A Multi-Modality Approach to Medical Case Retrieval for Alzheimer's Disease

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Keywords: Alzheimer's Disease, Medical Case Retrieval, Multi-Modal, ADNI, TADPOLE.

Abstract: In this research, we evaluate medical case retrieval for AD on the bases of descriptors generated by combining different modalities (Magnetic Resonance Imaging (MRI) markers, Fluorodeoxy-glucose Positron Emission Tomography (FDG-PET) based measures, Cerebrospinal Fluid (CSF) protein levels, and Apolipoprotein-E (APOE) genotype and age as risk factors). We investigated whether they would provide complementary information aiming to improve medical case retrieval for AD. According to the obtained results, we concluded that this approach outperformed the retrieval results in the current reported research by gaining MAP value of 0.98 yet providing an efficient medical case retrieval for AD and keeping low dimensional feature vector.

1 INTRODUCTION

Alzheimer's Disease (AD), as an irreversible, progressive, neurodegenerative disorder, is one of the most common forms of dementia. It causes neuronal loss, spreading through different parts of the brain (Alzheimer's Association, 2022; Porsteinsson, 2021).

A vast amount of data is continuously generated as part of the medical cases related to AD in the clinical and research centers, containing variety of data types. Those include medical imaging markers such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Diffusion Tensor Imaging (DTI), biological markers, namely Apolipoprotein E (APOE) status, cerebrospinal fluid (CSF) measures, cognitive tests results etc., carrying powerful information. The necessity for their efficient organization, storage, and representation so to be able to provide appropriate and easier access to the medical cases, as well as, precise, efficient, and clinically meaningful retrieval, analysis, knowledge discovery, prediction and prognosis, is evident and still, a challenge and an open question (Meyer, 2019).

The rapid development in machine learning (ML) is having a profound impact in biomedical domain, opening space for applying ML algorithms to provide a solution to this challenge. This could support and improve the diagnostic and therapeutic processes.

The aim of this research is to provide more efficient and more comprehensive medical case representation that will enable more precise and clinically relevant medical case retrieval for AD. Considering that multi-modality markers may capture the variety of crucial aspects of the disease and its progression (Marinescu, 2020; Moguilner, 2022), we base the medical case representation on multiple modalities, not the single one, to investigate whether they can provide a complementary information contribute to better retrieval results. Hence, we combined information from MRI imaging markers, Fluorodeoxyglucose (FDG) - PET based markers, cognitive tests scores, CSF derived protein levels, as well as risk factors provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI, 2022), to represent each medical case.

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[*] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report (http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

Dineva, K., Kitanovski, I., Dimitrovski, I., Loshkovska, S. and Alzheimer's Disease Neuroimaging Initiative, .
A Multi-Modality Approach to Medical Case Retrieval for Alzheimer's Disease.
DOI: 10.5220/0011939800003414
In *Proceedings of the 16th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2023) - Volume 5: HEALTHINF*, pages 554-561
ISBN: 978-989-758-631-6; ISSN: 2184-4305

The paper is organized as follows. Section 2 provides the related work. The materials and methods are covered in Section 3. The experimental results and discussion are presented in Section 4. Section 5 contains the concluding remarks.

2 RELATED WORK

During the past years, AD has been intensively researched, in an attempt to ensure an early diagnosis, prognosis, and ultimately finding an appropriate therapy, including a cure for the disease (Marinescu, 2020b; Weber, 2021; Alzheimer's Association, 2022;). In some research, the traditional approach for feature extraction from the MRI is used, meaning that the descriptors are based directly on the visual image content (Vinutha, 2019; Chethan, 2020; Sagayam, 2021). Other research is using the domain knowledge to overcome the limitations of the traditional approach. In this regard, baseline images were used to estimate of the volumes of the brain structures, and cortical thickness of the cerebral cortex regions are calculated in (Trojacanec, 2015; Kruthika, 2019) or to calculate Spatial Pattern of Abnormality for Early detection of Alzheimer's Disease (SPARE-AD score) in (Trojacanec, 2017). On the other hand, longitudinal approach to estimate static features at multiple time points is used in (Trojacanec, 2015), and to estimate dynamic features for patients' descriptors was proposed in (Trojachanec, 2017). Combination of static, dynamic features, as well as the SPARE-AD index (Dineva, 2022) was evaluated for image retrieval for AD. With the aim to increase the early detection performance for AD, authors in (Kruthika, 2019) used pre-trained 3D-autoencoder, 3D Capsule Network, and 3D-Convolutional Neural Network.

Most of the current research is based on a single modality, mainly MRI features. To induce improvements in the current research, aiming to provide more precise and relevant medical case retrieval for AD, our research is focused on multi-modal medical case retrieval. For that purpose, we use multiple biomarkers, usually available as part of the medical cases for AD acquired during the examination period in the clinical centres. In fact, this research aims to evaluate a representation based on a combination of a variety of biomarkers, extracted from MRI, FDG-PET, CSF protein levels, and risk factors, such as APOE genotype and age.

Providing efficient and precise medical case retrieval for AD might be very beneficial from different aspects: (1) decision support by providing clinicians with powerful and relevant information at the right moment at the right place on the bases of the existing medical cases of other examined patients; (2) knowledge discovery from the large, continuously growing, medical databases by retrieving the most similar cases; (3) pattern discovery and understanding of the disease, providing new insights, biomarkers identification, and analysis of the disease progression; (4) assessment and analysis of the response to a possible therapy; (5) providing valuable knowledge for students, clinicians and scientists.

3 MATERIALS AND METHODS

3.1 Medical Case Retrieval for Alzheimer's Disease

The medical case retrieval process consists of generating a representation of the query medical case and all the medical cases previously stored in the database using the same representation technique. After that, the feature vector (descriptor) of the query medical case is compared to the descriptors of all the other medical cases. All the medical cases in the database are then sorted by similarity to the query, so that the most similar one is at the top. This sorted list of the database medical cases is the result of the retrieval. We used leave-one-out strategy because of the small number of patients used in the evaluation.

To calculate the distance between the medical case descriptors, we used Manhattan and Canberra distance (Cha, 2007), chosen on an experimental basis because they led to the best retrieval results compared to several other distances such as Euclidean, Chebyshev, Square Euclidean distance, Bray-Curtis dissimilarity and Cosine similarity.

To evaluate the proposed strategy in this research, we used the standard evaluation metric MAP (Mean Average Precision) for quantitative measurement of the retrieval performance.

3.2 Medical Case Representation

According to the recent research regarding AD, a combination of different kinds of biomarkers may provide complementary and powerful information (Gupta, 2019; Marinescu, 2020b), possibly enriching medical case representation. Thus, we combine different biomarkers suggested by the TADPOLE challenge (TADPOLE, 2022; Marinescu, 2018) including MRI ROI derived measures, FDG-PET based measures, CSF protein levels, APOE status, and age, to represent the medical cases and we base the medical case retrieval on multimodal descriptors.

3.2.1 Magnetic Resonance Imaging

Regarding MRI measurements, we used dynamic and static measures of the brain structures, as well as SPARE-AD score, following the strategy used in (Dineva, 2022) and the fully automated longitudinal pipeline from the FreeSurfer version 5.3 (FreeSurfer, 2022; Reuter, 2012). According to the previous research (Trojachanec, 2017), percent change with respect to the value obtained from the linear fit at baseline (PCfit) and symmetrized percent change (SPC) of the volumetric measures of the cortical and subcortical regions have proven to be most powerful in longitudinal MRI retrieval for AD. Volumes and cortical thickness (static) measurements form the third and fourth time point (12- and 24- month follow-up), led to the best retrieval precision (Trojacanec, 2015). We also used SPARE-AD score (Davatzikos, 2009; Trojacanec, 2017), available in ADNI database.

In this research, we used a combination of PCfit or SPC of the volumetric measures (dynamic features), static volumetric and cortical thickness measurements at 12- and 24- month follow-ups, and SPARE-A, because, they provided superior results in longitudinal retrieval for AD (Dineva, 2022).

3.2.2 Fluoro-Deoxyglucose (FDG) PET

Molecular processes which are thought to be some of the earliest to become abnormal due to AD (Marinescu, 2020b), can be represented by PET. (Jack Jr, 2018). FDG-PET measures of angular, temporal, and posterior cingulate, are available on ADNI website and used in this research.

We also use values for two global indices that were recently added to ADNI: (1) hypometabolic convergence index (HCI) (Chen, 2011), and (2) statistical region of interest (sROI) (Chen, 2010; Van Dyck, 2019). HCI is a cross-sectional measure, indicating the extent to which the pattern and magnitude of hypometabolism for a given patient matches that of patients with AD, while, $sROI_{AD}$ was established longitudinally. representing the standard uptake value ratio between those regions affected by the disease and the regions spared by AD.

In contrast, measures of the amyloid-beta load in the brain (AV45 PET) and tau load in the brain (AV1451 PET), are not available for most of the subjects, hence, not used in this research.

3.2.3 Main Cognitive Tests

To be able to measure cognitive decline in patients, cognitive test is administered by medical expert as one of the latest indicators of AD, (Jack, 2013).

Regarding the cognitive tests results, as recommended by the TADPOLE challenge, we used the following: Clinical Dementia Rating Sum of Boxes (CDRsb), Alzheimer's Disease Assessment Scale (we used both ADAS11, and ADAS13 results), Mini-Mental State Examination (MMSE), and Rey Auditory Verbal Learning Test (RAVLT) (Marinescu, 2020b). Regarding RAVLT test results, we used the following features: RAVLT immediate, RAVLT learning, RAVLT forgetting, and RAVLT forgetting percent. The results of all cognitive tests are available through the ADNI database.

3.2.4 CSF Biomarkers

Representing the concentration of amyloid-beta and tau abnormal proteins, not related to any particular part of the brain, CSF based measurements are powerful AD indicator, reflecting abnormalities many years before symptom onset (Marinescu, 2020a; Marinescu, 2020b). CSF biomarkers are recommended by the TADPOLE challenge to be used as early AD indicators (Marinescu, 2018), and therefore we also use them in our research as amyloid-beta level in CSF (ABETA), tau level (TAU), and phosphorylated tau level (PTAU).

3.2.5 Risk Factors

APOE ε4 is found to be very powerful genetic risk factor lowering the age of onset AD (Marinescu, 2018; Gupta, 2019). Considering that the older subjects are more likely to develop AD, another important risk factor is the age (Marinescu, 2020b), and following the recommendations from the TADPOLE challenge, we used exactly these two.

3.3 Data

In this research, we used the data provided by ADNI, acquired for the participants from the standardized list from ADNI-1. The aim of ADNI is to enable research that will provide an answer to the question whether combining imaging markers and biological markers, along with neuro-psychological and clinical assessments, may indicate the presence and allow assessment of the progression of MCI and AD. Following the main goal of ADNI, we are investigating whether multi-modal markers may lead to a more precise and efficient medical case retrieval.

We also followed recommendations summarized for the TADPOLE challenge, in terms of different data modalities such as: (1) MRI, (2) main cognitive tests, (3) PET, (4) DTI, (5) CSF biomarkers, and (6) risk factors and demographic information.

We applied several levels of selection to be able to keep fully complete dataset, thus reducing the influence of the missing data or the algorithm used to cope with the missing data on the retrieval results.

Firstly, to provide the possibility of fair comparison with other research about medical case retrieval for AD, we selected the subjects that belong to AD or normal control (NL) group and have available MRI scans acquired at four time points, at baseline, and the 6-, 12-, and 24-month follow-ups. Thus, we obtained a total of 267 patients from the standardized list, 168 AD, and 99 NL.

After the MRI processing, we selected only the cases without global or regional failures in all time points (153 patients in total, 41 AD and 112 NL), to ensure a complete automatic processing and exclude the necessity to involve a medical expert.

The cognitive tests results were not available for three more patients, ending up with 150 patients in total, 39 AD and 111 NL (subset 1). Significant number of missing data were detected regarding FDG PET measures, resulting in 68 patients, 17 AD, 47 NL (subset 2). CSF biomarkers were available for 85 patients, 24 in AD group, 61 in NL group (subset 3).

3.4 Experimental Setup

To be able to obtain fully complete dataset for the evaluation, each of the evaluations was conducted using one of the subsets listed in subsection 3.3. The goal is to provide a fair comparison between different medical case representations, not influenced by the missing data or the algorithm used to overcome the problem of missing data. Hence, in this research, we performed three separate evaluations, described in the following subsections (3.4.1 – 3.4.3). To reduce the dimension of the descriptor, select the most relevant features, we also applied Correlation-based Feature Selection (CFS) algorithm (Hall, 2003), chosen on an experimental basis. The optimal feature subset was determined separately in case of each query.

Because most of the current research addressing the problem of medical case retrieval for AD is based on MRI (Trojacanec, 2015; Trojachanec, 2017, Trojacanec 2017; Kruthika, 2019a; Kruthika, 2019b, Vinutha, 2019; Chethan, 2020), in each evaluation scenario we used the case in which the descriptor contains only MRI features for reference.

3.4.1 MRI Measures, Cognitive Scores, and Risk Factors

The first evaluation was performed on using the scenarios in Table 1, based on the following features:

- MRI (combination of dynamic (VolPCfit or VolSPC), static measures (Vol34+CT34), and SPARE-AD)
- Cognitive tests (combination of CDRsb, ADAS11, ADAS13, MMSE, RAVLT immediate, RAVLT learning, RAVLT forgetting, and RAVLT forgetting percent)
- Risk factors (APOE ε4 and Age)

Table 1: Scenarios Based on MRI Measures, Cognitive Tests and Risk Factors.

Scenario	Descriptor
S1.1	MRI_VolPCfit+Vol34+CT34+SPARE-AD
S1.2	MRI_VolSPC+Vol34+CT34+SPARE-AD
S1.3	S1.1+CognitiveT
S1.4	S1.2+CognitiveT
S1.5	S1.1+RiskF
S1.6	S1.2+RiskF
S1.7	S1.1+Cognitive + RiskF
S1.8	S1.2+Cognitive + RiskF

3.4.2 MRI, FDG PET Measures, Cognitive Scores, and Risk Factors

The second evaluation was performed on the subset 2, following the scenarios given in Table 2 on the bases of the following features**:**

- MRI (combination of dynamic (VolPCfit or VolSPC), static measures (Vol34+CT34), and SPARE-AD),
- Cognitive tests scores (CDRsb, ADAS11, ADAS13, MMSE, RAVLT immediate, RAVLT learning, RAVLT forgetting, and RAVLT forgetting percent), and
- Risk factors (APOE ε4 and Age)
- FDG PET measurements (FDG PET, HCI, $sROI_{AD}$, for each of the following visits, baseline, 6th, 12th and 24th month follow-ups)

Table 2: Scenarios Based on MRI Measures, FDG-PET measures, Cognitive Tests and Risk Factors.

Scenario	Descriptor
S2.1	MRI_VolPCfit+Vol34+CT34+SPARE-AD
S2.2	MRI_VolSPC+Vol34+CT34+SPARE-AD
S2.3	S2.1+FDG_PET+HCI+$sROI_{AD}$
S2.4	S2.2+FDG_PET+HCI+$sROI_{AD}$
S2.5	S2.1+FDG_PET+HCI+$sROI_{AD}$+RiskF
S2.6	S2.2+FDG_PET+HCI+$sROI_{AD}$+RiskF
S2.7	S2.1+FDG_PET+HCI+$sROI_{AD}$ +CognitiveT
S2.8	S2.2+FDG_PET+HCI+$sROI_{AD}$ +CognitiveT
S2.9	S2.3+Cognitive + RiskF
S2.10	S2.4+Cognitive + RiskF

3.4.3 MRI Measures, Cognitive Scores, Risk Factors, and CSF Biomarkers

The influence of the CSF biomarkers ABETA, TAU, and PTAU to the retrieval performance is mainly evaluated through the evaluation scenarios listed in Табле 3. The following features are used to generate the feature vector in these scenarios:

- MRI (combination of dynamic (VolPCfit or VolSPC), static measures (Vol34+CT34), and SPARE-AD),
- Cognitive tests (combination of CDRsb, ADAS11, ADAS13, MMSE, RAVLT immediate, RAVLT learning, RAVLT forgetting, and RAVLT forgetting percent)
- Risk factors (APOE ε4, Age)
- CSF markers (ABETA, TAU, and PTAU)

Table 3: Scenarios Based on MRI Measures, FDG-PET measures, Cognitive Tests and Risk Factors.

Scenario	Descriptor
S3.1	MRI_VolPCfit+Vol34+CT34+SPARE-AD
S3.2	MRI_VolSPC+Vol34+CT34+SPARE-AD
S3.3	S3.1+RiskF
S3.4	S3.2+RiskF
S3.5	S3.1+CognitiveT
S3.6	S3.2+CognitiveT
S3.7	S3.1+CFS
S3.8	S3.2+CFS
S3.9	S2.3+CognitiveT+CFS
S3.10	S2.4+CognitiveT+CFS

4 EXPERIMENTAL RESULTS AND DISCUSSION

In this section, results of the medical case retrieval evaluated through the three evaluation scenarios described in subsection 3.4 are provided and discussed.

4.1 Results Based on MRI, Cognitive Scores, and Risk Factors

Results of the medical case retrieval based on a combination of MRI imaging markers, cognitive tests scores as well as risk factors, are given in Table 4. This table lists the MAP values for each scenario in case of two distances for calculation of the similarity between the query patient's descriptor and all the patients' descriptors stored in the database, Canberra and Manhattan. For each subset, we include the results for MRI based descriptors proposed in (Dineva, 2022) for reference.

Table 4: Evaluation of the Medical Case Representation Based on MRI ROI Measures and Cognitive Tests – value of MAP.

Descriptor	MAP (MD)	MAP (CD)
S1.1:MRI_VolPCfit+Vol34+CT34 +SPARE-AD	0.88	0.86
S1.2:MRI_VolSPC+Vol34+CT34+ SPARE-AD	0.88	0.86
S1.3:S1.1+CognitiveT	0.95	**0.97**
S1.4:S1.2+CognitiveT	0.95	**0.97**
S1.5:S1.1+RiskF	0.87	0.86
S1.6:S1.2+RiskF	0.88	0.86
S1.7:S1.1+Cognitive + RiskF	0.95	0.97
S1.8:S1.2+Cognitive + RiskF	0.95	0.97

Table 4 shows significant improvement of the value of MAP when cognitive tests are included in the descriptor (S1.3 i S1.4). The MAP value considering these scenarios increased to 0.95 in case of Manhattan distance, while in case of Canberra distance, the MAP is 0.97, meaning that the inclusion of the cognitive tests provides great improvement. Despite that Canberra distance is a weighted version of the Manhattan distance, we believe that its nature to be more robust to outliers, but very sensible to values around 0, which might happen in the case with cognitive scores values, led to these results.

Additional benefit in the case of the combination of MRI with the cognitive test scores is that the dimension of the descriptor is lower than in the case of MRI-based descriptor. In fact, in S1.3 and S1.4 scenarios, in most of the cases only 28-29 features were selected, while in S1.1 and S1.2 scenarios, 34-40 features were selected in most of the cases. From the cognitive tests taken into consideration in this research, CDR-SB, ADAS_13, MMSE, RAVLT (5_sum), RAVLT (perc. forgetting), and FAQ were selected in almost all cases as most relevant features.

On the other side, the combination of the MRI imaging markers and risk factors such the Age and APOE status (S1.5 and S1.6 scenarios), did not induce any improvement. In only 19 cases the age was selected to be a part of the descriptor, while the APOE status was not selected at all.

Similarly, the influence of the risk factors in terms of improvement of medical case retrieval for AD is not the case also when all measures were concatenated (S1.7 and S1.8 scenarios).

4.2 Results Based on MRI, FDG PET, Cognitive Scores, and Risk Factors

Results of the evaluation for the descriptors S2.1-S2.10 using the subset 2 are given in Table 5.

Table 5: Evaluation of the Medical Case Representation Based on MRI ROI Measures, Cognitive Tests, Risk Factors, and FDG PET measures – value of MAP.

Descriptor	MAP (MD)	MAP (CD)
S2.1:MRI_VolPCfit+Vol34+CT34+ SPARE-AD	0.87	0.84
S2.2:MRI_VolSPC+Vol34+CT34+S PARE-AD	0.87	0.84
S2.3:S2.1+FDG_PET+HCI+sROI$_{AD}$	0.88	0.84
S2.4:S2.2+FDG_PET+HCI+sROI$_{AD}$	0.88	0.84
S2.5:S2.1+FDG_PET+HCI+sROI$_{AD}$ +RiskF	0.89	0.82
S2.6:S2.2+FDG_PET+HCI+sROI$_{AD}$ +RiskF	0.89	0.82
S2.7:S2.1+FDG_PET+HCI+sROI$_{AD}$ +CognitiveT	**0.98**	**0.98**
S2.8:S2.2+FDG_PET+HCI+sROI$_{AD}$ +CognitiveT	**0.98**	**0.98**
S2.9:S2.3+Cognitive + RiskF	**0.98**	**0.98**
S2.10:S2.4+Cognitive + RiskF	**0.98**	**0.98**

According to the results, we came to the conclusion that FDG-PET based measures provide a slight increase of the MAP value (gaining a value of 0.88) when Manhattan distance is used to calculate the similarity. It should be emphasized that in this case, from the used FDG-PET measures, HCI at 6- and 24-month follow-up, as well as sROI$_{AD}$ at 12- and 24-month follow-ups were selected, and the descriptor was long 36 features in most of the cases.

Moreover, the inclusion of the risk factors APOE and age also led to an improvement when evaluation was performed on the subset 2 with Manhattan distance, by selecting the age as a relevant feature, but not the APOE. The dimension of the feature vector in most of the cases was 21 features.

Similarly like in the case of the evaluation based on the subset 1, the cognitive tests scores provided significant improvement of the retrieval precision in the case on both similarity measures. But the combination of all the features considered in this evaluation, did not contribute to additional improvement. In most of the cases, 23 features were selected.

4.3 Results Based on MRI, Cognitive Scores, Risk Factors, and CSF

Table 6 contains the results of the performed evaluation for the descriptors S3.1-S3.10. Their influence on the retrieval results is evaluated using the subset 3. It is selected so that contains fully competed data for all of the measures evaluated in this scenario (MRI, cognitive tests, risk factors, and CSF biomarkers: ABETA, TAU, and PTAU)

Table 6: Evaluation of the Medical Case Representation Based on MRI ROI Measures, Cognitive Tests, Risk Factors, and CSF biomarkers – value of MAP.

Descriptor	MAP (MD)	MAP (CD)
S3.1:MRI_VolPCfit+Vol34+CT34 +SPARE-AD	0.86	0.87
S3.2:MRI_VolSPC+Vol34+CT34+ SPARE-AD	0.86	0.87
S3.3:S3.1+RiskF	0.86	0.87
S3.4:S3.2+RiskF	0.86	0.87
S3.5:S3.1+CognitiveT	**0.96**	**0.98**
S3.6:S3.2+CognitiveT	**0.96**	**0.98**
S3.7:S3.1+CFS	0.86	0.88
S3.8:S3.2+CFS	0.86	0.88
S3.9:S2.3+CognitiveT+CFS	**0.96**	**0.98**
S3.10:S2.4+CognitiveT+CFS	**0.96**	**0.98**

The results showed that CFS biomarkers led to a slight improvement of the medical case retrieval precision. In almost all of the cases, ABETA level was selected automatically by the algorithm, and TAU and PTAU values were selected in fewer cases. In most of the cases, the dimension of the descriptor was 20 features.

Following the trend of the evaluation results obtained on the subset 1 and 2, the combination with the cognitive tests scores provided the best MAP.

4.4 Discussion

Instead of focusing on one modality, i.e. one type of data, usually MRI, this research takes into consideration multi-modal medical case representation appropriate to AD, and evaluates the medical case retrieval in terms of different information contained in the medical case descriptor. Following the TADPOLE recommendations, and the considering that the reported research about medical case retrieval for AD (mostly focused on information extracted from the MRI images, cross-sectionally or longitudinally) (Trojacanec, 2015; Trojachanec, 2017, Trojacanec 2017; Kruthika, 2019a; Kruthika, 2019b, Vinutha, 2019; Chethan, 2020; Dineva, 2022) and less on other modalities (Gupta, 2019), we performed a wide evaluation on different kinds of medical case representations.

We performed the evaluation using fully complete datasets, to be able to provide fair evaluation not influenced by the missing data or the strategy used to cope with the missing data. But, on the other hand, trying to provide fully compete datasets, we ended up with small subsets for some of the evaluation scenarios and unbalanced classes (subset 2 and 3). In this regards, FDG-PET measures were available for a

very small number of patients (64), while CSF measures for only 85 patients from ADNI 1.

According to the obtained results, with this research we got significant improvement over the current results in the reported research (Trojacanec, 2015; Trojachanec, 2017, Trojacanec 2017; Kruthika, 2019a; Kruthika, 2019b, Vinutha, 2019; Chethan, 2020, Gupta, 2019. In fact, cognitive tests scores significantly increased the MAP in all three evaluation subsets, leading to MAP value of 0.98. Among the cognitive scores, CDR-SB, ADAS_13, MMSE, RAVLT (5_sum), RAVLT (perc. Forgetting), and FAQ were most frequently selected features. Additionally, the FDG–PET based measures (among which HCI at 6- and 24- month, and $sROI_{AD}$ at 12- and 24- month follow-ups were automatically selected in most of the cases) and the age as a risk factor, provided a slightly better performance or no improvement at all. Regarding the CSF, the most frequently selected feature was ABETA level, but did not significantly improved the retrieval results.

It should be emphasized that the features (of a given modality) selected in most of the cases for a given scenario, were similarly selected through all the evaluations for which they were available. Despite the fact that most of them are significant markers for AD, this frequent automatic selection makes them stable and appropriate to be used to represent medical cases for AD.

The strategy for medical case representation used in this research reflects the current condition of the brain / atrophy, the degree of degeneration and the progression of the disease, the nerve cells damage and the brain metabolism, covering all the stages of the disease in the medical case retrieval for AD, using the entire cascade of disease indicators. Moreover, it can be easily adopted for addressing specific aspects of other neurological disease. Additionally, considering the low number of features in the descriptor and high precision at the same time, this strategy can be easily adopted and integrated as an efficient and clinically relevant decision support in the standard practice and to assist medical experts. However, the challenging part that needs to be addressed and involved in the clinical workflow is rapid information processing regarding different modalities for the a patient currently examined (all other medical cases may be processed off-line and stored in the database).

5 CONCLUSIONS

This research investigated the medical case retrieval for AD based on different modalities of data. For this purpose, we made a research in order to find a relevant and efficient representation of the medical case that will provide precise, efficient and clinically relevant retrieval. Particularly, we focus our research on multi-modal patient representation including the following kinds of data: structural MRI, FDG-PET based measures, CSF protein levels, and APOE genotype and age as risk factors.

According to the performed evaluation, we outperformed the results gained by the other research on medical case retrieval for AD, which is mostly based on single modality. We also provided a good basis for further investigation and analysis in this domain, by using a comprehensive approach. In the future, we are going to extend the research to a wider dataset, including more subjects and more phases of the disease (early-MCI, late-MCI, …). We are also are going to investigate deep learning methods in terms of feature engineering.

ACKNOWLEDGEMENT

Data collection and sharing for the research in this paper was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012).

REFERENCES

Alzheimer's Association, 2022. 2022 Alzheimer's disease facts and figures. [https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf] Accessed: 30.10.2022.

Alzheimer's Disease Neuroimaging Initiative: ADNI, 2017. [https://adni.loni.usc.edu/] Accessed: 5.11.2022.

Cha, S. H. (2007). Comprehensive survey on distance/similarity measures between probability density functions. City, 1(2), 1.

Chen, K., Langbaum, J. B., Fleisher, A. S., Ayutyanont, N., Reschke, C., Lee, W., ... & Alzheimer's Disease Neuroimaging Initiative. (2010). Twelve-month metabolic declines in probable Alzheimer's disease and amnestic mild cognitive impairment assessed using an empirically pre-defined statistical region-of-interest: findings from the Alzheimer's Disease Neuroimaging Initiative. Neuroimage, 51(2), 654-664.

Chen, K., Ayutyanont, N., Langbaum, J. B., Fleisher, A. S., Reschke, C., Lee, W., ... & Reiman, E. M. (2011). Characterizing Alzheimer's disease using a hypometabolic convergence index. Neuroimage, 56(1), 52-60.

Chethan, K., & Bhandarkar, R. (2020). Hybrid Feature Extraction Technique on Brain MRI Images for Content-Based Image Retrieval of Alzheimer's Disease. In Advances in Communication, Signal Processing, VLSI, and Embedded Systems (pp. 127-141). Springer, Singapore.

Davatzikos, C., Xu, F., An, Y., Fan, Y. and Resnick, S.M (2009). Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: the SPARE-AD index. Brain, 132(8), 2026-2035.

Dineva, K. T., Kitanovski, I., Dimitrovski, I., & Loshkovska, S. (2022). Combining Static and Dynamic Features to Improve Longitudinal Image Retrieval for Alzheimer's Disease. In International Conference on ICT Innovations (pp. 107-120). Springer, Cham.

FreeSurfer. [https://surfer.nmr.mgh.harvard.edu/]. Accessed: 21.10.2022.

Gupta, Y., Lama, R. K., Kwon, G. R., & Alzheimer's Disease Neuroimaging Initiative. (2019). Prediction and classification of Alzheimer's disease based on combined features from apolipoprotein-E genotype, cerebrospinal fluid, MR, and FDG-PET imaging biomarkers. Frontiers in computational neuroscience, 13, 72.

Hall, M. A., & Holmes, G. (2003). Benchmarking attribute selection techniques for discrete class data mining. IEEE Transactions on Knowledge and Data engineering, 15(6), 1437-1447.

Jack Jr, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... & Silverberg, N. (2018). NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia, 14(4), 535-562.

Kruthika, K. R., Maheshappa, H. D., & Alzheimer's Disease Neuroimaging Initiative. (2019a). Multistage classifier-based approach for Alzheimer's disease prediction and retrieval. Informatics in Medicine Unlocked, 14, 34-42.

Kruthika, K. R., Maheshappa, H. D., & Alzheimer's Disease Neuroimaging Initiative. (2019b). CBIR system using Capsule Networks and 3D CNN for Alzheimer's disease diagnosis. Informatics in Medicine Unlocked,14,59-68.

Marinescu, R. V., Oxtoby, N. P., Young, A. L., Bron, E. E., Toga, A. W., Weiner, M. W., ... & Alexander, D. C. (2018). Tadpole challenge: Prediction of longitudinal evolution in Alzheimer's disease. arXiv preprint arXiv:1805.03909.

Marinescu, R. V., Oxtoby, N. P., Young, A. L., Bron, E. E., Toga, A. W., Weiner, M. W., ... & Alexander, D. C. (2020a). The alzheimer's disease prediction of longitudinal evolution (TADPOLE) challenge: Results after 1 year follow-up. arXiv preprint arXiv:2002.03419.

Marinescu, R. V. (2020b). Modelling the Neuroanatomical Progression of Alzheimer's Disease and Posterior Cortical Atrophy. arXiv preprint arXiv:2003.04805.

Meyer, P.F., Tremblay-Mercier, J., Leoutsakos, J., Madjar, C., Lafaille-Maignan, M.É., Savard, M., Rosa-Neto, P., Poirier, J., Etienne, P., Breitner, J. and PREVENT-AD research group (2019). INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease. Neurology, 92(18), e2070-e2080.

Moguilner, S., Birba, A., Fittipaldi, S., Gonzalez-Campo, C., Tagliazucchi, E., Reyes, P., ... & Ibáñez, A. (2022). Multi-feature computational framework for combined signatures of dementia in underrepresented settings. Journal of Neural Engineering, 19(4), 046048.

Porsteinsson, A.P., Isaacson, R.S., Knox, S., Sabbagh, M.N. and Rubino, I. (2021) Diagnosis of early alzheimer's disease: Clinical practice in 2021. *The Journal of Prevention of Alzheimer's Disease*, 8(3), 371-386.

Reuter, M., Schmansky, N.J., Rosas, H.D. and Fischl, B (2012). Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage, 61(4), 1402-1418.

The Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge [https://tadpole.grand-challenge.org/] Accessed: 20.11.2022.

Trojacanec, K., Kitanovski, I., Dimitrovski, I. and Loshkovska, S. October. Medical image retrieval for Alzheimer's disease using data from multiple time points. In International Conference on ICT Innovations, pp. 215-224. Springer, Cham (2015).

Trojacanec, K., Kalajdziski, S., Kitanovski, I., Dimitrovski, I., Loshkovska, S. and Alzheimer's Disease Neuroimaging Initiative. Image Retrieval for Alzheimer's Disease Based on Brain Atrophy Pattern. In International Conference on ICT Innovations, pp. 165-175. Springer, Cham (2017).

Trojachanec, K., Kitanovski, I., Dimitrovski, I. and Loshkovska, S. Longitudinal brain MRI retrieval for Alzheimer's disease using different temporal information. IEEE Access, 6, 9703-9712 (2017).

Van Dyck, C. H., Nygaard, H. B., Chen, K., Donohue, M. C., Raman, R., Rissman, R. A., ... & Strittmatter, S. M. (2019). Effect of AZD0530 on cerebral metabolic decline in Alzheimer disease: a randomized clinical trial. JAMA neurology, 76(10), 1219-1229.

Vinutha, N., Sandeep, S., Kulkarni, A. N., Shenoy, P. D., & Venugopal, K. R. (2019, March). A Texture based Image Retrieval for Different Stages of Alzheimer's Disease. In 2019 IEEE 5th International Conference for Convergence in Technology (I2CT) (pp. 1-5). IEEE.

Weber, C. J., Carrillo, M. C., Jagust, W., Jack Jr, C. R., Shaw, L. M., Trojanowski, J. Q., ... & Weiner, M. W. (2021). The Worldwide Alzheimer's Disease Neuroimaging Initiative: ADNI‐3 updates and global perspectives. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 7(1), e12226.

Jack Jr, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., ... & Trojanowski, J. Q. (2013). Update on hypothetical model of Alzheimer's disease biomarkers. Lancet neurology, 12(2), 207.