Discriminative Analysis of Early Alzheimer's Disease Based on Two Intrinsically Anti-correlated Networks with Resting-State fMRI

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Abstract. In this work, we proposed a discriminative model of Alzhei--mer's disease (AD) on the basis of multivariate pattern classification and functional magnetic resonance imaging (fMRI). This model used the correlation/anti-correlation coefficients of two intrinsically anti-correlated networks in resting brains, which have been suggested by two recent studies, as the feature of classification. Pseudo-Fisher Linear Discriminative Analysis (pFLDA) was then performed on the feature space and a linear classifier was generated. Using leave-one-out (LOO) cross validation, our results showed a correct classification rate of 83%. We also compared the proposed model with another one based on the whole brain functional connectivity. Our proposed model outperformed the other one significantly, and this implied that the two intrinsically anti-correlated networks may be a more susceptible part of the whole brain network in the early stage of AD.

1 Introduction

Alzheimer's disease (AD) is the most common type of dementia associated with aging. The increased number of people suffering from AD makes it a major public healthy concern. If the disease is diagnosed in the earlier stage, AD patients can live an average of eight to twenty years. Therefore, a high quality and objective discriminative approach distinguishing the early AD patients from the healthy aging may be of great importance for clinical early diagnosis of AD.

Clinical observations of AD patients revealed that they often had great difficulty in performing everyday tasks at the very early stage of the disease. They were often described as being distractible and unable to concentrate when they performed the tasks that were previously easily done. These observations suggested that AD patients have attention deficits, and the attention deficits may

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be one of the possible factors underlying other cognitive deficits at the early stage of the disease [6,19]. From this perspective, attention deficits may also be seen as an early feature of AD.

Considering the fact that the attention process not only exists when people perform specific tasks but also maintains during the resting-state, it's reasonable to hypothesize that the attention deficits of AD patients may also have some expressions even during the resting-state. Recently, by using the resting-state fMRI, two pioneer studies by Fox et al. and Fransson identified two diametrically opposed brain networks on the basis of both correlations within each network and anti-correlations between networks [13,16]. They suggested that one of the two networks was "task-positive" network which was associated with the focused attention/goal-directed behavior and the other one was "task-negative" network which was associated with the stimulus-independent thought. They also proposed that the anti-correlations between the two networks might be interpreted as competition between focused attention and process subserving stimulus-independent thought. From this perspective, their findings offered a network model of attention in the human brain and suggested that it was an intrinsic organization of the brain function. In this paper, we used these two anti-correlated networks as a discriminative model of the brain functional deficits in early AD patients.

In this work, we hypothesized that the two anti-correlated networks may be abnormal in early AD patients and their alterations could distinguish AD patients from the elderly healthy controls. To test this hypothesis, we firstly obtained the two intrinsically anti-correlated networks using an anatomically labeled template. Then we analyzed the alterations of the two networks in early AD patients compared with the elderly healthy controls. In the end, we took the correlation/anti-correlation coefficients of all pairs of nodes within the two networks as the classification feature, and proposed a discriminative approach based on the Fisher Linear Discriminative Analysis (FLDA) to distinguish early AD patients from the elderly controls. MRI is noninvasive and has become more and more popular in the hospitals. In addition, resting-state fMRI has the advantage of easier manipulations relative to task-driven method, especially for patients. Hence a discriminative approach base on the resting-state fMRI may have potential in clinical applications.

2 Materials

To reduce the impact of head motion on the calculation of functional connectivity, we excluded the subjects with greater than 1 mm maximum displacement in either of x, y, z directions or greater than 1 degree of angular rotation. 14 AD patients and 14 elderly healthy controls were remained for further analysis. The AD patients and the elderly healthy controls were matched in gender , age and education levels. However, the Mini-Mental State Exam (MMSE) scores of AD patients were significantly lower than those of the healthy controls (23.1 ± 2.6 for patients, 28.8 ± 1.0 for controls). The diagnosis of AD patients fulfilled the Diagnosis and Statistic Manual Disorders, the Fourth Edition criteria for dementia

(DSM-IV) [1], and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD [7]. According to the results of a clinical progression and neuropathological study by Morris et al. [8], all the patients used here can be considered to be in the early-stage of AD. The AD patients were free of other diseases and the healthy controls were free of any medical, neurological and psychiatric disorders.

During the data acquisition, subjects were instructed to keep their eyes closed, relax their minds, move as little as possible, and staying awake at all times. The imaging processes of the AD patients and elderly healthy controls were performed on a 1.5 Tesla scanner. Echo Planer Imaging (EPI) Blood Oxygen Level Dependent (BOLD) images of the whole brain were acquired axially with the following parameters: 2000/60 ms (TR/TE), 20 slices, 90 degree (flip angle), 24 cm (FOV), 5/2 mm (thickness/gap), 64×64 (resolution). The fMRI scanning lasted for 6 minutes and 180 volumes were obtained. For each subject, the first 10 volumes were discarded for scanner stability. Preprocessing procedures for fMRI signals included time aligning across slices, motion correction, spatial normalization, voxels resampling to $3\times3\times3$ mm^3. All the above preprocesses were undertaken using SPM2 [12]. We also used a linear regression process to further remove the effects of head motion and other possible source of artifacts [13]: (1) six motion parameters, (2) whole-brain signal averaged over the entire brain, (3) the linear drift. In the end, the fMRI waveform of each voxel was temporally band-pass filtered ($0.01\text{Hz} < \text{f} < 0.08\text{Hz}$) by using the AFNI (http://afni.nimh.nih.gov/).

As described in the section 3, we pre-selected some regions in an anatomically labeled template to construct the two intrinsically anti-correlated networks. In order to test the validity of these regions, we also used another dataset of 17 young healthy participants (12 males and 5 females, age 25.71±5.62 years). The imaging processes were also undertaken on a 1.5 Tesla scanner. The data acquisition parameters and the preprocessing procedure were similar with those of the AD patients and elderly healthy controls.

3 The Two Intrinsically Anti-correlated Networks

In order to automatically obtain the two intrinsically anti-correlated networks, we used an anatomically labeled template previously reported by Tzourio-Mazoyer et al. [15]. This template divided the whole brain into 116 regions: 90 regions in the cerebra and 26 regions in the cerebella. According to the results of Fox et al. and Fransson [13,16], we selected 5 pairs of bilateral homologous regions in the "task-positive" network and 6 pairs of bilateral homologous regions in the "task-negative" network. The regions and their abbreviations were listed in the Table 1.

We obtained the mean time series of each of the 22 regions by averaging the fMRI time series over all voxels in the region. Correlations coefficients were computed between each pair of the regions. Then a Fisher's r-to-z transformation was applied to improve the normality of these correlation coefficients [14,21].

Table 1. The selected regions in the two anti-correlated networks and their abbreviations used in this paper

Task-positive network		Task-negative network	
Region	Abbreviations	Region	Abbreviations
Precentral gyrus	PRECG	Anterior cingulate gyrus	ACC
Superior frontal gyrus	SFG	Posterior cingulate gyrus	PCC
Middle frontal gyrus	MFG	Hippocampus	HIP
Supplementary motor areas	SMA	Parahippocampal gyrus	PHIP
Inferior parietal gyrus	IPG	Angular gyrus	ANG
		Precuneus	PCU

Because we used a labeled template to automatically obtain the two intrinsically anti-correlated networks, these regions were unlikely to exactly match what have been suggested by Fox et al. and Fransson [13,16]. Therefore, we should test whether these selected regions could represent those of the two intrinsic networks on the basis of both correlations within each network and anti-correlations between networks. Taking into account of the possible alterations of the two networks due to aging, we firstly tested the validity of the automatically obtained networks on the data of 17 young healthy participants. The results were shown in Figure 1 and Table 2. The correlation coefficients between each pair of regions were entered into one-sample two-tailed t test to determine the significant correlations ($p<0.05$, corrected for multiple comparisons [22]). Within the "task-positive" network, all the 23 significant correlations were positive. Within the task-negative networks, all the 31 significant correlations were positive. Between the task-positive network and the "task-negative" network, 46 correlations were significantly negative, 5 correlations were significantly positive, and others were not significant. This result suggested that the two automatically obtained networks were mainly positively correlated within each network and negatively correlated between networks. Therefore, the two networks of those selected regions could be used as a representation of the two intrinsically anti-correlated networks proposed by Fox et al. and Fransson [13,16].

We then used these pre-selected regions to construct the two intrinsically anti-correlated networks in the AD patients and elderly healthy controls, respectively. As shown in Table 2, the number of significant correlations/anti-correlations of both AD patients and elderly healthy controls was obviously less than that of the young healthy participants. As to the AD datasets, the number of significant correlations within the "task-positive" network in AD patients was more than that of elderly healthy controls. This was possibly because those regions in the task-positive network were mainly distributed in the prefrontal lobe. Many studies have reported increased functional connectivity associated with the prefrontal regions compared with elderly controls [2,3,4]. The increase of prefrontal functional connectivity has been interpreted as a compensatory reallocation or recruitment of cognitive resources [13]. The number of significant

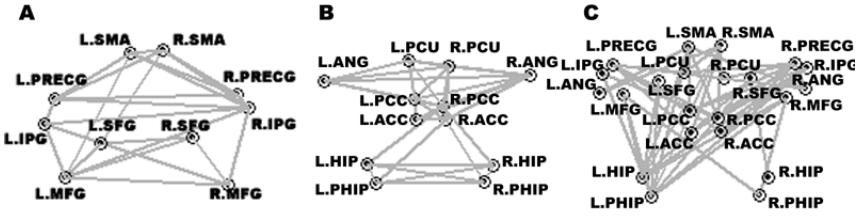

Fig. 1. Graphic representations of the significant correlations within the "task-positive" network/"task-negative" network and anti-correlations between the two networks in the dataset of young healthy participants. (A) The significant correlations within the "task-positive" network. (B) The significant correlations within the "task-negative" network. (C) The significant anti-correlations between the two networks. $P<0.05$ (corrected for multiple comparison using the method described by Benjamini and Yekutieli [22]) were used to determine the significant correlations/anti-correlations.

Table 2. The number of significant positive correlations within each network and significant negative correlations between the two networks

Subjects	NSPC in the task -positive network	NSPC in the task -negative network	NSNC between two networks
Young healthy participants	23	31	46
Elderly healthy controls	16	19	22
Early AD patients	19	18	16

NSPC: the number of significant positive correlations; NSNC: the number of significant negative correlations.

correlations within the "task-negative" network in AD patients was similar with that of the elderly healthy controls but the number of significant anti-correlations between the two networks was less than that of the elderly healthy controls. Fox and colleagues suggested that the anti-correlations of the two networks might be interpreted as competition between focused attention and process subserving stimulus-independent thought [13]. Fransson proposed that the two anti-correlated networks reflected a recurring switch between an introspective versus an extrospectively oriented attention state-of-mind [16]. From this view, the decreased number of significant anti-correlations indicated that when the AD patients tried to concentrate on some things they might have difficulty in effectively inhibiting other random thought, and this may partly interpret the attention deficits of AD patients.

The above results indicated that the number of correlations/anti-correlations of the two intrinsically networks were altered in early AD patients compared with elderly healthy controls. In the next section we used the correlation/anti-correlation coefficients of the two networks as the classification feature to discriminate early AD patients from elderly healthy controls.

4 Pseudo-Fisher Linear Discriminative Analysis

The primary purpose of the Fisher Linear Discriminative Analysis (FLDA) is to discriminate samples of different groups by maximizing the ratio of between-class separability to within-class variability [5,17,18]. The between-class scatter matrix is defined as formula (1) and the within-class scatter matrix is defined as formula (2):

$$S_b = (m_1 - m_2)(m_1 - m_2)^T \tag{1}$$

$$S_w = \sum_{i=1}^{N_1}(x_1^i - m_1)(x_1^i - m_1)^T + \sum_{i=1}^{N_2}(x_2^i - m_2)(x_2^i - m_2)^T \tag{2}$$

Where x_1^i and x_2^i are n-dimensional feature vectors of each sample. In this study the feature is the vector of the correlation coefficients and anti-correlation coefficients of the two intrinsically network obtained in the section 3; m_1 and m_2 is mean feature vectors of each group; N_1 and N_2 is sample size of each group. The main objective of FLDA is to find a projective direction ω that maximizes the objective function as (3):

$$J(\omega) = \frac{\omega^T S_b \omega}{\omega^T S_w \omega} \tag{3}$$

Theoretically, the optimal can be determined by:

$$\omega^* = S_w^{-1}(m_1 - m_2) \tag{4}$$

This is the standard FLDA procedure.

However, in many brain image analysis, the number of total training observations is very limited compared to the dimension of the feature space ($N_1 + N_2 << n$). In this condition, computing the inverse matrix of S_w is an ill-posed problem and therefore the standard FLDA may get unreliable result. To solve this problem, we used a Pseudo-Fisher Discriminative Analysis (pFLDA) which firstly applied a Principal Component Analysis (PCA) on the sample feature $x \in \Re^n$ to get a low-dimensional feature $x' \in \Re^{n'}$ ($n' = N_1 + N_2 - 1$). Then the standard FLDA procedure is used in the low-dimensional feature space to find $\omega^* \in \Re^{n'}$ [11,20].

In the end, we can project each sample $x' \in \Re^{n'}$ onto the direction $\omega^* \in \Re^{n'}$ to get a discriminative score z by:

$$z = \omega^{*T} x' \tag{5}$$

The classification threshold z_0 is determined by:

$$z_0 = (N_1 m_1^z + N_2 m_2^z)/(N_1 + N_2) \tag{6}$$

Where m_1^z and m_2^z are the mean values of the discriminative scores of the two classes in the training set.

5 Experimental Results

The generalization performance of the classifier was evaluated by using a leave-one-out (LOO) cross validation approach. The leave-one-out approach has been widely used as a reliable estimator of the true generalization performance, especially when the sample size is very limited. Classification results were listed in the top row of Table 3. The correct prediction rate performed on the AD patients and the elderly healthy controls were 93% and 72% respectively, and the total correct prediction rate reached 83%.

Table 3. Classification results

Discriminative model	LOO test correct rate		
	Elderly controls	AD patients	Total
Two intrinsically anti-correlated networks	72%	93%	83%
The whole brain network	78%	43%	61%

We then compared the discriminative ability of proposed model with the whole brain network model which used the correlation/anti-correlation coefficients of all pairs of the 116 regions as the feature. pFLDA was also applied to the new feature space and the results were shown in the second row of Table 3. We can see that its classification rate (61%) was obviously lower than that of the proposed classifier (83%). This result suggested that the discriminative model based on the two intrinsically anti-correlated networks was more effective than the whole brain network model. More importantly, this implied that the two intrinsically anti-correlated networks may be a more susceptible part of the whole brain network of AD patients in their early stage of the disease.

6 Conclusions

In this paper, we used a template to automatically obtain the two intrinsically anti-correlated networks that have been suggested by Fox et al. and Fransson [13,16]. Though not exactly the same, our results confirmed the existence of the two intrinsically anti-correlated networks on the basis of correlations within each network and anti-correlations between networks in a different set of subjects. In addition, we found that there were alterations of the correlations/anti-correlations associated with the two networks in early AD patients compared with age-matched elderly healthy controls. We then used the correlation/anti-correlation coefficients as the feature to discriminate the AD patients and the healthy controls. The results indicated that the proposed classification method based on the two intrinsically anti-correlated networks may be an effective and promising tool for the discrimination of early AD patients. As resting-state fMRI is non-invasive, objective and more easily manipulated especially for patients, it may have potential ability to improve the current diagnosis and treatment evaluation of AD. Future work will involve the evaluation of the proposed method

with larger sample size and multi-center imaging data. Moreover, we believe the combination with other features may add more valuable information and possibly get better classification performance.

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