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The AD classification model based on multimodality MRI

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ABSTRACT

Alzheimer's disease (Alzheimer's disease, AD) is a common chronic mental decline disease with highly morbidity. Mild cognitive impairment is a transitional stage between normal aging and AD. Currently the analysis of magnetic resonance imaging of these two diseases mainly judged through the doctor's experience with a heavy workload and a strong subjective. To solve this problem, a combination of structural and functional features was proposed in this study based on the multi-modal magnetic resonance imaging data, rather than only relying on a single structure or functional property to distinguish two types of diseases in previous work. In this research, the multi-modal magnetic resonance imaging data were used to construct rest functional networks, then, the network properties and the gray matter volume of atrophy gray matter in structures images were extracted as the classification features to train the SVM classifier. Experimental results show that the combination of structural and functional characteristics that can differentiate MCI and normal control (accuracy of 91.7%), AD and normal controls (accuracy of 100%), AD and MCI (accuracy of 87.8%), effectively improve the classification accuracy rate of two types of diseases. The method can be verified as an auxiliary diagnostic model of Alzheimer's disease in the future.

KEYWORDS

sMRI, fMRI; Rest functional connectivity; Alzheimer's disease; Classification.

INTRODUCTION

Alzheimer's (Alzheimer's disease, AD) is a kind of chronic mental degenerative diseases usually at the onset of old age with a high incidence rate. Expected by 2050, the world's one person every 85 people suffers from this disease[1]. The role of existing medications for AD is very limited. However, the early diagnosis and treatment can slow the disease progression. MCI is a transitional stage between normal aging and AD among patients with memory or other cognitive impairment, but not reach the diagnostic criteria for dementia[2]. Studies have shown that about 44 percent of MCI patients after three years converted into AD, the average annual conversion rate was 15%[1]. While the normal elderly only 1% - 2% per year developed into AD[2]. Since AD is irreversible, therefore preclinical warning and early intervention is particularly important for patients with MCI.

Currently, diagnosis methods of AD and MCI mainly include: neuropsychological testing, neuroimaging studies and cerebrospinal fluid examination and so on. Because of non-invasive and high resolution features, MRI (Magnetic Resonance Imaging, MRI) examination has gradually become a major inspection method. Among them, the structural imaging (structural MRI, sMRI) and functional imaging (functional MRI, fMRI) applications have been particularly extensive. The resting state fMRI can reflect the spontaneous function of brain activity. It is help to investigate the synchronization of spontaneous activity of brain region and spontaneous functional neural networks that exist in the brain. Pathological mechanisms of Alzheimer's disease can be studied by functional brain networks based on the resting-state fMRI from the whole brain perspective. The results showed that abnormal changes have taken place in topological properties of functional brain networks in patients with AD. Structural imaging studies also show that, compared with normal subjects, the hippocampus and entorhinal cortex atrophy occurred in patients with MCI. However, the current imaging mainly relies on the doctor's experience and heavy workload. It cannot fully exploit the wealth of information contained in the image. The way using machine learning algorithms to extract the abnormal topological properties of resting state functional networks and sMRI abnormal gray matter volume and other characteristics to establish the auxiliary diagnostic model of Alzheimer's disease will help to improve the current status of the diagnosis of a heavy workload. Neuroimaging studies have shown that AD and MCI patients have changes in the structure or cognitive function in some brain regions such as the hippocampus, temporal lobe and frontal. Many studies have found that bilateral hippocampus, amygdale, entorhinal cortex, temporal lobe groove spacing, posterior cingulate and thalamus exhibited structural or functional abnormalities.

Compared with normal control group, the activation of the medial temporal lobe decreased in MCI and AD patients during the memory tasks completion, but the increase in activation degree of the right parahippocampal gyrus in memory encoding [3-6]. Upon completion of the visual memory task, activated functional areas increased significantly compared with normal elderly controls, mainly located on the right superior frontal gyrus, bilateral middle temporal gyrus, middle frontal gyrus and bilateral anterior cingulate gyrus. Besides, the activation area increased in MCI group compared to the AD group in the right parahippocampal gyrus, the right lentiform nucleus, the right fusiform gyrus, left inferior frontal gyrus, the left supramarginal gyrus and bilateral cingulate gyrus. These studies show that AD and MCI cognitive impairment were not caused by a handful of brain damage, but were diffuse brain disease. In recent years, many researchers have analyzed the global characteristics and nodes properties of the brain network by the method of constructing the brain structure or functional network, and using graph theory, so as to explore the abnormal changes of brain networks in key brain regions and critical path [7-8].

The article builds on existing research on the use of sMRI, fMRI multi-modal magnetic resonance data, by constructing resting state functional brain networks to extract unusual network nodes properties, and will be on the basis of VBM (Voxel-based morphometry, VBM) to extract the gray matter volume of regions of interest as features, training SVM classifier and establish AD and MCI auxiliary diagnostic model.

RESEARCH METHODS

Technical route used in this study as shown in figure 1. AD and MCI classification model uses two types of classification features, which were structural and functional characteristics.

On the one hand, the gray volume of region of interest was extracted based on VBM, on the other hand, using fMRI data to construct resting state functional brain networks. Then we computed local and global properties of these networks and select node properties of brain regions which have significant differences as functional imaging features.

Subjects

The research used ADNI (Alzheimer's Disease Neuroimaging Initiative, ADNI) data set that met the more stringent diagnostic criteria.

The data set includes MCI, AD, normal controls (Normal Control, NC) and many other sets of data. Inclusion criteria for each group of subjects were as follows:

(1) NC: Mini-Mental State Examination (MMSE) scores between 24 and 30, Clinical Dementia Rating (CDR) scores 0, non-depressed, non-MCI and non-dementia;

(2) LMCI: subjects: MMSE scores between 24 ~ 30, CDR score of 0.5, Wechsler Memory Scale Logical Memory I scores 9-11;

(3) AD subjects: MMSE scores between 22 ~ 26, CDR of 0.5 or 1.0, meet NINCDS / ADRDA criteria.

The subjects participated in this study meeting the above criteria and were derived from the same scan in ADNI. They have

both fMRI and sMRI imaging data and scores of MMSE. The basic information of subjects was shown in TABLE 1.

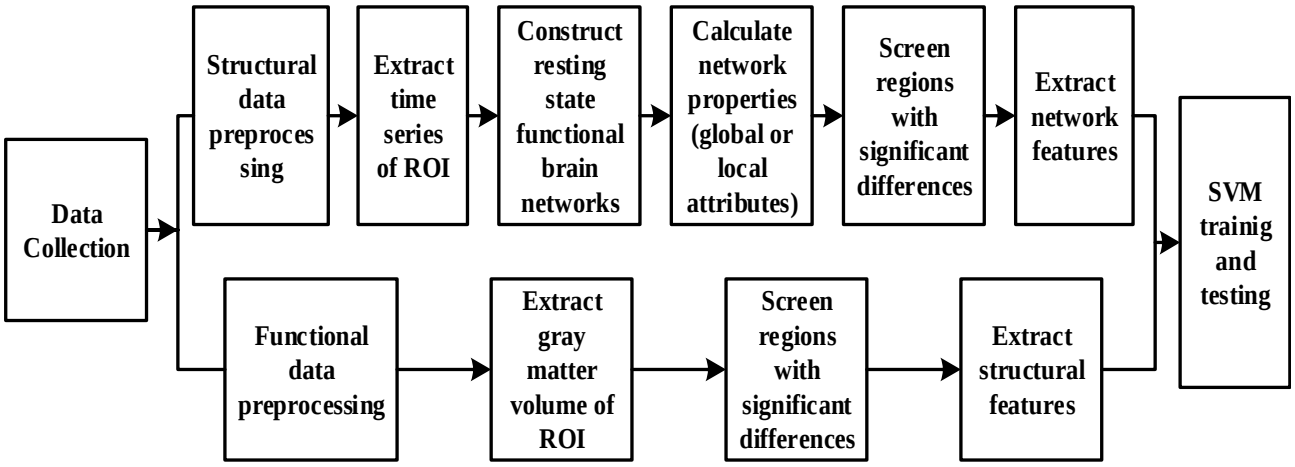

Figure 1 : Classification model of Alzheimer's disease and mild cognitive impairment

TABLE 1 : The Basic Information of Subjects

	AD	MCI	NC	P-value
Gender (female/male)	8/6	11/18	17/18	0.67a
Age	76.5±7.3	73.2±7.3	74.3±5.9	0.36b
MMSE	21.1±3.8	27.2±2.3	28.9±1.6	<0.01b

a: Two-tailed chi-square test. b: One-way ANOVA test.

Data preprocessing

Data preprocessing of fMRI data was carried out using DPARSF[9]. Time slice and head correction on datasets were accomplished first to ensure that all levels of subjects were less than 2mm head movement and rotation of less than 2 degrees. Then images were standardized to the MNI standard space of 3 mm voxels. Finally, filtering low frequency of 0.01-0.08(Hz) to reduce the low frequency drift and high frequency biological noise.

SPM was used in sMRI data pretreatment. Preprocessing includes spatial normalization, segmentation of brain tissue and smoothing (smoothing kernel of 8mm).

Statistical test to each voxel was carried out using statistical parametric testing method, then locate these voxels to the anatomical position. Then analyze differences between the groups using variance test. According to the unified threshold and the number of voxels, we get regions with group difference in gray matter density or volume.

Build Functional Brain Networks

The whole brain was divided into 90 brain regions using AAL template[10], with left and right hemispheres each of 45. Each brain region was defined as a network node. Calculate an average time sequence of all the voxels in the same brain region as a time sequence of the region. To time sequence obtained by each brain region, Partial correlation coefficients were calculated between each two and the correlation matrix of 90×90 can be obtained.

Typically the correlation matrix was converted into a binary adjacency matrix according to the set threshold. That was to say when the partial correlation coefficient between node i and node j was greater than a certain threshold, the element of matrix aij has a value of 1 which indicates the connection between nodes i and j, otherwise aij was 0.

However, if four groups of subjects set the same correlation coefficient threshold value, the edge numbers of the network to each group of subjects was inconsistent so as to the network size also inconsistent. Analysis of network properties and node attributes on this basis was not meaningful.

Therefore, sparsity S was used in most studies to determine whether to create edges between nodes, so that the brain networks have the same scale to different subjects. In which S was the ratio of the actual number of edges presented in the network and the maximum possible number of edges in the network (N).

The study compared NC, MCI and AD brain networks at the same sparsity. Specific methods as follows: After setting the sparsity threshold, make the correlation coefficient of correlation matrix in descending order. If the correlation coefficient between node i and node j was prior to S * N, then establish a unidirectional edge between node i and node j.

Since there was no gold standard of threshold setting to single sparsity, different sparsity ranges always cause the different results. In this study, the selection of the sparsity was 8% -30%. The interval was 0.01.

Network Features and Analysis

Commonly used node attributes of brain network include node degree, node centrality degree and node efficiency. Node attributes of undirected and unweighted brain networks were described as follows, where N is the total number of nodes in the network, K represents the number of edges:

Node Degree

The degree of node i was defined as the number of edges connected to the node. It reflects the relationship between the node and other nodes in the network G, also the status and role of the node in the network. The formula can be expressed as (1):

$$D_i = \sum_{j \in G} a_{ij} \quad \textbf{(1)}$$

Wherein a_{ij} represents the number of connections between the node i and the node j in the network.

Node Centrality Degree

The centrality degree of node i was defined as the number of shortest paths through the node to all shortest paths among all other nodes. It reflects the importance of the node i in the network. Nodes with high centrality degree are information exchange hub in a network. The formula can be expressed as (2):

$$\mathrm{B}_i = \sum_{m \neq i \neq n} \frac{\sigma_{mn}(i)}{\sigma_{mn}} \quad \textbf{(2)}$$

Wherein, σ_{mn} represents the number of shortest paths between node m and node n, $\sigma_{mn}(i)$ indicates the number of shortest paths from node m to n.

Node Efficiency

The node efficiency of node i was defined as the harmonic mean of shortest path among the node i and other nodes in the network. It can measure the information dissemination capabilities of a node to other nodes in the network, which can be expressed as the formula 3:

$$E_{g\_i} = \frac{1}{N-1} \sum_{j \neq i} \frac{1}{d_{ij}} \quad \textbf{(3)}$$

d_{ij} represent the shortest path length between nodes i and j, which reflects the degree of difficulty from the node to other nodes in the network.

Classifier training and testing

The results were analyzed with one-way anova, taking $P<0.001$ as statistically significant difference to analyze the regions of gray matter atrophy in patients. Then extract gray matter volume in these regions as the fMRI classification characteristic.

K-S test (Kolmogorov-Smirnov) was done on the average value of AUC to each node attributes in different sparsity. Finally, selecting AUC value of brain regions with a significant difference ($p < 0.05$) as the sMRI data classification features. SVM algorithm was adopted in this study, and the parameters were optimized to obtain the best classification accuracy using the grid algorithm. Using the 5-fold cross-validation, the data samples were randomly divided into 5 parts, the one as a test set, and the remaining four as the training set. Repeat 5 times, and putting the average accuracy as the final accuracy of the classification model.

Results

Regions of gray matter atrophy and gray matter volume

In this study, gray matters were analyzed using SPM8 software with one-way anova, taking $P<0.001$ as statistically significant difference. 10 adjacent voxels were selected as the threshold value to analyze the regions of gray matter atrophy in patients. The SPM results were shown in figure 2.

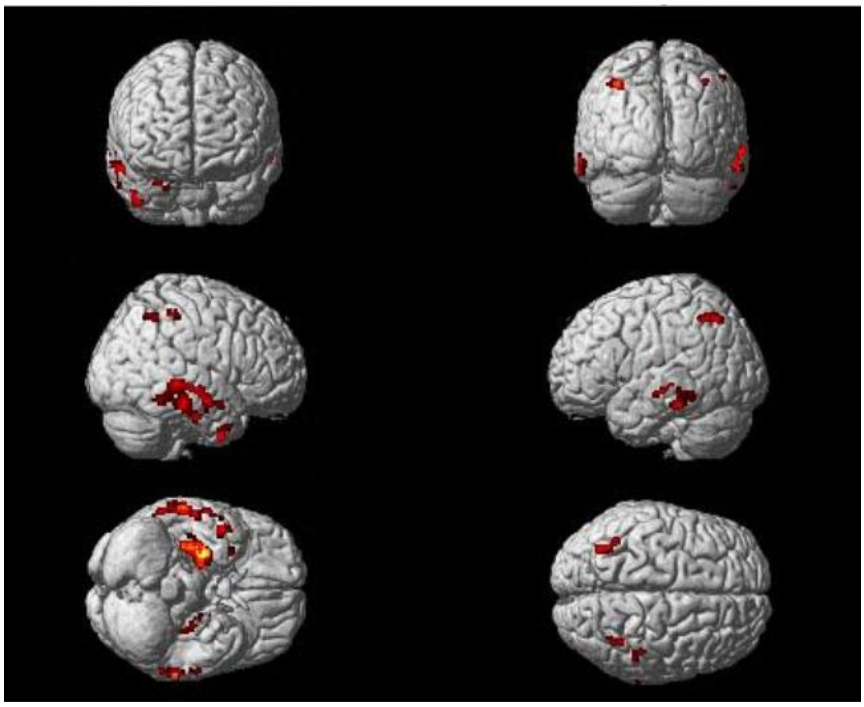

Figure 2 : Result of SPM

Variance test results show that AD and MCI have significant differences between the groups in R1-R9 regions, where R1-R9 respectively represent the right hippocampus(R1), left hippocampus(R2), right middle temporal gyrus(R3), left middle temporal gyrus(R4),right inferior temporal gyrus(R5), left inferior temporal gyrus(R6), right fusiform gyrus(R7). These regions of gray matter atrophy were taken as the regions of interest, and then using REST software to extract the gray matter volume of them. The results were shown in figure 3.

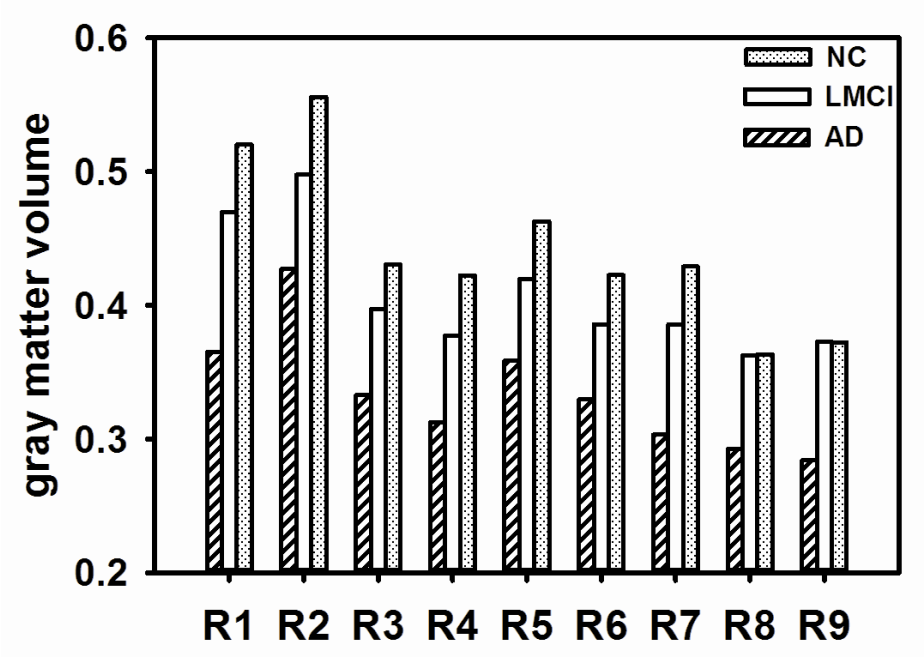

Figure 3 : Gray matter volume in regions of gray matter atrophy

Figure 3 shows the gray matter volumes in these regions in AD, MCI and NC. The results show that: in addition to bilateral precuneus, gray matter volumes in most regions have a trend of decreasing with the aggravation of the disease.

Abnormal Nodes of Functional Brain Network

Node attributes comparative of normal elderly with MCI patients in various brain regions revealed that, in a number

of sparsity, the centrality degree of node in brain regions had significant differences ($p<0.05$) in Heschl gyrus (HES), Superior occipital gyrus (SOG), Inferior parietal (IPL), Anterior cingulate and paracingulate gyri (ACG), Gyrus rectus (REC), Precuneus (PCUN), Middle frontal gyrus, orbital part (ORBmid). Node efficiency also has significantly differences ($p <0.05$) in multiple sparsity in HES, SOG and Superior parietal gyrus (SPG).

The analysis also revealed that compared with EMCI, the node centrality degree of Inferior frontal gyrus, triangular part (IFGtriang) and Olfactory cortex (OLF),the nodes efficiency of IFGtriang and Inferior frontal gyrus, orbital part (ORBinf) and other brain regions in many sparsity had significant differences ($p<0.05$) to LMCI.

Relative to LMCI, the node centrality degree of IFGtriang, Inferior frontal gyrus, opercular part (IFGoperc), Angular gyrus (ANG) and other brain regions were significantly different ($p <0.05$) in the multiple network sparsity to AD patients. There were also significant differences in the nodes efficiency in the multiple network sparsity ($p <0.05$) of IFGoperc, Supramarginal gyrus (SMG), IFGtriang, Superior temporal gyrus (STG) and other brain regions.

Classification Results

TABLE 2 shows the 5-fold cross-validation results using SVM.

TABLE 2 : Results of Classification (%)

Feature	AD& NC	MCI& NC	AD &MCI
Brain Network properties	70.6	78.3	71.4
Brain Network Properties +MMSE	83.9	80.0	72.2
Brain Network Properties +VBM	100.0	91.7	85.6
AUC+MMSE+VBM	100.0	91.7	87.8

The result showed that: the classification accuracies using local attributes of brain network for AD and NC, MCI and NC, AD and MCI were 70.6%, 78.3% and 71.4%. After adding MMSE scores, the accuracies were 83.9%, 80.0% and 72.2%. The accuracies were 100%, 91.7% and 87.6% after adding structural features. While if using a combination of structural features, functional network characteristics and MMSE scale, the accuracy could reach 100%, 91.7%, 87.8%.

Result Analysis

The study found that both function and structure of AD and MCI had some differences with the normal control. These differences were consistent with the existing research results.

The results in figure 2 showed that gray matter volume of some regions decreased gradually which were the right hippocampus, right middle temporal gyrus, right inferior temporal gyrus, right fusiform gyrus, left middle temporal gyrus, left inferior temporal gyrus, left hippocampus.

A lot of researches based on VBM method have shown that, AD patients and MCI patients existed cortical atrophy in bilateral hippocampus[11-12]. The pathological development of AD was that neuron loss on entorhinal cortex, parahippocampal gyrus and temporal parietal regions in the early days, and then gradually spread to the anterior brain regions[13].

The results of this experiment showed that the gray matter atrophy of AD and MCI in the hippocampus region were the most serious, followed by the temporal lobe and frontal lobe. This was close to the scope and the occurrence of AD pathologic changes.

The study also found that the network topology properties of multiple nodes in some regions were abnormal, including frontal lobe, temporal lobe, limbic system and basal ganglia. This showed that the AD and MCI impaired cognitive function was not caused by a few brain regions, but the whole brain multiple brain regions had different degrees of damage. These brain areas were closely related to memory, hearing, language, attention and other cognitive functions. This was consistent with the performance of AD patients with the cognitive dysfunction.

That was: In addition to the obvious memory impairment, other cognitive functions of AD also had varying degrees of damage, such as language, attention, visuospatial functions, in which the most common was the injury memory function.

SUMMARY

This study proposed a comprehensive method for extracting structure features and functional characteristics, combined with MMSE scale of AD and MCI diagnosis model.

Abnormal node attributes was extracted from resting state functional brain network as functional characteristics. Structural characteristics was extracted from the gray matter volume in some regions which were the right hippocampus, right middle temporal gyrus, right inferior temporal gyrus, right fusiform gyrus, left middle temporal gyrus, left inferior temporal gyrus and left hippocampus.

The classification accuracy of AD and NC, MCI and NC, AD and MCI were all higher than 85%, which indicated that the classification model proposed in this paper was a better auxiliary diagnostic model.

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