Preclinical Stages of Alzheimer's Disease Classification by a Rs-fMRI Study

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Abstract—**A new method for classifying the preclinical stages of Alzheimer's disease (AD) and positioning the related brain areas is described in this paper in order to slow the progress of AD. The method is based on multi-voxel pattern analysis (MVPA), which is used to classify normal control (NC) participants and patients and find the changes in different brain areas with AD progression. In the classification, each voxel's blood oxygen level dependence (BOLD) signal during resting-state functional magnetic resonance imaging (rs-fMRI) was extracted as the basic features. To reduce the amount of features, principal component analysis (PCA) and two-class support vector machine (SVM) were applied to classify 62 NC participants and 162 different stages of patients, which included 47 subjective cognitive decline (SCD) patients, 60 amnestic mild cognitive impairment (aMCI) patients and 55 AD patients respectively. The accuracy of classification reached to 62.71% in SCD, 70.67% in aMCI and 86.36% in AD (all of them were classified with NC participants). Based on the accuracy, we innovatively combined "weight vectors" in SVM with permutation test as discrimination patterns to further investigate the related brain areas. The discriminating areas, including middle cingulum (right), insula (left), paracentral lobule (right) and middle temporal (left) are responsible for different cognitive functions and could provide a large application of AD biomarkers. Our method and results suggest the potential of real-time diagnosis and cognitive therapy because of no complex feature calculations.**

Keywords- multi-voxel pattern analysis, weight vectors, permutation test, Alzheimer's disease

I. INTRODUCTION

Alzheimer's disease (AD), a progressive neurological degenerative disease, is common in elderly people. Patients of AD often show significant damage in memory and other cognitive domain damage, which greatly affects the quality of patients' life [1]. To decrease the bad effects on patients, accurate delivery of medicine in the target brain region can slow down the disease process. For this purpose, it is important to precise diagnosis of preclinical AD and then localize the AD related brain areas. Preclinical AD stages are including first stage, subjective cognitive decline (SCD) and second stage, amnestic mild cognitive impairment (aMCI). SCD and aMCI often serves as a symptomatic indicator of preclinical AD by researchers because early detection before the irreversible brain tissue impairment caused by AD is essential for efficient AD treatments [2].

To detect preclinical AD stages, machine learning as a rising field has recently shown the capability to be applied to automatic classification of different stages of AD with different kinds of features. Different modalities imaging data can be used as different features, including nuclear magnetic resonance imaging (MRI) and positron emission tomography (PET) [3]. In the analysis of structural MRI, the cortical volume and thickness have been used to differentiate aMCI and AD participants from NC participants [4]. Besides, some researchers have found the AD related atrophy of brain regions based on the structural MRI data [5]. Compared with structural MRI, resting-state functional MRI (rs-fMRI) reflected the AD related abnormality of brain function [6]. For example, regional homogeneity (ReHo) is one of the effective classification features based on rs-fMRI in voxel level [6]. Besides, AD patients also showed the functional network level abnormality, such as default mode network [7].

The studies mentioned above are based on complex calculation of features to improve the accuracy of classification. Compared with complex feature calculation, simple calculation can improve the speed of classification in real-time analysis [8]. Multi-voxel pattern analysis (MVPA) is a good example for real-time analysis in classifying normal control (NC) participants and aMCI or AD patients [9]. Wee et

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al. and Dyrba et al. applied a MVPA to rs-fMRI data classification study for aMCI and AD participants, and both of them obtained higher accuracies [10, 11]. As for the classifier, supervised [12] and semi-supervised [13] classifiers are popular these years. Among these classifiers, support vector machine (SVM, supervised classifier) performs well [14] on targeting the related brain areas. Liu et al. used weight vectors to target the related regions based on the highest accuracies [15]. According to our best of knowledge, AD related brain areas are not clear and there are few studies focusing on MVPA of healthy people and SCD participants using rs-fMRI data.

In this study, considering the promising results from utilizing MVPA into differentiating aMCI participants from NC participants, we intended to further apply MVPA methods into the classification study of SCD participants. Based on the classification, we tried to measure the brain region changes by using machine learning methods, which can build a new perspective for combining brain pathophysiological mechanism studies with machine learning methods. In terms of machine learning methods, we proposed a MVPA-based machine learning classification and damage brain areas targeting algorithm to discriminate SCD participants from NC participants. The classification model adopted features from rs-fMRI data and summarized weight vectors to target the brain regions between SCD participants and NC participants during modal training.

II. METHODS

A. Subjects

Two hundred and twenty-four right-handed Chinese adult volunteers signed informed consent to participate in this experiment and are assessed according to clinical evaluation. 62 normal control (NC) participants were recruited from local community. One hundred and sixty-two subjects were screened according to clinical memory scale in Beijing Xuanwu hospital. Forty-seven subjects suffered subjective cognition decline, sixty subjects suffer aMCI, and fifty-five subjects suffer Alzheimer Disease. All subjects completed functional magnetic imaging according to diagnostic guide and five clinical cognitive scales, including the mini-mental state examination (MMSE), the Beijing version of Montreal Cognitive Assessment (MoCA), the auditory verbal learning test (AVLT)-immediate recall (AVLT-I), AVLT- delayed recall (AVLT-D) and AVLT-recognition (AVLT-R).

B. Data acquisition

Data were acquired using a Siemens 3.0 Tesla resonance magnetic imaging device. A cushion and head phone were used to reduce the influence of subjects' head movement and noise of the device. For axial functional magnetic resonance data, EPI sequence was used. The sequence parameters were as followed: repetition time = 2000 msec; echo time = 40 msec; flip angle = 90°; angle of view = 240 ×240 mm^2; matrix = 64×64; slice number = 28; slice thickness = 4 mm; voxel size = 3.75×3.75×4 mm^3; interval = 1 mm. At the beginning of the experiment, participants were instructed to close their eyes and keep still. Their minds should keep clear and relaxed. The duration of data collection was 478 seconds, so every subject had 234 functional imaging. Parameters for T1-weighted MR images were as followed: repetition time = 1900 msec; echo time = 2.2 msec; flip angle = 9°; flip time = 900 msec; angle of view = 256×256 mm^2; matrix= 256×256; slice number = 176; slice thickness = 1 mm; voxel size = 1×1×1 mm^3.

TABLE I. GROUP CHARACTERISTICS AND SUBJECT DEMOGRAPHICS

Group	NC	SCD	aMCI	AD	P
Gender (female/ male)	39/23	26/21	31/29	35/20	0.48[a]
Age (SD)	63.27(8.1)	65.33(8.4)	67.27(9.4)	70.62(10.1)	0.000[b]
Years of education (SD)	10.95(5.0)	11.70(4.6)	9.75(4.9)	8.85(5.6)	0.022[b]
AVLT-D (SD)	10.00(3.0)	8.47(2.7)	3.88(2.9)	1.04(1.6)	0.000[b]
AVLT-I (SD)	9.09(1.9)	8.18(1.8)	6.09(1.7)	3.67(1.6)	0.000[b]
AVLT-R (SD)	11.94(2.5)	10.98(2.7)	7.83(3.8)	3.56(3.3)	0.000[b]
MMSE (SD)	28.03(2.2)	27.94(1.9)	24.70(4.1)	16.96(6.1)	0.000[b]
MoCA (SD)	25.89(3.4)	25.14(2.9)	19.71(4.3)	12.65(5.1)	0.000[b]

[a]The differences were checked by chi-squared test.

[b]The differences were checked by one-way analysis of variance.

C. Data preprocessing

The toolkit GRETNA on the MATLAB platform was used to process the data [16]. The main steps ran as followed: First, the first ten time points was deleted in considering the stability of the images and the environmental adaptation of the subjects. Second, the functional sequence remained after deletion was corrected and added the first MR image. The data collection started from the even layers and the sequence was scanned. Repetition time was 2 seconds. Third, the subject's head movement was rectified with linear conversion and was added to the first diagram. Fourth, every subject's structural diagram was aligned to the functional diagram. Associated scheme for segmentation was used for separating the structural image to grey matter, white matter and cerebrospinal fluid. The realigned functional images must fit in the MNI (Montreal Neurologic Institute) standard space and the resample of the realigned functional images should be 3×3×3mm^3 isotropic voxel in accordance to the associated scheme for segmentation.

D. Classification model

We used MVPA to construct models for the classification of SCD and NC participants, aMCI and NC participants, AD and NC participants. For the two classes of samples, we could get a dataset N × V, where, N=1 … Number of participants, V=1 … Number of brain gray matter voxels. In order to avoid overfitting [17], we used principal component analysis (PCA)

to extract features and reduce the number of features, which can mostly keep the information [18]. In this study, we kept N-1 components as the features.

After the application of PCA, a linear SVM-based classification method was used. SVM aims to find a hyperplane with the largest margin to separate the two sets of data. In this research, SVM implementation was based on scikit-learn, which was an open source machine learning library written in python (https://www.python.org/). It was noteworthy that the weight vector could be transformed to 3-dimensional brain space, and each voxel reflected the weight value.

In this study, we performed the leave-one-out cross-validation (LOOCV) test to assess the classifier in classifying. During every train, data from N-1 subjects were used to train the classifier, and data from the remaining subject were used to test the classifier. This procedure would be repeated until every subject was tested. In the end, the probability of correct predictions was calculated as accuracy to quantify the performance of this classifier.

Based on the previous studies, the weight vector evaluated the importance of the voxel when classifying the two samples [15]. Thus, many studies regarded the weight as discriminating volume. However, we obtained the weight vector in the N-1 (sample size)-dimension brain space. So we needed to transform the weight vector back to the original voxel space. PCA and the dimension transform were also based on scikit-learn.

E. Permutation test

In order to get a stable result, we performed 1000 permutation test. During each permutation, the weight value was calculated. Thus, we could get the significance of each feature's value. Every feature was based on the voxel, so we calculated the mean weight value in every brain region, which was defined by automated anatomical labeling (AAL). According to the weight of every brain region, we calculated the whole brain ranking results and compared them among the three classification model.

III. RESULTS

A. Sociodemographic and clinical characteristics

The demographics and clinical data of the subjects, including normal control (NC) participants, subjective cognitive decline (SCD), amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) patients, were shown in Table 1. The gender differences between the three groups are not significant. Comparing to this, the age differences, the years of education differences and the cognitive scale differences are significant.

B. Preprocessed data

A total of 224 participants, including 62 NC participants, 47 SCD participants, 60 aMCI participants and 55 AD participants were for discriminative analysis. Four kinds of preprocessed data, original data (Org), normalized data (Nor), filtered data (Fil) and regional homogeneity (ReHo), were shown in Figure 1 for classification.

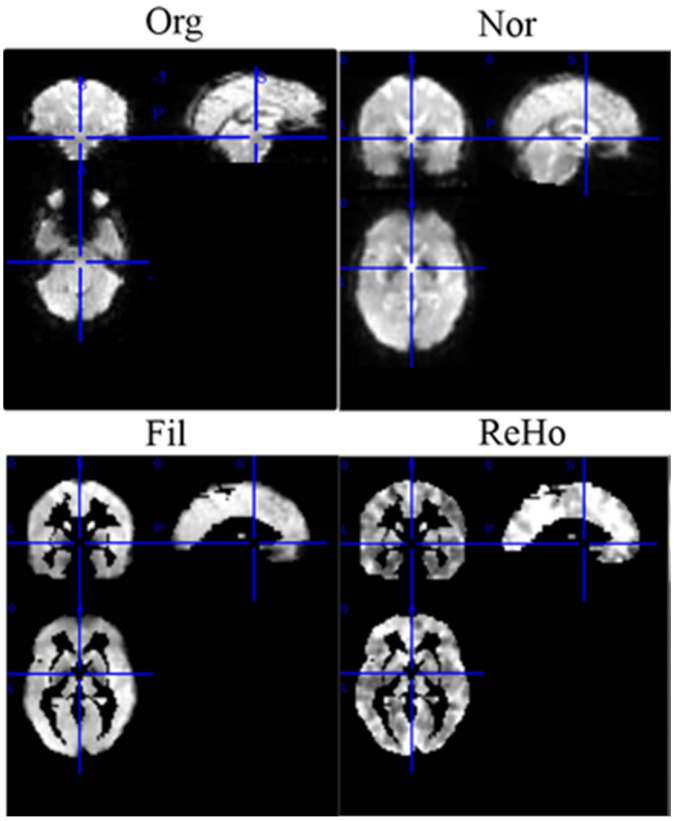

Figure 1. Preprocessed data. Four kinds of data for classifications: original data (Org), normalized data (Nor), filtered data (Fil) and regional homogeneity (ReHo).

C. Classification results

Classification of different kinds of data was implemented by leave one out cross-validation (LOOCV) because of the small sample size. Each classifier was trained and tested with the N samples. Thus, N rounds of LOOCV were performed to evaluate the predictive power of the classifier. The performance, accuracy (ACC) and area under curve (AUC), was summarized in Table 2 and Figure 2. Among the four kinds of data, normalized data achieved better accuracy. For SCD classification, we achieved a cross-validated accuracy of 62.71%. For aMCI classification, we achieved a cross-validated accuracy of 70.67%. For AD classification, we achieved a cross-validated accuracy of 86.36%. From SCD to AD, we got a higher and higher accuracy.

TABLE II. CLASSIFICATION ACCURACY OF DIFFERENT KINDS OF DATA (%)

Samples	Org (ACC/AUC)	Nor (ACC/AUC)	Fil (ACC/AUC)	ReHo (ACC/AUC)
NC vs SCD	60.5%/0.59	62.71%/0.66	61.86%/0.66	59.32%/0.58
NC vs aMCI	57.89%/0.61	70.67%/0.73	66.92%/0.72	67.67%/0.69
NC vs AD	75.57%/0.84	86.36%/0.89	82.58%/0.89	79.55%/0.87

[a]Accuracy (ACC) and area under curve (AUC) were showed in this table.

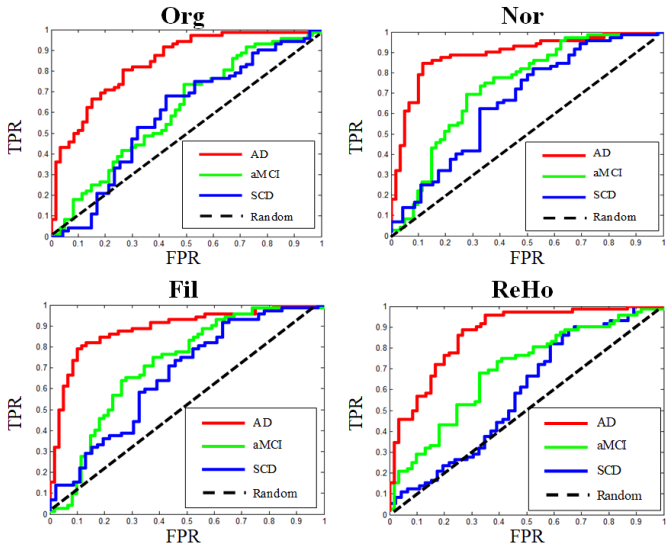

Figure 2. Receiver operating characteristic (ROC) curves. Comparisons about different group (SCD, aMCI and AD) classification experiment were shown in each subfigure and comparisons about different kinds of data (Org, Nor, Fil and ReHo) classification experiment were shown among subfigures.

Moreover, the receiver operating characteristic (ROC) curves were shown in Figure 3, which were the comparison about different group classification experiment in each subfigure and comparison about different kinds of data classification experiment among subfigures. The accuracy and ROC results showed that preclinical stages of AD were not easy to diagnose.

D. Permutation test results

The permutation test was performed to obtain the significant spatial patterns on normalized data, which achieved the best accuracy. The spatial patterns, showing the differences between NC and SCD, aMCI and AD patients, were displayed in Figure 3 (the threshold of p was 0.02 [15]). The discriminative regions included the lingual gyrus and inferior temporal gyrus for SCD stage, frontal orbit, fusiform gyrus, olfactory cortex and orbital frontal gyrus for aMCI stage, and left superior temporal gyrus, left middle temporal gyrus, left inferior temporal gyrus, left temporal cortex and right entorhinal cortex for clinical AD stage. For clinical AD stage, the discriminative regions were too small to be shown in Figure 3.

Moreover, we used weight vector to assess the importance of the brain areas. The brain areas were ranked during every classification, and more front rankings meant more important areas. Figure 4 showed the ranking results. More front rankings meant more important during the classification, so left and right pallidum showed importance in SCD stage.

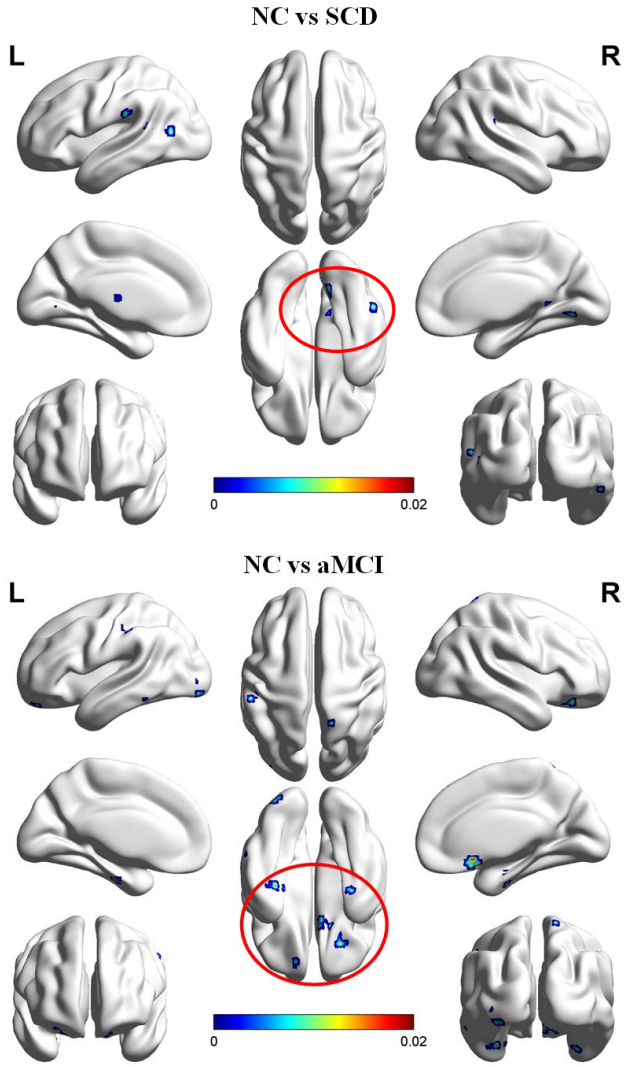

Figure 3. The discriminative regions. The permutation test p values ($p<0.02$) were shown in this figure.

IV. DISCUSSION

The aim of this research is to explore the neurological mechanisms of Alzheimer's disease (AD) by studying differences between patients and normal control (NC) participants. In our study, we applied multi-voxel pattern analysis (MVPA) to investigate the topologic alterations of brain functional connectivity in participants with subjective cognitive decline (SCD), which exhibit an increased risk of progression to amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) compared with healthy elderly individuals. By applying MVPA, we achieved the accuracy of 62.71% between SCD and NC, the accuracy of 70.67% between aMCI and NC, the accuracy of 86.36% between AD and NC. Moreover, permutation test results showed that AD-related important regions included right midcingulate area, left insula, left middle temporal gyrus and right paracentral lobule. Moreover, the results revealed that SCD-related differences

were found in the brain regions, including the left and right pallidum, which is an important part of subcortical structures.

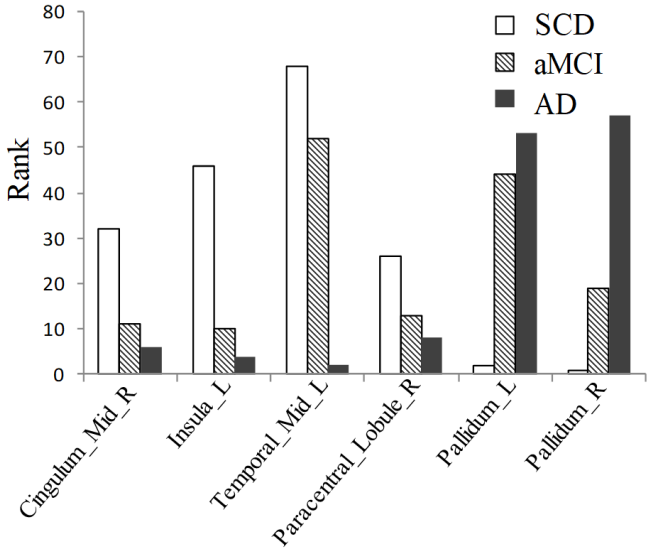

Figure 4. Ranking of the important areas by weight vector. The brain regions were defined by automated anatomical labeling. Cingulum_Mid represented the midcingulate area, temporal _mid represented the middle temporal gyrus and paracentral_lobule represented the paracentral lobule. L represented the left hemisphere and R represented the right hemisphere.

Previous studies have found that MVPA has the potential to reflect the differences between patients and normal controls by rs-fMRI data [8, 15]. In this study, the local average of the weight based on MVPA is an easy and effective method, which simply analyzed the brain patterns by ranking the weight values of different brain regions during classification. Previous studies have proved that the ranking provided the possibility of comparison between different features and tried to explain the contribution of the features [2, 19].

We further combined the ranking with permutation test to obtain a significant result. The ranking results showed that right midcingulate area, left insula, left middle temporal gyrus and right paracentral lobule contributed more to classification of AD and NC participants. A recent study revealed the significance of right midcingulate area on hallucinatory in AD patients [20]. As for left insula, the abnormality has been found in AD patients [21], and even in MCI participants [22]. Besides, a recent machine learning analysis showed that left middle temporal gyrus was one of the most important predictors in classifying and predicting AD [23]. Moreover, a functional connectivity analysis revealed that the functional connectivity of paracentral lobule increased in AD patients [24]. Taken together, the above studies emphasized that many brain regions showed abnormality in AD patients.

Comparing to the abnormality in AD patients, only the pallidum showed abnormality in SCD participants. The major effect of pallidum is to transform the information in subcortical areas [25]. Previous studies have detected the importance of subcortical structures in Alzheimer's pathology's development [26, 27]. Subcortical brain regions are not the most memory related brain regions. Similarly, a recent study showed that in SCD group, peripheral regions behaved abnormally earlier than rich club regions [28].

In this study, some limitations have to be emphasized. First, the SCD group's accuracy is much lower than AD and aMCI groups because the similarity between NC and SCD participants. Second, the differences on ages and education among the three groups are significant, which need more study to exclude the influence. Based on it, we should focus on the data collection, such as follow-up study or developing new algorithms.

V. CONCLUSION

In conclusion, our study used the MVPA and permutation test to reveal the brain functional patterns among NC, SCD, aMCI and AD by evaluating rs-fMRI data. To note, the different brain functional patters of SCD and NC were mainly characterized in the pallidum, which showed the development of AD. All the above results showed the effectiveness of PCA and SVM in MVPA, especially referring to SCD research. We hope the present study could be used for AD related diagnosis and treatment, such as neuro-feedback for future work.

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