BEYOND THE PANSS …

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The current RCT of CBT for psychosis was set in a routine outpatient service with non-expert clinicians, and widened the primary outcomes to include more CBT relevant measures, such as beliefs about voices. Seventy-four patients, with at least one distressing positive symptom of psychosis, were randomised into an immediate therapy group (n = 36), or a waiting list control group (n = 38). The therapy group was offered six months of therapy and was followed up three months later. The control group also received therapy after waiting for nine months (becoming the delayed therapy group). Ten patients dropped out from the immediate therapy group, and 9 from the control group; a further 7 either dropped out or could not be assessed from the delayed therapy group. Differences between the immediate and delayed therapy groups were assessed and groups combined for those variables where no significant differences were found. Post treatment, the therapy group showed improvements in positive and general symptoms from the PANSS, as well as depression, anxiety, suicidal ideation, social and occupational functioning, and belief flexibility, compared to the control group. For positive symptoms and belief flexibility this was true only in the delayed, and not the immediate, therapy group. CBT was also shown to reduce resistance to voices and beliefs about the uncontrollability of thoughts, although the latter reached significance only in the immediate therapy group. At the three months follow-up, depression, positive symptoms, belief flexibility, and uncontrollability of thoughts continued to be significantly improved. General symptoms, anxiety, functioning, suicidal ideation, and resistance to voices were no longer significantly different. However, beliefs in omnipotence about voices and negative symptoms of psychosis became significantly reduced in the therapy group compared to the control group at the follow-up stage. There were no improvements in self-esteem, insight, or executive functioning, at either time point. These results demonstrate that improvements in a number of different domains can be obtained even when non-experts deliver therapy in a routine service setting. In addition, both emotional variables (such as depression, anxiety, and suicidal ideation), and cognitive variables (such as beliefs about voices, uncontrollability of thoughts, and belief flexibility), are key factors that can be improved by CBT for psychosis.

IMPACT OF FAMILY MEMBERS' SUBSTANCE ABUSE OR DEPENDENCE ON SCHIZOPHRENIA

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HYPOTHESIS: Patients suffering from Schizophrenia who have a family history of substance abuse/dependence (but not Schizophrenia) will negatively impact individuals with Schizophrenia and their course of illness. BACKGROUND: Schizophrenia has an onset in late adolescence and early adulthood. Substance use disorders often co-occur with Schizophrenia. Dual diagnosis is a common finding in patients with chronic mental illnesses such as Schizophrenia and has posed significant challenges in terms of etiologies, psychopathology, onset & course of illness, complications and overall management. In an individual who is vulnerable to developing Schizophrenia in the future, psychosocial and genetic factors such as having a family member who is suffering from substance abuse or dependence can be influential. Such a stressor may significantly affect the development and course of Schizophrenia. This study examines the impact of having a family member suffering from either substance abuse or substance dependence on individuals suffering from Schizophrenia. MEASURES: 1. Age of onset of illness 2. Course of illness: number of admissions, length of stay in each admission, number of medications 3. Co-morbidity with substances METHOD: Prospective study of patients visiting the local emergency department or admitted into the Acute Inpatient Unit. QUESTIONNAIRE 1. Family history of Substance Abuse – Yes/No 2. Family history of Substance Dependence – Yes/No 3. First Psychiatric Hospitalization (age in years) 4. Number of admissions 5. Average length of Stay 6. Number of different antipsychotic medications 7. Any Depot medications – Yes/No 8. Any Substance Abuse – Yes/No 9. Any Substance dependence – Yes/No 10. How many Substances (excluding Caffeine & Nicotine) PURPOSE OF THIS STUDY Important and helpful in prevention and/or management of patients having dual diagnoses.

STABILITY IN INTELLECTUAL, MEMORY AND ATTENTION DEFICITS 5-10 YEARS AFTER THE ONSET OF PSYCHOSIS: DATA FROM THE EPPIC LONG TERM FOLLOW-UP STUDY

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Working memory deficits have been consistently identified in schizophrenia, with evidence that they are present from illness onset, and relatively static. Whilst cross-sectional research suggests less stability in some aspects of memory and executive functioning, prospective longitudinal studies are better placed to address the question of cognitive change over the course of psychotic illness. In the current study we set out to examine the long term cognitive outcome of an Australian first-episode psychosis (FEP) sample, first tested from 1996 to 2001. The cognitive test battery included the following measures: the CANTAB Spatial Working Memory (SWM) & Pattern Recognition Memory subtests, the Wechsler Memory Scale-Revised Verbal Memory Index & Visual Reproduction subtest, the Trail Making Test & the Ward's WAIS-R short-form. The initial assessment occurred within the first 7 weeks of illness: a healthy control (CTL) cohort was also assessed. Re-assessment of the cohorts occurred between 2002 and 2006, and was nested within a larger follow-up study of patients treated at the Early Psychosis Prevention & Intervention Centre in Melbourne. At follow-up 63% of the FEP were in remission from their last psychotic disorder. The CTL (n=26) and FEP (n=43) subjects were matched for gender and handedness (mean time between assessments=87.9 months, range=63.0–139.7

months). Data analysis revealed no significant decline in the FEP group on any of the cognitive measures i.e., there were no significant time x group interactions (RM ANCOVA controlling for differences in age & premorbid IQ). The effect of time was statistically significant for the Visual Reproduction measure only ($F[1,58]= 5.47$, $p<0.05$). A significant group main effect was found for all measures except for Pattern Recognition: SWM Total Between-Search Errors ($F[1,58]= 4.14$, $p<0.05$), Visual Reproduction ($F[1,58]= 5.23$, $p<0.05$), Verbal Memory Index ($F[1,57]= 15.43$, $p<0.001$), FSIQ ($F[1,55]= 21.91$, $p<0.001$), TMT Part A ($F[1,61]= 9.78$, $p<0.01$) & TMT Part B ($F[1,60]= 7.47$, $p<0.01$); reflecting relatively impaired functioning in the FEP group. Data from this prospective longitudinal study provides support for a relatively stable cognitive deficit state across the first 5-10 years of psychotic illness. Further analysis of the clinical and psychopathological data we have obtained on the cohort (e.g. course of illness, comorbidity) is planned, in order to determine the factors which best predict cognitive outcome.

IS LANGUAGE-RELATED PSYCHOPATHOLOGY A PREDICTOR OF PSYCHOSOCIAL FUNCTIONG IN SCHIZOPHRENIA? RESULTS FROM A 4 YEAR FOLLOW UP STUDY

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Abnormalities of language are key symptoms of schizophrenia. Language symptoms like formal thought disorder are associated with structural and functional temporal lobe abnormalities. The goal of this study is to investigate whether the presence of language related symptoms predicts impairment in psychosocial functioning after 4 years. Data from the TUEFOS Tuebingen schizophrenia follow up-study were analysed. Language related symptomatology was defined as verifiable symptoms in at least one of 3 of the most language related items in the PANSS (P2 conceptual disorganization, N5 difficulties in abstract thinking, N6 lack of spontaneity). At baseline (remission from hospital) n=38 patients had verifiable symptoms in these items, whereas n= 77 had none. Preliminary results indicate that patients with language symptoms had significantly poorer premorbid functioning. Psychosocial functioning as assessed with the gaf-score is significantly lower in patients with language symptoms at baseline as well as at follow up after 4 years. A significant negative correlation was found between the sum score of the PANSS items P2, N5, N6 at baseline and the GAF-score after 4 years. The influence of attitude towards medication and treatment on this result is discussed. We conclude language related symptoms, which are as well correlated with structural and functional brain abnormalities (Shenton et. al. 2002) are associated with poorer psychosocial functioning in schizophrenia.

MEDIATORS OF FUNCTIONAL OUTCOME FOR INDIVIDUALS WITH SERIOUS MENTAL ILLNESS

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Several studies document the role of cognition in predicting community functioning in persons with serious mental illness, cognition accounts for only a modest portion of the variance. Thus, it is important to identify other mechanisms that lie between basic cognition and skill performance. This presentation will focus on two such factors, skill knowledge and learning potential. Part 1: Skill knowledge and skill performance This study examined skill knowledge as a mediator of cognition and real world skill performance. Fifty one individuals with serious mental illness were administered measures of cognition, skill knowledge and skill performance. Real world skill performance was assessed with the Test of Grocery Shopping Skills (TOGSS, 1). Skill knowledge was assessed with a pen and paper measure of shopping knowledge (e.g., knowledge about store layout). Multiple regression analyses were used to examine skill knowledge as a mediator in the relationship between cognition and real world skill performance. When skill knowledge was introduced as a mechanism through which cognition influences shopping performance skill performance, almost perfect mediation was achieved (slope of regression dropped from B = .32 to B = .03). Part 2: Learning potential and skill acquisition It has been suggested that "learning potential" (capacity for learning) may provide more predictive utility than traditional measures of cognitive functioning. The aim of this study was to explore the role of "learning potential" as a predictor of skill acquisition following a skills training intervention. Participants included 25 individuals with serious mental illness who completed a grocery shopping skills training intervention and a test-train-test version of the Wisconsin Card Sorting Test, which yielded indices of both static performance and learning potential. Skill acquisition was measured with the TOGSS. Results indicate that learning potential predicted skill acquisition over and above the static measure of WCST performance. Thus, these data suggest that learning potential has more utility, as compared to traditional cognitive assessment, when predicting improvement in real world outcomes following intervention. References (1) Hamera E, Brown C: Developing a context-based performance measure for persons with schizophrenia: the test of grocery shopping skills. Am J Occup Therapy 54: 20-25, 2000.

CLINICAL CORRELATIONS OF AMOUNT OF DRUG USE IN PATIENTS WITH PSYCHOTIC DISORDERS

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Use of illicit drugs among patients with severe mental disorders has in some studies been related to deterioration in many outcome measures, and in other studies to fewer negative symptoms and better social function. The reasons for these apparent diverging findings are poorly understood. The current study addressed the hypothesis that the amount of drug consumption would contribute to outcome in severe mental disorders. A representative sample of patients with SCID-verified schizophrenia, schizoaffective disorder and bipolar disorder from a Norwegian city hospital catchment area (n=282) were divided into three groups according to their level of drug use in the past 6 months: "no use" (0 exposures), "low use" (1-11 exposures) and "heavy use" (12 and more exposures). Symptoms were assessed using the Inventory of Depressive Symptoms (IDS), Positive and Negative Symptoms Scale (PANSS), Young Mania Rating Scale (YMRS) and Global Assessment of Functioning (GAF), split version. Data were collected about smoking habits, education, occupation, housing, marital/civil status, hos-

pitalisations, number of psychotic and affective episodes, suicidal attempts and length of eventual actual remission. The mean age was 35.5 years (SD = 11.4). 49 % had a schizophrenia spectrum disorder, 43 % bipolar spectrum disorder, 8 % other psychotic disorders and 10 % a diagnosis of alcohol abuse or dependency. Drug-using patients were younger, more likely single and had less education than their abstaining counterparts. Singleness was associated with any drug use, and lower educational level was associated with heavy use. More pathological symptom scores were seen in the "heavy use" group, both comparing with the "no use" and the "low use" groups. Interestingly, the mean symptom scores of the "low use" group were consistently less pathological than for the "no use" group, significantly so for the PANSS negative symptoms score. Shorter remission times were found in the "heavy use" group. This suggests that the amount of drug use is a central factor when assessing the significance of drug use in patients with severe mental disorder. Heavy use is associated with more pathology and worse function, while the picture for those with a moderate consumption is more mixed, with indications of better performance than abstaining patients, especially for negative symptoms.

DO THE EFFECTS OF ENVIRONMENTAL SUPPORTS LAST ONCE HOME VISITS ARE WITHDRAWN?

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Cognitive Adaptation Training (CAT) uses environmental supports such as signs, checklists, and alarms to cue and sequence appropriate behavior in the home environment. Ninety-four outpatients with schizophrenia received baseline assessments and then were randomized into one of 3 treatment groups; 1) Full-CAT (CAT treatment focused on many aspects of functioning including medication adherence), 2) Pharm-CAT (CAT treatment focused only on medication and appointment adherence) or 3) treatment as usual. Treatment lasted 9 months and patients were followed for 6 months after home visits were withdrawn. Note that supports such as pill containers and signs were not removed from the home. Medication adherence (unannounced, in-home pill counts), symptoms and functional outcomes were assessed at 3 month intervals. Group differences over time by treatment were examined using repeated measures analyses of variance for mixed models. Symptoms and functional outcome baseline scores were used as covariates. Results indicated significant main effects for group for both medication adherence and functional outcome. Both CAT and PharmCAT were better than treatment as usual in terms of improving adherence to prescribed medication. This effect remained significant throughout the follow-up even after home visits were stopped. With respect to functional outcome, individuals in CAT did better than those in PharmCAT who did better than those in standard treatment. While the effect initially persisted for those in CAT after in-home visits were stopped, by the end of the 6 month follow-up period, there were no significant group differences in functional outcome. For individuals with schizophrenia, we do not expect the treatment effects for medication to endure after medication is withdrawn. However, this standard is often applied to psychosocial treatments, and may need to be reevaluated. Results suggest that while some effects may remain with the withdrawal of treatment, some important improvements may be sustained only if treatment is sustained.

PSYCHOBIOLOGICAL RESEARCH: PERSPECTIVES OF PERSONS WITH MENTAL ILLNESS

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Objectives: The present study focuses on the subjective experience of psychiatric patients who participate in psychobiological research, based on patients' self-reported evaluations of the experience. Methods: We studied 313 persons with mental illness admitted to an inpatient research unit. Each participant was administered the Patient Satisfaction Questionnaire, a structured self-report questionnaire designed to assess satisfaction with research participation and clinical care. Results: 1) Individuals who completed the research protocol were significantly more satisfied globally and more likely to express that treatment had been effective. Factors contributing to willingness to participate in future research included favorable perceptions of: a) psychoeducation, b) safety, and c) comfort level with research procedures. Research participants were willing to participate in future research regardless of their perception of medication efficacy. Conclusions: This study emphasizes the importance of understanding the opinions of persons with mental illness who participate in research. Overall the data suggest that persons with mental illness find psychiatric research to be beneficial. Although, therapeutic misconception can not be ruled out given the methodology used at the very least the data indicate no sign that subjects found research participation to be harmful. Further studies should explore the source of this perception and attempt to separate the effect of 'therapeutic misconception' from possible real benefit of protocol driven assessment and treatment in a reputable clinical environment.

THE ASSOCIATION BETWEEN ANTIPSYCHOTIC TREATMENT AND UNINTENTIONAL INJURY IN PATIENTS DIAGNOSED WITH PSYCHIATRIC DISORDER

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This study examined the relationship between antipsychotic treatments, categorized by published somnolence adverse event rates, and unintentional injury (UI). In a large, healthcare insurance database, eligible patients (ages 18-64 years) had claims between January 2001 and December 2004 and diagnoses of schizophrenia or affective disorder (ICD-9 295-296). A nested case-control design was used. Cases had an E-code claim (i.e., a specified external cause of injury) for selected UIs (e.g., falls or non-passenger vehicle accidents), with the first injury designated as the index date. Controls had no injury claim and a randomly selected medical claim designated as the index date. Both groups had a prescription for either a first or second generation antipsychotic (FGA/SGA) within 120% of supply days of the index date to account for partial compliance. Patients treated with clozapine, depot or more than one antipsychotic were excluded. Somnolence categories were defined as low—aripiprazole or ziprasidone, medium—risperidone, high—olanzapine (OLZ) or quetiapine (QUE), or any single FGA. A logistic regression was used to estimate adjusted odds ratios (AOR) and 95% confidence intervals (CI),

where control variables included age, gender, diagnoses, concomitant medications (e.g. antidepressants and short and long acting benzodiazepines) and year. In the total sample of 649 cases and 5215 controls, the mean age was 41.7 (SD 11.5) and females were 61.7%. Diagnostic groupings of schizophrenia only, affective disorder only, and both were 8.6%, 68.1% and 23.3% in cases and 13.6%, 74.6% and 11.9% in controls. Antipsychotic somnolence classifications were: 7.9% low, 25.4% medium, 55.6% high, and 11.1% FGA in cases and 9.1%, 28.0%, 50.6%, and 21.5% in controls. Relative to low, high somnolence SGAs had an AOR of 1.41 CI (1.03-1.9) for risk of UI, while medium and FGAs had AORs of 1.17 CI (0.83-1.64) and 1.19 CI (0.80-1.77), respectively. In a model where OLZ and QUE were disaggregated, the AOR for QUE was 1.61 CI (1.15-2.25) and significant, while the AOR for OLZ was 1.25 CI (0.89-1.75). Medium and FGA categories had non-significant AORs. High somnolence SGAs were associated with a 41% increase in risk of unintentional injury relative to low somnolence SGAs. Further analyses showed that QUE had a 61% increased risk, while the elevation in risk with OLZ was 25% and not significant. Clinicians should consider somnolence induction when prescribing antipsychotics.

VALIDATION OF AN OBJECTIVE MEASURE OF FUNCTIONAL STATUS IN SCHIZOPHRENIA

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Studies have demonstrated that symptoms and cognitive impairment found in patients with schizophrenia impair multiple areas of functioning such as social function, employment capabilities, living status and higher-order activities of daily living (Bryson & Bell 2003). Improvement in cognition is a target for some of the newer treatments in development thus it is important that future clinical trials have appropriate methodologies for assessing the functional aspects of cognitive improvement. The Schizophrenia Objective Functioning Instrument (SOFI) was developed as an enhancement of existing instruments. The SOFI is interview-administered to patients and/or caregivers and consists of four comprehensive domains: Living Situation, Instrumental Activities of Daily Living, Productive Activities and Social Function. A combination of semi-structured questions and close-ended Likert scales provide guidance for a domain global score and an overall global score. Data were collected from 104 patients at 9 US clinical sites (80% schizophrenia, 20% schizoaffective). Stratified recruitment ensured a range of living situations: 49% unrestricted, 20% semi-restricted, 31% restricted. Psychometric statistics included test-retest reliability, and assessment of construct and discriminant validity. Test-retest reliability indicated stability of global ratings with ICCs ranging from 0.72 (Social Functioning – Patient) to 0.94 (Living Situation/IADLs – Informant). ICCs for family and friends ranged from 0.75 (Productive Activities) to 0.98 (Living Situation) while for paid caregivers the ICCs ranged from 0.77 (Social Function) to 0.93 (IADLs). Patients and caregivers had high agreement on rating of Productive Activity (ICC = 0.80). The lowest estimate of concordance was found on Social Functioning (ICC = 0.65). Construct validity was demonstrated with moderate to high correlations between the SOFI and the QLS and PSP (range r = 0.39 to 0.76). SOFI scores differentiated between high and low psychopathology (based on PANSS) except for Productive Activities and Extent of Living Environment Restriction. SOFI global scores also differentiated between high and low cognitive impairment as measured by a schizophrenia-specific cognitive test. The SOFI is a valid and reliable measure that can be used to measure function in an objective observable fashion. It can easily be implemented into randomized trials to monitor treatment progress and demonstrate functional changes.

THREE-MONTH STABILITY AND PREDICTORS OF DECISIONAL CAPACITY IN SCHIZOPHRENIA

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The purpose of this study was to examine stability of capacity to consent to research among patients with schizophrenia over a 3-month follow-up period. Data from 89 outpatients with schizophrenia ages > 40 years (M=52.1, SD=7.0) were collected as part of a larger study on capacity to consent to research. Decisional capacity was evaluated at baseline, 1-week, and 3-month visits with the Understanding, Appreciation, and Reasoning subscale scores from the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Subjects were also evaluated with standard clinical rating scales, a measure of insight, and a comprehensive neurocogntive test battery. Examining variance around the slopes (by means of mixed models analysis) for Understanding, Appreciation and Reasoning, we found that individual differences accounted for 48%, 44% and 21% of the variance, respectively (all ps <.001). Age, education, and baseline (as well as slopes) of severity of positive and negative clinical symptoms, severity of depression, and level of insight did not significantly predict the variance in any of the slopes of the three subscales. Neuropsychological test performance was a significant predictor of variance in the Understanding and Appreciation subscales slopes (b=4.187 and b=1.096, respectively; p <.001). Although individual differences appeared to account for substantial variance in the pattern of performance on decisional capacity scores over time, there also appeared to be some fluctuations in performance that could not be explained by fluctuations in symptom severity. Further research is needed to determine the degree to which such fluctuations reflect psychometric factors versus ethically relevant changes in capacity to consent to research. Regarding the latter, these preliminary findings suggest that level of cognitive functioning may be an important characteristic to consider in identifying those at risk for fluctuating decisional capacity.

PREMORBID, BASELINE AND OUTCOME DIFFERENCES BETWEEN ADOLESCENT AND ADULT ONSET PSYCHOSIS IN A REPRESENTATIVE FIRST EPISODE COHORT

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Objective: Adolescent onset psychosis was reported to be associated with a lower level of premorbid functioning and a longer duration of untreated psychosis (DUP). If replicated this is an important finding, since both variables were reported to be independent predictors of outcome. The aim of this study was (i) to confirm that early onset psychosis would be associated with lower premorbid functioning, longer

DUP, as well as poorer outcome compared to adult onset psychosis. Method: The Early Psychosis Prevention and Intervention Centre admitted 786 first-episode psychosis (FEP) patients from 1998-2000. Data on DUP, premorbid, baseline, and outcome characteristics were collected from patients' medical records (MR) of 637 patients who met inclusion criteria. Age at onset was dichotomized in 'below and above 19 years of age' consistent other studies. Results: The mean age at onset in the complete sample was 21.3 years (SD 3.6) with 27.3% (n = 174) experiencing their first psychotic symptoms below age 19 (range 8.2 – 18.9). Subjects were treated for a mean duration of 63.4 weeks (SD 34.2). Subjects with adolescent onset psychosis had achieved a significantly lower level of premorbid functioning, and suffered from a longer DUP. The rate of bipolar disorder at baseline in the adult onset group was twice as high as in the adolescent onset group. The longer DUP in the adolescent onset group was not accounted for by differences in premorbid functioning or rate of bipolar disorder. Sequential logistic regression with premorbid functioning, DUP, gender, time in treatment, and severity of illness at baseline as covariates revealed that the adolescent onset group were less likely to achieve remission of positive symptoms (OR = 1.44; CI = 0.98 – 2.13; p = 0.067). Age at onset (as a continuous variable) significantly predicted remission controlling for the same set of covariates (OR = 1.07; CI = 1.01 – 1.12, p = 0.013). Conclusions: Our results confirm previous reports that premorbid functioning is worse and DUP longer in adolescent compared to adult onset psychosis. The lower rate of remission of positive symptoms in adolescent onset psychosis was partly but not completely explained by the longer DUP and worse premorbid functioning.

THE EPPIC LONG-TERM FOLLOW-UP STUDY: VOCATIONAL FUNCTIONING 7.5 YEARS AFTER A FIRST PSYCHOTIC EPISODE

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This study aims to identify correlates of vocational functioning in a first episode psychosis (FEP) sample 7.5 years after presentation at a specialized early psychosis treatment service. The study involved a prospective, naturalistic follow-up of FEP patients commencing treatment with the Early Psychosis Prevention & Intervention Centre (EPPIC) in Melbourne, Australia, between 1995 and 1997. At treatment entry the Royal Park Multidiagnostic Instrument for Psychosis was used to assess duration of untreated psychosis (DUP), age at onset of psychotic disorder, and premorbid work/social functioning. At 7.5-year follow-up measures included the Brief Psychiatric Rating Scale (Thinking Disturbance subscale), Scale for the Assessment of Negative Symptoms (Alogia subscale), WHO Life Chart Schedule (to assess course of illness, treatment history, and duration of receipt of a disability support pension (DSP)), and the Structured Clinical Interview for DSM-IV (to derive Axis I diagnoses). Analyses involved 180 participants. Univariate and multivariate logistic regression analyses were used to estimate the effects of demographic, clinical and treatment variables on two outcomes: current employment; and durable employment (employment for more than 6 months in the past 2 years). The sample was primarily male (72%), with a mean age at follow-up of 29 years (sd=3.4). 45% reported current participation in competitive employment at 7.5 year follow-up (28% full-time, 17% part-time), and 53% reported recent durable employment. Multivariate analyses showed that, after controlling for other variables (including positive and negative thought disorder, premorbid functioning, and recent psychiatric treatment), current employment was negatively associated with continuous or episodic illness course characterized by worsening trajectory or incomplete remissions, disrupted education, and receiving a DSP for longer than 2 years. Lifetime diagnosis of schizophrenia, receipt of a DSP (regardless of duration) and disrupted education were negatively associated with durable employment. Educational attainment appears to be an important predictor of vocational outcome in the Australian labor market, although its relationship with premorbid functioning requires further investigation. The inverse relationship between DSP and employment, after controlling for symptom levels and course of illness, supports evidence from US studies that such payments may act as a disincentive to employment.

SUICIDE AMONG PERSONS AT RISK FOR SCHIZOPHRENIA

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OBJECTIVE: The rate of suicide is elevated among relatives of those with schizophrenia. The reason for the finding is not fully understood. We hypothesized that rates of suicide would be higher among offspring of mothers with schizophrenia and that the higher rates of schizophrenia among offspring would be associated with this relationship. METHOD: We tested these hypotheses in 208 children at risk for schizophrenia (and 103 low risk controls) of the Copenhagen high-risk-for-schizophrenia cohort. We followed children of women with serious schizophrenia from mean age 15 years to mean age 58 years. When the study began, in 1962, none of the offspring had suicidal ideation or was diagnosed with mental illness. In 2005, when subjects were mean age 58, we examined death registers to ascertain suicide. RESULTS: Increased risk for suicide was highly significantly associated with maternal schizophrenia and with an offspring diagnosis of schizophrenia. Schizophrenia in the offspring was also highly significantly associated with suicide at a higher rate than previously reported in the literature. CONCLUSIONS: Our hypotheses were supported: Children of women with schizophrenia are at significantly greater risk for suicide than their low risk counterparts. Their higher rate of suicide is partially mediated through their mental illness. The rate of suicide in persons with schizophrenia is also higher in our study than previously reported in the literature.

ALLIANCES AND FAMILY PSYCHOEDUCATION: A PROSPECTIVE CHANGE-PROCESS STUDY

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THE PROBLEM. The purpose of this study was to examine the alliance between the therapist and individual family members, the within-family alliance, and the therapist's contribution to the alliance in Behavioral Family Management (BFM) and to determine how these alliances relate to outcome in the treatment of schizophrenia. METHOD. The System for Observing Family Therapy Alliances (SOFTA), an observational coding schema, was used to determine the therapeutic alliance in an early treatment session of BFM. Audiotapes of one session each from 29 families were examined. The relationship between the alliance and the number of days until prodromal symptoms was determined. RESULTS. Survival analyses indicated that patients did better when relatives and therapists were

engaged in treatment. No relationship was found between the patient's alliance with the therapist and days until prodromal symptoms. DISCUSSION. A positive therapeutic alliance between therapists and families is an important predictor of outcome in BFM. It may be more important for relatives, compared with patients, to be engaged in family treatment.

CONTEXT PROCESSING AT ILLNESS ONSET PREDICTS FUNCTIONAL OUTCOME AT LONG-TERM FOLLOW-UP IN EARLY-COURSE SCHIZOPHRENIA

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This study examined the predictive relationship between cognitive control at illness onset and 'real-world' functional outcomes at long-term follow-up in schizophrenia (SCZ) patients. The AX version of the Continuous Performance Task (AX-CPT) has been used extensively to tap context processing, a cognitive control function proposed to be a core deficit in schizophrenia. It was hypothesized that context processing deficits in the early unmedicated phase of illness would predict deficits in social and daily activity functioning over the course of several years. At baseline, ten medication-naive SCZ patients performed a version of the AX-CPT and at follow-up they completed a battery of self-report and performance-based daily functioning tasks, including the UCSD Performance-Based Skills Assessment (UPSA), the Social Skills Performance Assessment (SSPA), the Medication Management Ability Assessment (MMAA), and the Social Functioning Scale (SFS). Functional outcome tasks assessed a range of abilities, such as medication management, interpersonal interaction, grocery shopping, bill-paying, appointment scheduling and planning recreational activities. In the AX-CPT, patients viewed sequences of letters presented one at a time and were instructed to respond positively to target trials, defined as a cue-probe sequence in which the letter A appeared as the cue and the letter X appeared as the probe (70 % target frequency). Subjects must represent and maintain the cue-context in order to successively respond to target AX pairs or inhibit the prepotent target response for BX pairs, where "B" is any letter other than A. As a specific index of sensitivity to context, d-prime-context was computed using hits and BX false alarms only and compared to d-prime traditionally computed using hits and all false alarms. AX-CPT d-prime-context at baseline correlated significantly with all measures of social functioning at long-term follow-up ($p < .05$, one-tailed): UPSA, $r = .58$; SSPA, $r = .66$; MMAA, $r = .65$; and the SFS, $r = .57$. In contrast, traditional d-prime at was not significantly correlated with any functional outcome measure. Results suggest that context processing in schizophrenia at illness onset is predictive of functional outcome 1 to 9 years later over a wide range of functional abilities. Context processing deficits may represent a specific cognitive target for early intervention which may in turn impact real-world functional outcomes in early-course schizophrenia.

LOW CARDIOVASCULAR FITNESS LEVEL IN COMMUNITY-DWELLING PATIENTS WITH SCHIZOPHRENIA

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Physical inactivity is a prominent behavioral risk factor for cardiovascular disease (CVD) morbidity and mortality, as cardiovascular fitness is strongly associated with CVD outcomes. High rates of CVD have been observed in the schizophrenia population, translating into a markedly reduced life expectancy as compared to healthy controls. Surprisingly however, while cardiovascular fitness is an eminent indicator for overall cardiovascular health, no studies have systematically assessed associated parameters in schizophrenia patients. We present data on overweight community-dwelling schizophrenia patients (BMI>22) who underwent graded-exercise tests for measurements of maximal oxygen uptake (VO_2peak) at baseline, considered to be the gold standard for the evaluation of cardiovascular fitness and overall functional capacity, as part of an ongoing large structured behavioral weight loss program. Patients exercised on a stationary bike at increasing resistance loads while cardiac responses and respiratory gas exchange measurements were performed. Data for n=84 subjects (41 % male, 46 % white) was analyzed. Mean age (y) was 43.2±9.9, and subjects on average were obese (mean BMI was 37.2±7.3). Peak HR attained during exercise was 145.6±19.6 beats per minute, after 8.05±3.6 min, which was 81% of their age-predicted maximal heart rate (APMHR). The maximal work attained was 111.2±44.2 Watts, and VO_2peak was 1.72±6.6 l/min. This is in contrast with 33 non-patient obese subjects who achieved 2.27±0.65 l/min and 96% of their APMHR. The test was generally well received and tolerated; compliance with the protocol was good. Among participants with schizophrenia, cardiovascular fitness was, with a few exceptions, exceedingly poor compared to non-patient obese subjects. Future studies should be performed in patients with schizophrenia to examine whether their poor exercise capacity and physical fitness can be improved with lifestyle modification programs including weight loss and increased physical activity.

COMPUTER ASSISTED COGNITIVE REMEDIATION FOR SCHIZOPHRENIA: A RANDOMIZED CONTROLLED TRIAL

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As cognitive impairment has been increasingly recognized as a core feature of schizophrenia and has been linked with poor community functioning, there has been an upsurge of interest in cognitive remediation in schizophrenia. The Maryland Computer Assisted Cognitive Remediation program (MCACR) was developed to address a range of cognitive deficits, from more basic processing speed and attention through integrative executive and cognitive control functions. The core components of MCACR are (1) training and behavioral shaping of organized, strategy-based problem solving, (2) guided practice on a curriculum of computer exercises during 36 training sessions, and (3) a supportive, one-on-one training model. Components of the program were formulated to enhance participant engagement: building from accessible, intuitive problem solving strategies (e.g., verbalization to enhance encoding and guide problem solving); using appealing computer exercises; and employing a warm and encouraging training style. We are currently testing the program in two randomized, controlled pilot trials with stable, mainly outpatient, schizophrenia participants. The control condition provides comparable duration of computer activity and therapist contact but consists of tasks with minimal cognitive demand. Outcome measures include metrics derived from the training exercises, neuropsychological test performance, and role-play-based proxy measures of community

functioning. In very preliminary analyses of data from 23 participants, significant effects were observed for 9 of 11 training exercise metrics, with effect sizes ranging from 0.5 to 1.0 SD. Differences between groups on composite scores for episodic memory, working memory, attention, processing speed, executive functioning, and everyday functioning were non-significant in the preliminary analysis but a number of individual cognitive and functional measures did appear to show small positive effects of training. Results suggest that MCACR is quite effective in producing performance gains on the training exercises but it remains to be seen whether these enhancements generalize and lead to improved performance on cognitive and functional outcome measures. Preliminary analyses will be updated for presentation at ICOSR; results will reflect data from approximately double the number of participants. Supported by MH 67764 (DD), VA Merit D3153R (ASB and DD), and the VISN 5 Mental Illness Research, Education, and Clinical Center.

HEDONIC CAPACITIES IN SCHIZOPHRENIA

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Although deficits in emotional experience have been hypothesized in schizophrenia since Kraepelin, laboratory studies have consistently shown that individuals with schizophrenia (IWS) report the same degree of pleasantness and unpleasantness when compared to non-patient control subjects (NCS). However, in these studies stimuli varied by their valence only (positive or negative), and it is hypothesized that other stimulus characteristics could reveal differences between IWS' and NCS' emotional evaluative systems. Thirty-nine patients with a SCID diagnosis of schizophrenia and 17 NCS participated in the study. The stimuli were 48 photographs from the International Affective Pictures System, 48 sounds from the International Affective Digitized Sounds, and 48 words from the Affective Norms for English Words. The stimuli varied in valence (neutral, positive, or negative), intensity (moderate or high), and sociality (social or not). After each stimulus, participants rated the degree of pleasantness, unpleasantness and arousal that they experienced. They also rated their anticipated and post-test interest for each task. IWS did not differ from NCS on global hedonia (pleasantness ratings with positive stimuli), global negativity (unpleasantness ratings with negative stimuli), and anticipated and post-test interest. IWS rated all stimuli as more arousing than NCS. IWS showed some specific differences in their positivity ratings only: they gave higher pleasantness ratings for neutral stimuli and showed a higher positivity bias (the difference between pleasantness and unpleasantness ratings for neutral stimuli) than NCS. More importantly a highly significant interaction, group by intensity by sociality, was found with positive stimuli. IWS rated social positive stimuli of moderate intensity as more pleasant than NCS, and this difference showed a large effect size. Among IWS, the pleasantness ratings of moderately positive stimuli were inversely correlated with the degree of negative symptoms. In this evocative test, IWS did not show global anhedonia, anticipatory anhedonia, or global negativity. However they showed higher positive reactivity to positive stimuli of moderate intensity, which are the stimuli that people encounter most often in their daily life. These results suggest that impaired social motivation is not secondary to an absence of emotional reactivity, but a disconnection between the emotional system and the motivational system can be suspected.

SOCIAL COGNITION AND EMOTIONAL EXPERIENCE PREDICT SOCIAL ADJUSTMENT IN SCHIZOPHRENIA

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Introduction: Kraepelin emphasized the importance of impaired emotional functional in schizoprhenia ("no human feelings"), although more recent work has challenged this viewpoint, suggesting that while SCZ patients have impaired emotional expression, they have comparable emotional experiences, particularly negative ones. Given the importance of general and social cognition on patient outcome, we sought to investigate the relationship between self-report measures of emotional experience, functional measures of general/social cognition, and social adjustment. Method: Twenty-two stable, schizophrenic/schizoaffective patients (7 females; Age=40.0±9.7) and 21 healthy controls (6 females; Age=39.4±10.3) matched for age, sex, and parental education completed a battery of tests of cognitive functions (BACS) and social cognition ("Eyes" and MSCEIT). Subjects also completed questionnaires measuring hedonic capacity (Physical and Social Anhedonia Scales), emotion intensity (AIM: Affect Intensity Measure), emotion frequency (Differential Emotion Scale-Modified), and social adjustment (SAS: Social Adjustment Scale). Results: The self-report measures exhibited good internal reliability, (alpha>0.85), except for AIM positive, alpha=0.69; negative<0.1). Although equivalent on WRAT-R reading, patients scored 0.5-1.5 SD less than controls on general and social cognition. Although patients had impaired hedonic capacity and experienced less positive emotions than controls, affect intensity for positive experience was comparable. They also reported greater frequency of negative emotions and poor social adjustment. Emotional experience was significantly correlated with social adjustment (r=.44-.75), as well as total and positive symptoms (BPRS ratings), but not negative symptoms. Poor general cognition (r=.55) and social cognition (r=.62) were correlated with poor social adjustment, but Sobel's test of mediation suggested that the relationship between general cognition and social adjustment was mediated by social cognition (p<.01). Conclusion: These data support the notion that SCZ patients have equivalent levels of emotional experience, along with impaired emotional capacity. Furthermore, the findings emphasize the importance of overcoming the 'Kraepelinian bias' around emotions in SCZ, since emotional experience correlates with social adjustment and psychotic symptoms.

IMPACT OF SUBSTANCE MISUSE ON ONE YEAR OUTCOME IN PATIENTS PRESENTING WITH FIRST EPISODE PSYCHOSIS

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It has been suggested that the presence of comorbid substance use disorders in patients with psychosis has a negative effect on outcome. We sought to investigate the impact of persistent substance misuse on functional, symptomatic and clinical outcome over one year in a first episode psychosis sample. 180 of 256 incident cases of psychosis were followed up at one year. Patients were divided

into three groups depending on presence of substance misuse at presentation and at follow up. Univariate analyses of variance were performed to determine the effect of substance misuse on Global Assessment of Functioning (GAF), Positive and Negative Syndrome Scale (PANSS) and clinical outcomes (Hospitalisation and recovery rates) at one year, adjusting for gender and age of onset. 63% of the sample was male. Mean age of presentation was 34 (SD 12.3) years. 86 patients (48%) reported no substance misuse at presentation or at follow up, 44 patients (24%) reported substance misuse at presentation but not at follow up and 50 patients (28%) reported substance misuse at presentation and at follow up. Presence of substance misuse at both presentation and at follow up resulted in poorer functional outcome on GAF-total (p=0.05) but not GAF-symptoms or GAF-disability at one year. Persistent substance misuse also resulted in poorer recovery rates (p=0.01) and increased hospitalisation (p=0.02) at one year. In each case within this persistent substance misuse group there was a significant effect of alcohol misuse/dependence but not cannabis or other substance use. There was no effect of substance use on PANSS symptom scores at one year. Male gender also had a main effect resulting in poorer functional outcome on all GAF scales and more severe PANSS-Positive and PANSS-Negative symptoms. Persistent substance misuse in first episode psychosis is associated with poorer functional and clinical outcome, though not more severe symptoms at one year. This highlights the need for early and effective intervention in first episode psychosis patients presenting with comorbid substance use disorders.

PERSONAL AND FAMILIAL COSTS ASSOCIATED WITH THE FIRST EPISODE OF PSYCHOSIS

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The first episode of psychosis often strikes in the late high school or early university years, imposing a devastating toll on social and vocational functioning. The objective of the present study was to quantify the personal costs associated with the onset of schizophrenia. The Experience of Caregiving Inventory (CBI) and the Henrich's Quality of Life Scale (HQLS) were administered to the families and patients, respectively, attending the Edmonton Early Psychosis Intervention Clinic (EEPIC). Assessments were completed at baseline, and again after 2, 6, and 12 months of EEPIC involvement. Early intervention may minimize functional declines, thus improving the long-term outcome of these individuals. The results suggest that caregiver burden is evident at the outset of EEPIC involvement. Similarly, patients report considerable social, vocational (educational, occupational), and negative syndrome debilitation shortly after the onset of acute psychosis. These findings are grossly in excess of expectations given the very short duration of the acute psychotic symptoms. Although improvement in CBI and HQLS is evident after 6 and 12 months of treatment, considerable impairment remains. In summary, although recovery from psychosis depends on a variety of factors, decline in psychosocial functioning is likely to represent the most salient impediment to rehabilitation. Early identification and intervention during the prodromal phase of the illness will be required to maximize the long-term potential of these individuals. In addition, providing prompt and sufficient support for the caregivers will also be needed to reduce caregiver stress and prevent the deterioration of family relationships.

COGNITIVE ADAPTATION TRAINING IMPROVES ADHERENCE TO MEDICATION AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

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Cognitive Adaptation Training (CAT) uses environmental supports such as signs, checklists, and alarms to cue and sequence appropriate behavior in the home. In an NIMH funded trial 94 outpatients with schizophrenia (SCID-DSMIV) received baseline assessments and then were randomized into one of 3 treatment groups; 1) Full-CAT (CAT focused on many aspects of functioning including medication adherence), 2) Pharm-CAT (CAT focused only on medication and appointment adherence) or 3) treatment as usual. Treatment lasted for 9 months. Medication adherence (unannounced, in-home pill counts), symptoms and functional outcomes were assessed at 3 month intervals. Group differences over time by treatment were examined using repeated measures analyses for mixed models. For symptoms and functional outcome baseline scores were used as covariates. Results indicated significant main effects for group and group by time for medication adherence ($F(2,85)=21.15$; $p<.0001$ and $F(8,237)=2.14$; $p<.03$). Both CAT and PharmCAT treatments were superior to treatment as usual for improving adherence to prescribed medication. There was a significant main effect for group on functional outcomes as rated by the Social and Occupational Functioning Scale ($F(2,116)=14.56$; $p<.0001$; and $F(10,321)=2.44$; $p<.008$), with post-hoc analysis supporting the best results for full CAT followed by PharmCAT followed by treatment as usual (all groups differences significant). There were no significant differences among groups with respect to symptomatology as rated from the BPRS. This is the first systematic study to demonstrate that the use of environmental supports can improve medication adherence for patients with schizophrenia. Results confirm earlier reports of improved functional outcomes with CAT. Results do not support early studies suggesting that symptoms improved for patients in CAT. In effect, taking medication as prescribed did not result in fewer symptoms. Lack of accurate information on adherence available to treating psychiatrists may make it difficult to optimize medication regimens to produce the best outcomes in terms of symptomatology. Alternatively, symptom scores remaining stable in CAT interventions may reflect the combination of better adherence plus the additional stress produced by increased participation in social and occupational roles. Environmental supports may be important tools in improving medication adherence and outcomes for individuals with schizophrenia.

NEGATIVE SYMPTOMS AS MEDIATORS OF THE RELATIONSHIP BETWEEN NEUROCOGNITION AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA: A META-ANALYSIS

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Background: Neurocognition has been found to be a robust predictor of functional outcome in schizophrenia patients (Green et al., 2004). However, psychiatric symptoms, in particular negative symptoms, have

also been shown to be robust predictors of functional outcome (McGlashan and Fenton, 1992; Herbener and Harrow, 2004). The high degree of intercorrelation of these key dimensions of schizophrenia leaves unclear whether neurocognition has a direct effect on outcome or whether that relationship is mediated by negative symptoms (Harvey et al, 2006). Methods: A meta-analysis of 35 English language studies published from 1980 to 2006 was conducted to determine the magnitude of the correlational relationships between neurocognition and symptoms, and between symptoms and functional outcome. In addition, we modeled a possible direction of these relationships. Using the Sobel test, we evaluated whether positive and negative symptoms (separately) mediate the relationship between neurocognition and functional outcome. Functional outcome was defined using measures of social relationships, school and work functioning, and laboratory measures of social skill acquisition. Results: We found that when positive and negative symptoms were combined, symptoms were mediators of the relationship between neurocognition and functional outcome (Sobel test, $p < .05$). However, when examined separately, the relationship between neurocognition and positive symptoms was not significant (average $r = .14$, $n = 140$, $p > .10$). In contrast, there was a significant relationship between neurocogntive functioning and negative symptoms (average $r = .19$, $n = 140$, $p < .05$) and between negative symptoms and functional outcome (average $r = .33$, $n = 643$, $p < .05$). Negative symptoms were found to be a mediator of the relationship between neurocognition and functional outcome (Sobel test, $p < .05$). Conclusions: This meta-analysis supports the role of negative symptoms as predictors of functional outcomes. The pattern of correlations is consistent with a role for negative symptoms as a mediator of the relationship between neurocognition and functional outcome. Treatment studies that created changes in either neurocognition or negative symptoms would be needed to test these directional relationships directly. If negative symptoms do serve this mediator role, then successfully treating neurocognitive deficits or negative symptoms should improve functional outcomes.

SCHIZOPHRENIA AND SOCIAL PARTICIPATION: USER`S PERCEPTION REGARDING STIGMA

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Stigma towards mental disorders is a relevant subject worldwide, especially considering schizophrenia, since there is a tendency of the population in general to consider individuals with schizophrenia to be unpredictable and dangerous. This produces fear, repugnance and a desire for social distance. To deal with this problem, effective anti-stigma actions and interventions should include patient's perceptions. This study investigated how people diagnosed with schizophrenia feel and qualify the effects of their conditions in several aspects of their routine, social participation and interactions. The study was conducted within the INDIGO (International Study of Discrimination and Stigma Outcomes)Study, a multisite comparative study of the impact of the diagnosis of schizophrenia from the user/consumer perspective conducted within the framework of the WPA Global Programme to Fight Stigma and Discrimination because of Schizophrenia. 25 outpatients from the Schizophrenia Program at Sao Paulo Federal University answered the semi-structured questionnaire named "Discrimination and Stigma Scale - 10" (Thornicroft et al, 2005). Preliminary findings indicate that the participants identify stigmatizing attitudes from relatives (52%), neighbors (44%), employers (40%). Furthermore, 76% reported the need to hide their diagnosis, since they are afraid of suffering prejudice and become socialy marginalized. Most of the patients (64%) do not circulate in social places very often, keeping their relationships limited to mental health services. The findings show that stigma has a direct influence on the social participation of these patients, as well as being directly involved in their rehabilitation and prevention, detection and treatment of the disorder.

SOCIAL FIRMS (OR AFFIRMATIVE BUSINESSES) FOR PEOPLE WITH MENTAL ILLNESS

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Social firms, or affirmative business as they are known in North America, are businesses created with a dual mission – to employ people with disabilities and to provide a needed product or service. The model was developed for people with psychiatric disabilities in northern Italy in the 1970s and, by diffusion, has gained prominence in Europe. Principles of the European model include: (a) over a third of employees are people with a disability or labor-market disadvantage, (b) every worker is paid a fair market wage, (c) accommodations are made for disabled workers' needs, (d) all employees have the same rights and obligations, and (e) the business operates as a viable concern, free of subsidy. Independent of European influence, affirmative businesses have also developed in Canada, the United States, Japan, and elsewhere. The authors have developed social firms and studied them in Europe, North America, East Asia and Australasia. The success of individual social firms is enhanced by locating the right market niche, selecting labor-intensive business opportunities, the public orientation of the business, and strong links with psychiatric treatment services. The growth of the social-firm movement is aided by government policies favoring employment of the disabled and by support entities that facilitate technology transfer. Advantages of the social-firm model include opportunities for empowerment, the development of a feeling of community in the workplace, and the enhancement of employee commitment resulting from the organization's social mission. If affirmative businesses prove viable in US rehabilitation systems they will expand the spectrum of normalized and integrated work opportunities for people with mental illness.

DO PATIENTS WITH SCHIZOPHRENIA EXPERIENCE GRIEF AND MOURNING IN RESPONSE TO LOSSES ENGENDERED BY THEIR ILLNESS?

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This study examined whether patients diagnosed with schizophrenia identify, grieve and mourn losses engendered by the illness. Depression and suicidality, but not grief, are symptoms reported in patients with schizophrenia (Addington, 2004, Power, 2004,

Birchwood, 2005). 21 patients with schizophrenia and psychosis responded to a questionnaire that asked them to indicate whether their illness led to losses, and to describe their responses to the losses. Their responses were also correlated with their beliefs about the illness, level of symptomatology, and sense of self-efficacy . 20 patients named specific losses, 18 patients (90%) reported having experienced feelings associated with grief and mourning. Patients who reported less sense of safety and self-esteem at the onset of the illness feel more ashamed ($r = -.580, -.637, p < .01$), those who reported a marked lessening of ability to think and concentrate at the onset of the illness feel an ongoing sense of loss ($r= -.562, p< .01$), and patients whose romantic relationships were negatively affected by the illness feel more social isolation ($r =-.552, p < .01$). Those who continue to be symptomatic feel less able more socially isolated ($r = .562, p =<.01$). Greater reported ability to manage emotions and behavior at the onset of the illness was correlated with greater self-efficacy ($r = .646, p < .01$). Our results suggest that patients who experienced themselves as very impaired by the illness continue to feel a greater sense of loss, possibly because they have not fully grieved their losses or because living with the losses is the dominant aspect of their daily experience. Further study of the process of grief is recommended. In clinical practice, it would be fruitful to differentiate between depression and unresolved grief because griefwork can offer a more hopeful outcome for those able to engage in it. References: Addington, J., Williams, J., Young,J., Addington, D. (2004). Suicidal Behaviour in Early Psychosis. Acta Psychiatr. Scand., 109:116-120. Allen, J.N.S., & Hafner, R.J. Birchwood, M., Iqubal, Z., Upthegrove, R. (2005). Psychological Pathways to Depression in Schizophrenia. Studies in acute psychosis, post psychotic depression and auditory hallucinations. European Archives of Psychiatry Clin. Neurosci, 255:202-12. Power, P. (2004). Suicide Prevention in Early Psychosis. In Psychological Interventions in Early Psychosis. John Wiley & Sons, Ltd.

REMEDIATION IN ADOLESCENT ONSET-RESULTS OF A RANDOMISED CONTROL TRIAL

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Background: People who first experience schizophrenia in adolescence have been suggested to have a poorer outcome which seems to be exacerbated by the presence of cognitive difficulties. These impairments have an impact on quality of life and particularly on social inclusion as they interfere with all aspects of education, training and social interaction. Cognitive Remediation Therapy (CRT) has been shown to be effective for those at later life stages but as yet there is no study investigating very early intervention. This randomised control study attempts to fill this gap in the evidence base. Aims: (i) To evaluate the efficacy of CRT in alleviating cognitive deficit compared to treatment as usual. (ii) To test whether CRT has a moderating or mediating effect on social and symptomatic functioning outcomes. Method: 40 young patients (average age 18 years) with recent onset schizophrenia and evidence of cognitive and social behavioural difficulties were randomised to two groups, one receiving CRT and the other standard care. Cognition (WCST, Six elements, Digit Span) and secondary outcomes (symptoms, social contacts and self esteem) were compared post-therapy and three months post treatment. Results: All cognitive tests showed an advantage for the CRT group but there was only a significant effect of cognitive remediation on the WCST (effect size 0.55). Normal score attainment was higher in the CRT group for WCST and Digit span. All improvements in cognitive function had an effect on social functioning. Therapy itself had a moderating effect on symptomatic outcome – i.e. it only improved in the context of therapeutic improvement on planning. Conclusions: Cognitive Remediation Therapy can ameliorate some of the cognitive deficits of schizophrenia and can therefore contribute to improved social functioning.

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