Differential Diagnosis of Alzheimer's Disease and Mild Cognitive Impairment Using the Structural and Diffusion MRI Features of the Brain

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Abstract

Introduction: Accurate, fast, and reliable diagnosis of Alzheimer's Disease (AD) from Mild Cognitive Impairment (MCI) is crucial for prescribing proper treatment and prevention of disease progression. At first glance, structural and diffusion MRI images, are affected by neurodegenerative proceedings in AD and MCI. In this study, we are looking for the most effective features to detect and differentiate between healthy normal control (NC), AD, and MCI groups by non-invasive Magnetic Resonance Imaging (MRI) method and propose the automatic multi-class classification using the structural and diffusion MRI Features of the brain.

Methods: The structural and diffusion MRI data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database on three groups including AD, MCI, and NC subjects. Four famous classification models of machine learning were used to discover the best classification as a diagnostic tool for separation of the NC, AD and MCI groups.

Results: Taken together, our results from this study lead to classify three groups for differentiation between the NC group and patients with MCI and AD, with average accuracy factor 89.9% for Support Vector Machine (SVM) and 91.9% for Artificial Neural Network (ANN) using selected features.

Conclusions: Top 9 regions repetitive of WM based on four types of features are the caudate nucleus, corpus callosum, hippocampus, para hippocampus, temporal gyrus, putamen nucleus, cingulate gyrus, the region of 36 and 3 Brodmann. Therefore, these regions could be considered for identifying, monitoring, and future drug trials that could target this brain region to AD and MCI Management.

1. Introduction

Alzheimer's disease (AD) is the most common kind of dementia which is considered a progressive neurodegenerative disorder and it affects millions of people in the world. Disability to remember is one of the first signs of AD. Although, memory problems can be formed by Mild cognitive impairment (MCI). The AD consists of four stages: very early signs and symptoms, Mid AD, Moderate and, Severe AD. The first stage of AD is similar to MCI, also, with the available diagnostic tools people often are diagnosed in the mid AD stage. About eight of every ten elderly people with MCI go on to expand AD within 7 years; However, exactly unclear why some people with MCI do not advance to AD (1).

Neuroimaging technologies, such as magnetic resonance imaging (MRI) or positron emission tomography (PET) are useful for AD diagnosis by detecting structural or functional markers at the early stage.(1) MRI scans use magnetic fields and radio waves for the detection of the hydrogen atoms in tissues; However, PET uses radionuclides nuclear material for monitoring functional brain (2).

Thus, the MRI scan is a more Non-invasive method than the PET scan. In the past, studies based on structural magnetic resonance imaging (sMRI), significant results have been achieved to distinguish between healthy normal control (NC) from AD groups with the help of machine learning. Nevertheless,

conventional MRI is not able to highlight the construction of white matter (WM) regions (3). Extracted Parameters of segmented areas in SMRI include morphometry features such as volumetric and thickness measurements, or curvature of regions, and features based on pixel intensity of regions (4).

Diffusion tensor imaging (DTI) is an MRI scan protocol that detects the random Brownian motion of water molecules in the body. This protocol identifies neural pathways by using data reconstruction models. In particular, DTI is an excellent tool for the identification of microstructural white matter degeneration in Alzheimer's disease (5, 6).

DTI data reconstruction can be divided into two categories: the free-model and model-based methods.

One of the models of reconstruction is based on diffusion tensor imaging (DTI) (7, 8). Features derived from DTI inclusive: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and, radial diffusivity (RD) and these mentioned features are obtained from diffusion matrix eigenvectors and eigenvalues. On the other, one of the free model reconstruction methods such as Generalized Q sampling Imaging (GQI) and Q-space diffeomorphic reconstruction (QSDR) is no assumption on the distribution. The QSDR method reconstructs data in the MNI space (9). Extractable features from QSDR methods include quantitative anisotropy (QA) related to tract compactness, the isotropic value (ISO) related to free water diffusion and, restricted diffusion imaging (RDI) (10).

In the DTI reconstruction model, the fractional anisotropy (FA) parameter was measured for each voxel of the whole brain volume and the FA map was performed for each subject. FA generally is considered as an index of structural brain connection because it is sensitive to the axonal structure. Important factors affecting FA are myelin of axons. Subsequently, an analytical relation is provided in the reconstruction based on the GQI model. The calculation is not a numerical estimation but it is a direct calculation with using simple matrix multiplication. So the GQI is more accurate in terms of its mathematical form due to numerical estimation. Also, GQI can achieve with a linear and nonlinear transformation to reconstruction data in the T1W or MNI space. QSDR provides connectometry analysis and template construction. QA is more reliable than FA simply because it is less affected by the inflammation and edema that is due to the existence of the independent metric called ISO, which is calculated and extracted in this model. The QA factor is more sensitive to Pathological changes in the neurons. DSI Studio uses a voxel with water-free diffusion to calibrating the QA factor for ensuring better repeatability and compatibility (10–12).

Recently, several studies have demonstrated that the features obtained from diffusion and structural measures contribute useful information for more accurate classification (13–16).

In this study, the parameters extracted from brain images were used as features for classification.

After extracting the features, the feature selection step is performed. Feature selection is a way of pre-processing features before entering the machine learning phase. It is a process of picking out a proper subset of all features so that the feature space is optimally decreasing matching to a specified evaluation criterion (17). The importance of feature selection is in eliminating idle and unused features, enhancing

performance in machine learning models, improving learning efficiency such as predictive accuracy and raising the comprehensibility of learned conclusion (18, 19).

With the advancement of technology in recent years which consists of exponential growth in computing power, big data processing technologies, accessibility to large clinical data sets using electronic health records, and machine learning in medicine can lead to more precise diagnostic algorithms and individualize patient treatment (20). Machine learning is mathematical focuses on the predictive performance and generalization of models around cross-validation and iterative improvement of the algorithm (18, 21). In this study, we used four classified models for diagnosis which included: Decision Tree (DT), k-Nearest Neighbors (KNN), Support Vector Machines (SVM) and, Artificial Neural Networks (ANN) and subsequently performed classification into three groups AD/MCI/NC simultaneously.

Furthermore, we investigated which type of extracted features that were measured with MRI by using machine learning models can use as a tool for the diagnosis of normal aging from MCI and AD.

2. Materials And Methods

2.1. Data acquisition and preprocessing

Participants in this study were selected from the Alzheimer's disease neuroimaging initiative (ADNI) database (<http://www.loni.ucla.edu/ADNI/>). The images that were used for analyzing included: diffusion-weighted, T1 weighted, T2 weighted and, FLAIR scans of 72 participants. Subjects including 24 NC (Male (M)/Female (F) = 11/13, mean age = 75.32 ± 8.31 year, Mini-Mental State Examination)MMSE(= 29.04 ± 1.23), 24 AD patients (M/F = 16/8, mean age = 76.47 ± 8.23 year, MMSE = 20.17 ± 4.97) and, 24 MCI (M/F = 12/12, mean age = 76.04 ± 8.65 year, MMSE = 26.70 ± 2.07). Two MCI levels (early or late) are generally defined according to the Wechsler Memory Scale Logical Memory II(22). In this paper, we considered early and late groups that each of them contains 12 subjects to create MCI. NC subjects do not have a history of neurological or psychiatric disorders; subjects with AD who have signatures of the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) criteria which means AD's disorder. Also, MCI subjects have symptoms a subjective memory concern; However, they were without any significant disability in other cognitive domains (they follow everyday activities with any signs of dementia). All scans that used in this study, were acquired by a 3T MRI Scanner (GE Medical Systems scanner). We collected structural MRI from all participants: T1- SPGE: TR=6.9 ms, TE=2.8 ms, slice thickness=1.2 mm; T2: TR=650 ms, TE=20 ms, slice thickness=4 mm; and FLAIR: TR=11000ms, TE=147.9 ms, slice thickness=5 mm; also, we collected diffusion MRI from all participants: matrix size = $256 \times 256 \times 46$; voxel size = $1.36 \times 1.36 \times 2.7$ mm; the sequence contained 5 images acquired without diffusion weighting and with diffusion weighting along 41 non-collinear directions ($b = 1000$ s/mm²).

2.2. Structural MRI processing

We performed the processing of morphometrically and intensity level assessment by using the FreeSurfer image analysis pipeline (23) (version 6 on ubuntu 16.04) based on T1 and T2-FLAIR weighted images. The results of this process were divided into two parts that consisted of subcortical and cortical. In the first place, we performed the subcortical processing steps which included: volume, intensity pixel value, range of intensity, maximum, and minimum intensity pixel value in each region of atlas available in FreeSurfer (Desikan-Killiany atlas). In the second place, the measurements related to cortical were done which included: thickness, surface area, gray matter volume and the curve in each region of Desikan-Killiany atlas from the right and left brain hemispheres. Part of the FreeSurfer pipeline conforms to the MRI scans to $1 \times 1 \times 1 \text{ mm}^3$ resolution and corrects for bias field using the non-parametric non-uniform intensity normalization (N3) algorithm.

Briefly, this processing includes removal of non-brain tissue, automated Talairach transformation, surface deformation, tessellation of the grey matter-white matter boundary, topology correction, and segmentation (24, 25).

Finally, after doing all the processing in this section, 496 features were extracted from every subject and saved in CSV format.

2.3 Diffusion MRI processing

The diffusion MRI data were preprocessed using DSI-Studio software (developed by Fang-Cheng Yeh from the Advanced Biomedical MRI Lab, National Taiwan University Hospital, Taiwan, Supported by Fiber Tractography Lab, University of Pittsburgh, and made available at <http://dsistudio.labsolver.org/Download/>). For skull stripping and filtering the background region, we used the masks provided by DSI-Studio. Before DTI parameter measurement, head motion and eddy current effects were corrected using the DSI-Studio toolbox. We used two different reconstruction methods include model base (DTI) and free model (QSDR); with two different attitudes to process the diffusion images. Four general feature categories were extracted from the images; the first type of features was diffusion-based parameters in each region of the structural freesurferseg and Brodmann atlases, the second type of features was tract-based parameters in each region of the same atlases and the third type of features was structural connectome with two atlases that were mentioned above. Finally, the last type of feature was the graph network.

This process was performed for DTI model according to the following recommended parameters:

FA index was used to determine the fiber tracking threshold and Otsu's method was used to set the anisotropy (FA) threshold to stop the fiber tracking, the number of seed points = 1,000,000, max angle = 60° , step size = half of the spatial resolution, length constraint = 30–300 mm, and no spatial smoothing. Also, DSI studio software was implemented to calculate the connections and graphs of the "connectivity matrix and graph Network" tool with two "End" and "Pass" views.

In total, 92763 features were extracted from 72 participants. The features extracted of structural and diffusion processed MRI images in our work are given in the chart below. (Shown in Figure 1)

2.4. Feature selection and Classification

Feature selection means recognizing the most relevant features for pattern recognition and noise reduction that usually used in studies where the number of data is extremely high while few studied subjects are available. The Fast Correlation-Based Filter (FCBF) method was better than the other models among all the feature selection models because less than quadratic time complexity (17). FCBF selected 66 features for the next step.

After the feature selection step, we performed four classification models including the DT, KNN, SVM and ANN with 5, 10, 15, 20, 30, 40, 50-fold cross-validation were used to evaluate the performance of the classifier. To evaluating the ANN model, training, validation and test phase was repeated for 30 times and finally the mean and standard deviation were reported. For this purpose, data set was divided into three parts: 60% for training, 20% for validation, and 20% for test. The MATLAB software R2012 (The Math Works, USA) was used to design and implement classification models.

3. Result

The number of extracted features using structural and diffusion processed MRI images for each subject were 92763.

Features extracted from the DTI model included region-based and tract-based features of structural freesurferseg and Brodmann atlases. Features extracted from QSDR model include Region-based, Tract-based, connectivity and Network features from structural freesurferseg and Brodmann atlases; Eventually, Features extracted from the structural MRI images from structural freesurferseg atlas include Morphometric and Voxel intensity features (Figure 1).

Table 1 shows the number of selected features with the FCBF model. According to this table, related features, Connectivity and Network have the most weight of selected features. However, it should be noted that the features selected for the three groups AD/MCI/NC classification. So, removing any of them has a significant effect on the classification performance. In total, 66 features were selected.

In table 2, the performance of each classification model (DT, KNN, and SVM) is provided to classify three groups of AD / MCI / NC. These classification models were evaluated by cross validation fold of 5, 10, 15, 20, 30, 40, and 50. We have considered the accuracy factor to compare the performance of all classification models.

In table 3 the performance of ANN is presented to classify three groups of AD / MCI / NC. This process is repeated 30 times and the mean and standard deviation are calculated.

We run the SVM, DT, KNN and, ANN models for the diagnosis of AD/MCI/NC using MATLAB tools. These results showed good performance using selected features such as morphometry, network, connective, and tract base for the classifying AD/MCI/NC. Two highest accuracy for the classification of three groups (NC, MCI, and AD individuals) were obtained 89.9% and 90.7% for the SVM and ANN model respectively by 66 selected features.

4. Discussion

In this study, we evaluated the structural and diffusion MRI brain images of the Alzheimer's patients from the ADNI dataset with machine learning techniques to classify the three groups AD, MCI and NC. For high-throughput imaging analysis, we used a well-established automated pipeline for morphometry (Freesurfer) and a pipeline to estimate rigorously individualized white matter structure (DSI_Studio).

the study, which has used only structural image T1W ADNI databases, it was performed by Lauge Sorensen et al. In 2016, to simultaneously classify the three groups AD, MCI and NC by using the extracted features of the Freesurfer and Hippocampal texture area. The accuracy obtained for the three-group classification is 62.7%. The extracted areas are classified as Hippocampal, Parietal lobes, Cingulate cortex and ventricles (24).

By comparing between our study and previous study: The study that only considers the diffusion image ADNI database for the classification of AD from NC is Luis R. Peraza et al., 2019, with an accuracy of 89.07% using 401 Connectivity feature extraction. For automated classification, only 89 features were selected between the two groups of AD and NC. In this study the regions involved in the temporal lobe, subcortical-posterior, occipital brain were introduced (26).

Also, the study that used both structural and diffusion imaging to diagnose AD, MCI, and NC, it was performed by Yun Wang et al in 2019. The Structural images that were taken from the ADNI database, were processed by Freesurfer software and the diffusion images were processed by MRtrix3 software. The current results are also in broad agreement with a recent SVM study that used connectivity measures and morphometry. Accuracy for AD-NC, NC-MCI, and AD-MCI was 96%, 70%, and 75% respectively. For this classification, the selected areas are not mentioned (25).

The current study results show that it is possible to classify the three groups NC, MCI and AD subjects with a high degree of accuracy using an automated procedure that combines DTI, QSDR, and morphometry sMRI. Our results from NC and MCI and AD classification which achieved an average accuracy of 89.9% and 90.7% for the SVM and ANN model respectively. Due to the high standard deviation in the ANN model, the SVM model is reported as a result of this study. The results of the KNN and DT classification performance were not considered due to the low accuracy.

Many brain imaging studies have shown that some brain regions may play a key role in the diagnosis of MCI and AD that the present study can confirm these results.(27–30)

The extracted significant features could be used to find the most vulnerable regions of the brain to distinguish AD, MCI, and healthy elderly peoples. In the current study, the features of brain regions such as the caudate nucleus, corpus callosum, hippocampus, Para hippocampus, temporal gyrus, putamen nucleus, cingulate gyrus, the region of 36 and 3 Brodmann are the most important features for the separation of these three groups, especially the temporal lobe. Moreover, the Amygdala is the only brain region of which both left and right hemispheres are exposed to changes in imaging values between the three groups. According to similar studies, the areas are considered vulnerable and this data can provide a clinician with additional information.

Top 9 regions repetitive of WM based on four types of features are the caudate nucleus, corpus callosum, hippocampus, Para hippocampus, temporal gyrus, putamen nucleus, cingulate gyrus, and the regions of 36 and 3 Brodmann. These areas have the highest frequency in various measurements such as connectivity and network of this region with another area, the volume of tracts on these regions, and the thickness of regions. Generally, the features extracted from the Atlas of Structure were much more efficient than the Broadman Atlas.

5. Conclusion

In this study we evaluated different three-group classification approaches using combine the neuroimaging modalities MRI and DTI. Combining anatomical and diffusion features, provided information indicating changes in the brain of patients with AD and MCI. Considering the results, three-group classification compared to two-group classifications used in above studies have significantly more important. The highest frequency in this study could be considered for identifying, monitoring, and future drug trials that could target these brain regions to AD and MCI Management. Eventually, the MRI can be combined with machine learning algorithms to detect damage in the early stages of Alzheimer's disease.

Abbreviations

AD : Alzheimer's disease

MCI : Mild cognitive impairment

DTI : Diffusion tensor imaging

DT : Decision Tree

KNN : k-nearest neighbors

SVM : support vector machines

ANN : Artificial Neural Networks

Declarations

Ethics approval and consent to participate:

The study was reviewed and approved by the Ethical Committee of Mashhad University of Medical Sciences. (Ethical number: IR.MUMS.MEDICAL.REC.1397.410)

Consent for publication :

Not applicable.

Availability of data and material :

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests :

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions :

Dr. Hoda Zare Seyed Amir Zamanpour and Bahare Bigham conceived of the presented idea and developed the theory and performed the computations.

Dr. Hoda Zare and verified the analytical methods and supervised the findings of this work.

Dr. Hoda Zare , Seyed Amir Zamanpour and Mohamad-Hoseyn Sigari discussed the results and commented on the manuscript. All authors contributed to and have approved the final manuscript.

Each named author has substantially contributed to conducting the underlying research and drafting this manuscript. Additionally, to the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

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Tables

Table 1: The number of selected features with the FCBF feature selection model

	Type of features	Number of selected features	Percentage of total selected features
DTI Model	Region Base	4	6%
	Tract Base	9	13.6%
QSDR Model	Region base	3	4.6%
	Tract base	1	1.6%
	Connectivity	30	45.5%
	Network	11	16.7%
Structural MRI	Cortical Region	5	7.5%
	Sub-Cortical Region	3	4.5%

Table 2: the performance of DT, KNN, and SVM with cross validation fold in term of the accuracy factor.

	cross validation fold	5	10	15	20	30	40	50	average	Sd
DT	CN	54.2	54.2	50	58.3	50	58.4	45.8	52.9	4.6
	MCI	62.5	62.5	50	41.7	62.5	66.6	62.5	58.3	8.9
	AD	70.8	70.8	75	70.8	66.6	70.8	75	71.4	2.8
	all	62.5	62.5	58.3	56.9	59.7	65.3	61.1	60.9	2.8
KNN	CN	83.3	95.8	95.8	95.8	95.8	95.8	95.8	94.0	4.7
	MCI	79.2	45.8	54.2	51.2	54.2	66.6	58.3	58.5	11.1
	AD	83.3	91.7	95.8	91.7	91.6	91.7	91.7	91.0	3.7
	all	81.9	77.8	81.9	80.6	80.6	84.7	81.9	81.3	2.0
SVM	CN	95.8	95.8	91.6	95.8	95.8	95.8	91.7	94.6	2.0
	MCI	83.3	87.5	87.5	87.5	83.3	83.3	87.5	85.7	2.2
	AD	87.5	91.6	91.6	87.5	91.7	87.5	87.5	89.2	2.2
	all	88.9	91.7	90.3	90.3	90.3	88.9	88.9	89.9	1.0

Table 3: the performance of ANN in term of the accuracy factor and the mean and standard deviation

ANN									
index	CN	MCI	AD	All					
1	100	83.3	91.7	91.7	17	83.3	87.5	100	90.3
2	95.8	83.3	91.7	90.3	18	95.8	87.5	91.7	91.7
3	100	83.3	91.7	91.7	19	83.3	87.5	91.7	87.5
4	91.7	83.3	100	91.7	20	91.7	79.2	91.7	87.5
5	87.5	83.3	91.7	87.5	21	100	87.5	95.8	94.4
6	95.8	87.5	95.8	93.1	22	100	87.5	95.8	94.4
7	91.7	83.3	83.3	86.1	23	91.7	95.8	91.7	93.1
8	95.8	95.8	95.8	95.8	24	91.7	91.7	95.8	93.1
9	91.7	83.3	95.8	90.3	25	95.8	91.7	100	95.8
10	100	70.8	100	90.3	26	91.7	87.5	95.8	91.7
11	95.8	91.7	95.8	94.4	27	95.8	54.2	91.7	80.6
12	91.7	83.3	91.7	88.9	28	100	66.7	100	88.9
13	91.7	87.5	95.8	91.7	29	83.3	87.5	75	81.9
14	95.8	83.3	100	93.1	30	100	70.8	100	90.3
15	100	79.2	95.8	91.7	mean	94.3	83.7	94.0	90.7
16	100	87.5	87.5	91.7	Sd	5.1	8.6	5.4	3.5

Figures

Figure 1

the steps of processing and extracted features