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Research Report

Functional segregation of executive control network and frontoparietal network in Alzheimer's disease

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ABSTRACT

Functional connectivity pattern altered of default mode network (DMN) is gaining more attention as a potential noninvasive biomarker to diagnose incipient Alzheimer's disease. However, the changed functional connectivity except for DMN, the longitudinal changes in executive control network (ECN) and frontoparietal network (FPN) also has attracted wide interest. Moreover, AD-related functional connectivity abnormalities within the DMN are well replicated research, but the (increased/decreased and reduced) functional connectivity in ECN and FPN weren't receive adequate attention. To address the above issues, in this paper, we adopt sparse inverse covariance estimation (SICE) approach to investigate the changed functional connectivity of ECN and FPN on the ADNI2 dataset. Our experimental results indicate the left superior frontal gyrus (SFGmed.L) and left thalamus (THA.L) regions of ECN has shown increased functional connectivity, the left anterior cingulate (ACG.L) region of ECN has shown decreased functional connectivity. The Superior Parietal Gyrus (SPG) regions and left paracentral lobule (PCL.L) of FPN has shown increased functional connectivity, the left supramarginal gyrus (SMG.L) regions has shown decreased functional connectivity in AD patients. On the other hand, the ACG.L regions in ECN, SMG.L and left inferior parietal (IPL.L) in FPN have shown significantly reduced functional connectivity. These results demonstrate that increased/decreased functional connectivity and reduced functional connectivity not only within DMN, but also associated with ECN and FPN. It also suggest that AD is associated with the characteristics of large-scale functional networks, and these changed functional connectivity possibly as a potential noninvasive biomarker to diagnose incipient Alzheimer's disease.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that accounts for approximately 50–80% of all dementia cases, the main characteristics are cognitive decline, irreversible memory loss, disorientation, and language impairment. Early signs of AD include loss of short-term memory function followed by a progressive decline in other cognitive domains including language, attention, orientation, visuospatial skills, executive function, as well as emotional and behavioral disturbances. Ultimately, it will lead to loss of memory and some of the functions. With both the proportion of older people and the length of life increase throughout the world, AD has now become a major public health concern. The number of affected patients is estimated to triple and reaches 13.4 million, in the United States by the year 2050 (Mueller et al., 2005). To prevent or delay the progression of AD, researchers have focused on the search for a sensitive, noninvasive, in vivo biomarker that would enable earlier, more accurate clinical diagnosis, monitoring disease progression and the effectiveness of therapeutic intervention (Dubois et al., 2007; Fennema-Notestine et al., 2009; Galasko, 2005; Thal et al., 2006). Recent from neuroimaging community report, the functional connectivity of default mode network (DMN) as a potential noninvasive biomarker to diagnose incipient Alzheimer's disease was gain more attention. Moreover, the changed functional connectivity except for DMN, the other longitudinal changes functional networks has attracted wide interest, e.g., Executive Control Network (ECN); Frontoparietal Network (FPN). In neuroscience community view, these functional connectivity networks (e.g., DMN, ECN) may sometimes work together to perform tasks and the changes functional connectivity of these functional networks perhaps leading causes of morbidity (Godwin et al., 2017; Littow et al., 2015). Therefore, it would be worthwhile to explore abnormal functional connectivity of these functional networks for AD diagnose.

Functional connectivity is defined as temporal correlations between spatially distinct brain regions, and by measuring the level of co-activation of resting-state Functional magnetic resonance imaging (fMRI) time-series between brain regions have revealed interesting new findings about the functional connections of specific brain regions and local networks (Friston, Frith, Liddle, & Frackowiak, 1993). These findings have shown that AD subject's brain may have different connectivity patterns from normal subject, and resting-state functional connectivity was sensitive to functional brain changes related to AD pathology across the clinical spectrum (Damoiseaux, 2012). Functional connectivity change as a biomarker of AD holds promising for guiding treatment before the occurrence of significant functional impairment or irreversible neuronal damage (Franzmeier et al., 2017; Hohenfeld, Werner, & Reetz, 2018; Mueller et al., 2005; Sui et al., 2015; Thal et al., 2006). Therefore, exploring and detecting abnormal functional connectivity of intrinsic connectivity networks preserve a promising to diagnosis and treatment of AD (Yang et al., 2011).

A large body of methods have been proposed to analyze functional connectivity. These methods included pearson correlation, partial correlation, mutual information, independent component analysis (ICA), graphical model and sparse representation methods (Lv et al., 2015; Wee, Yap, Zhang, Wang, & Shen, 2014). Pearson correlation and partial-correlation are also called region of interest (ROI) or "seed-based" methods, and correlation method (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Marrelec et al., 2006; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007; Worsley, Charil, Lerch, & Evans, 2005) is one of the most frequently application methods, any two brain regions of the time courses correlation, allows one to infer whether the regions are functionally connected. Although, correlation-based methods are used widely, these methods can only capture pairwise information and cannot fully reflect the interaction among multiple brain regions (Huang et al., 2010; Wee et al., 2014).Furthermore, correlation cannot reveal anything about causality or even whether connectivity was direct versus indirect (Marrelec et al., 2006; Smith et al., 2013). Due to the limitation of correlation method, ICA method has been developed to study brain functional connectivity, which several distinct resting state networks (RSNs) in which distinct brain areas exhibit consistent synchronization at very low frequencies when at rest were detected and separated, on the basis of their spatial patterns, voxel values selected reflect the degree to which the time series of each voxel was correlated with the mean time series of the RSNs. ICA method can examine multiple functional networks connectivity simultaneously, but determining the optimal number of components and separating noise related components are still challenging tasks (Beckmann, DeLuca, Devlin, & Smith, 2005; Sheline & Raichle, 2013).

Recently, graphical models have been introduced to study brain connectivity, such as Lin, Meng, Karunanayaka, & Holland (2011), developed a spectral graphical model approach for learning brain connectivity network of Children's Narrative Comprehension. Ng, Varoquaux, Poline, & Thirion (2012), proposed a novel multimodal integration approach based on sparse Gaussian graphical model for estimating brain connectivity, casting functional connectivity estimation as a sparse inverse covariance learning problem, and adopt the level of sparse penalization on each connection based on its anatomical capacity for functional interactions. Ortiz et al. (2015) used sparse inverse covariance estimation (SICE) method to learn undirected graphs in order to derive functional and structural connectivity patterns from position emission tomography (PET) data and segmented Magnetic Resonance images (MRI) from the ADNI database. However, most of these methods exist limitations, that make them inadequate for studying AD brain connectivity, since little prior knowledge (such as which brain regions are involved and how they are connected) was available, but it was often required in those methods (Huang et al., 2010).

The abnormal functional connectivity as a diagnose biomarker has already shown its potential clinical value as well as providing rich and sensitive markers for AD (Damoiseaux, 2012). However, there are still some additional issues that need to be addressed, e.g., the increased/decreased functional connectivity of brain networks are well replicated research, but the reduced functional connectivity rarely study. Secondly, AD-related abnormalities functional connectivity

within the DMN are well replicated research findings(Andrews-Hanna et al., 2007; Damoiseaux et al., 2007; Koch et al., 2010; Sheline et al., 2010; Zhang et al., 2009), but the abnormal functional connectivity and the pathologic changes in ECNand FPN has been little investigated. Furthermore, these functional networks (ECN,FPN) also have associated AD, at least recent studies warrant these networks have significant reduced functional connectivity (Agosta et al., 2012; Andrews-Hanna et al., 2007; Sorg et al., 2007; Zhao, Lu, Metmer, Li, & Lu, 2018). For example, Sorg et al. (2007) found reduced connectivity in the superior parietal lobule (SPL) and prefrontal cortex (PFC) in mild cognitive impairment (MCI). The second one, Agosta et al. examined the DMN, ECN (fractured into ECN and a few "fronto-parietal" networks) and salience network in AD and MCI. In the DMN and frontoparietal components, they found both reduced connectivity in specific regions in AD compared to MCI and NC (Normal controls) and reduced mean connectivity across the whole component (Agosta et al., 2012; Zhao et al., 2018). In summary, these results suggest that AD reduced functional connectivity not only associated with DMN, but also associated with the ECN and FPN. Therefore, exploring the functional connectivity of ECN and FPN networks were have significant implications for early diagnose AD.

In this paper, we used a "sparsity" constraint on the maximum likelihood estimation (MLE) of inverse covariance matrix to explore the functional connectivity in DMN, ECN and FPN networks. Our experimental results showed this method could reliable estimation of the functional connectivity, and these functional networks have shown significant increased/decreased functional connectivity. Furthermore, experimental results also present that the AD patients have reduced connectivity in the FPN, DMN and ECN. These results possibly suggest AD is not only associated with DMN, but also associated with other functional networks.

2. Materials and methods

In this section, we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. *Participants*

One hundred and nine cognitively normal elderly subjects (CN) and one hundred and four subjects with AD dementia (ranging in age from 55 to 90 years) participated in this study. Normal Subjects: Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), the CDR of 0, non-depressed, non-MCI, and non-demented. AD Subjects: MMSE scores between 20–26 (inclusive), the Clinical Dementia Rating (CDR) of .5 or 1.0, and meets National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD. The subjects obtained from the Alzheimer's disease Neuroimaging Initiative 2 (ADNI2) database (http://adni.loni.usc.edu/adni-go-adni-2-clinical-data-available). The Alzheimer's Disease Neuroimaging Initiative (ADNI) unites researchers with study data as they work to define the progression of Alzheimer's disease (AD). Access is contingent on adherence to the ADNI Data Use Agreement and the publications' policies outlined in the documents (http://adni.loni.usc.edu/data-samples/access-data/). The application process includes acceptance of the Data Use Agreement and submission of an online application form. The application includes the investigators institutional affiliation and the proposed uses of the ADNI data. ADNI data may not be used for commercial products or redistributed in any way. In this study, we use resting-state functional MRI (fMRI) data of ADNI2, the ADNI2 resting state fMRI data include 209 NC, 208 subjects with early stage mild cognitive impairment (EMCI), 183 subjects in a more advanced stage of MCI (LMCI), and 121 subjects with AD dementia. For more detail information and inclusion criteria/exclusion criteria on these subjects, see the https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf.

2.2. *Imaging acquisition*

MRI scans were conducted on a 3.0 T Philips MRI scanner. All participants performed resting state Functional MRI scanning (Field Strength = 3.0 T; 8-channel head coil, Flip Angle = 80.0°; Matrix X = 64.0 pixels; Matrix Y = 64.0 pixels; Pixel Spacing X = 3.3125 mm; Pixel Spacing Y = 3.3125 mm; Pulse Sequence = Gradient Recalled; Slices = 6720.0; Slice Thickness = 3 mm; TE = 30.0 msec; TR = 3000.0 msec). Functional MR images were acquired while at resting, to avoid initiating goal-directed, attention-demanding activity during the scanning sessions, subjects were instructed to keep their eyes closed, and to remain awake.

2.3. *Data preprocessing*

The unprocessed images from MRI scanners inevitably contain several types of spatial distortion, noise, artifacts, and biases. To make best use of the ADNI2 datasets, it was critical to compensate as much as possible for these distortions, biases, and artifacts. Data preprocessing were carried out with FMRIB Software Library (FSL) tools (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009) and Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI) (Yan, Wang, Zuo, & Zang, 2016). The preprocessing pipelines included: head motion correction by using MCFLIRT, non-brain removal by using Brain Extraction Tool (BET), Spatial smoothing by using a Gaussian kernel of full width at the half maximum (FWHM) 5 mm; Registration of each subject's FMRI data to MNI152 standard space was achieved by using FMRIB's Linear Image Registration Tool (FLIRT) affine registration, then via detrended and band-pass filtered (.01–.08 HZ) to remove the extremely low and high-frequency artifacts, and further regressed out nuisance signals. The registered to MNI152 space FMRI data were partitioned via using the anatomically labeled template (Tzourio-Mazoyer et al., 2002), and the whole brain was divided into 116 regions: 90 regions in the cerebra and 26 regions in the cerebella, finally extracted the mean time series of the whole brain by averaging the fMRI time series over all voxels in the regions.

2.4. Functional connectivity analysis via sparse inverse covariance estimation

In this section, we adopt sparse inverse covariance estimation (SICE) method for functional connectivity modeling, this method also known as Gaussian graphical models or graphical Lasso. This method imposes a "sparsity" constraint on the maximum likelihood estimation (MLE) of inverse covariance matrix, which leads to reliable estimation of the inverse covariance with small sample sizes. Here, "small" means that the sample size can be close to or even less than the number of brain regions modeled. Using SICE to model brain connectivity is appropriate because many past studies based on anatomical brain datasets have shown that the true brain network is sparse (Kötter & Stephan, 2003; Sojoudi, 2016; Sporns, Chialvo, Kaiser, & Hilgetag, 2004; Yang et al., 2015). Hence, we introduce this method to analyze functional connectivity.

In this study, we assume there are i brain regions to be modeled, i.e., $X = \{x_1, \ldots, x_i\}$ and follows a multivariate Gaussian distribution. The measurement data for each region is the regional time series. Let $x_1, x_2, \ldots, x_i \sim N(\mu, \sum) \in R^n$ where $x_i, 1 \le i \le n$, $\mu \in R^n$ is the mean, and $\sum \in R^{n \times n}$ is the covariance matrix, many applications require estimation the meanμ, and either the covariance $\sum$ or its inverse $\sum^{-1}$, let $\Theta = \Sigma^{-1}$ and it is also called the precision matrix. Both the mean vector μ and the covariance matrix $\sum$ are often approximated using the standard maximum likelihood estimation (MLE), which leads to $\hat{\mu} = (1/m)\sum_{i=0}^{m} x_i$. The empirical covariance is denoted as S:

$$S = \frac{1}{m}\sum_{i=0}^{m}(x_i - \hat{\mu})(x_i - \hat{\mu})^T \quad (1)$$

which is also called the empirical covariance matrix. Specifically, according to the MLE, it can be derived that maximum log likelihood estimation of Θ, and multivariate Gaussian model can be obtained as follows:

$$\hat{\Theta} = \underset{\Theta \succ 0}{argmax}(\log(det\Theta) - tr(S\Theta)) \quad (2)$$

where Θ and $\hat{\Theta}$ denote inverse covariance matrix and its estimation, S is the sample covariance matrix, $det(\cdot)$ and $tr(\cdot)$ denote the determinant and trace of a matrix. If the number of subjects is smaller than the problem dimension, i.e., $m < n$ then S in (2) is rank deficient, whereas the true Σ is assumed to be positive definite, hence full-rank, and estimate $\sum^{-1}$ assuming that it is sparse (Dempster, 1972, pp. 157–175).

Several existing literature in machine learning and statistics naturally connects sparse precision matrices with Gaussian graphical models (Dempster, 1972, pp. 157–175), and it has motivated numerous application (Lauritzen, 1996). To estimate sparse precision matrices for Gaussian distributions, many methods in the past decade have been proposed based on the sample covariance estimator, e.g., Banerjee, Ghaoui, & d'Aspremont (2008), Yuan & Lin (2007) and Friedman, Hastie, & Tibshirani (2008) take advantage of the Gaussian likelihood proposed the graphic lasso (GLASSO) estimator by solving:

$$\hat{\Theta} = \underset{\Theta \succ 0}{argmax}(\log(det\Theta) - tr(S\Theta) - \lambda||\Theta||_1) \quad (3)$$

where parameter $\lambda > 0$ is the regularization parameter. Solving this problem can used GLASSO package developed by Zhao, Liu, Roeder, Lafferty, & Wasserman (2012). Thus SICE finds an estimation for the inverse covariance matrix ($\hat{\Theta}$) of the brain regions connections by solving equation (3), where $||\cdot||_1$ denotes the sum of absolute values of all the entries in a matrix.

In equation (3), when the value of λ is smaller, the constraint has less impacted, and the SICE becomes the usual MLE. Conversely, the value of λ becomes larger, the Θ is estimated by SICE has more influenced. This monotone property has proved by Huang et al. (2010). On the other hand, a common characteristic of the SICE methods is that they are good at discovering which entries in the inverse covariance matrix are zero and which are non-zero, they may not be good at estimating the magnitude of the non-zero entries due to the "shrinking" effect. Therefore, SICE method may be more appropriate to be used for identifying the inverse covariance matrix structure. As a result, once an estimate Θ is obtained from SICE, we could use the information (i.e., zero and non-zero entries) in to Θ build a brain connectivity model (Huang et al., 2010). Besides, if two brain regions are not connected (there is not a path between them) in the connectivity model at a certain λ, they will never become connected as λ goes larger. This property can be derived structural and functional connectivity models for different values of sparseness, corresponding to models with different strength of connections (Huang et al., 2010; Levina, Rothman, & Zhu, 2008; Sun et al., 2009).

3. Results

3.1. Functional connectivity analysis via sparse inverse covariance estimation

In this study, we used SICE evaluated functional connectivity of different brain regions. To compare the functional connectivity differences between SICE and other state-of-art methods, the four different functional connectivity methods matrices are shown in Fig. 1. The first row shows Pearson correlation, Kendall rank correlation, sparse representation, and SICE four different methods functional connectivity matrices of Normal Controls. The second row show corresponding functional connectivity matrices of AD patients. From these four different correlation matrices, we can see that Pearson correlation, Kendall rank correlation matrix can capture pairwise ROI interaction of 116 regions obviously, and have a great quantity non-zero elements in both of these matrices. From Fig. 1, we can observed sparse representation [Fig. 1(c) and (g)] that the connectivity are relatively sparsity and have fewer non-zero elements. However, compared with SICE [Fig. 1(d) and (h)] in Fig. 1, we can observe that SICE matric not only even sparsity, but also could keep main connections. In addition, although Pearson correlation and Kendall rank correlation matrices also could capture pair-wise ROI connections strength, these correlation matrices are not sparsity. Furthermore, these two methods exist plenty of irrelevant functional connectivity that results in difficulty to distinguish which functional connectivity is important. For example, in Fig. 1(b) and (f), both normal controls and AD have plenty of relevant connections, its difficulty to identify the significant

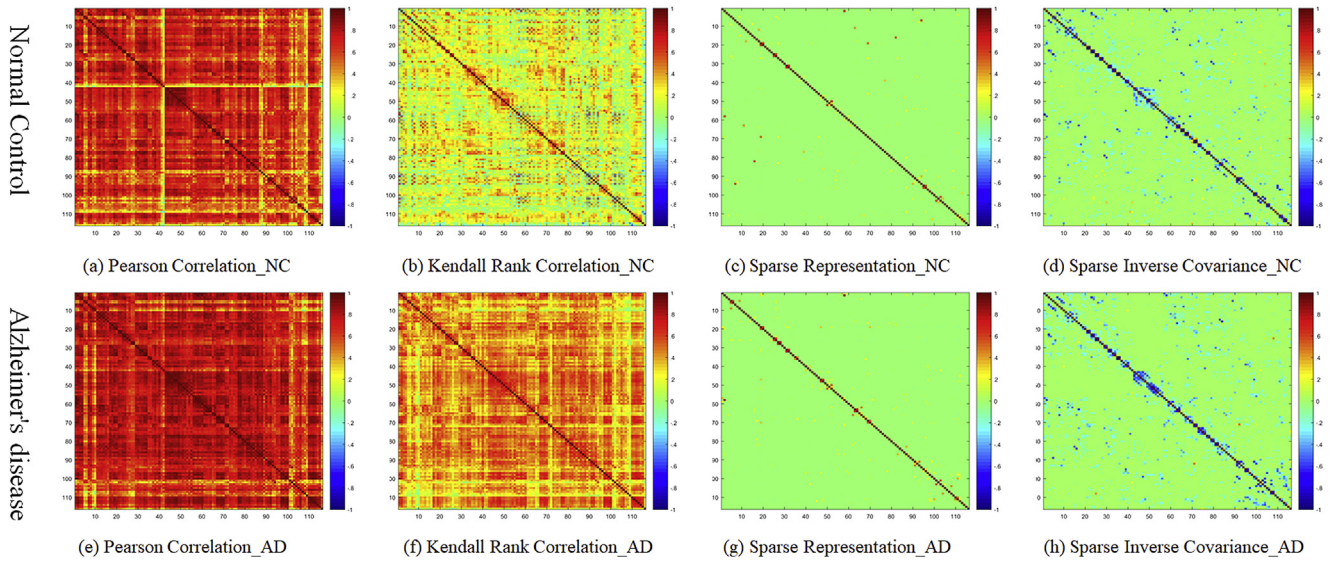


Fig. 1 – Comparison two group (NC and AD) weight matrices of the same subject estimated by four different methods.

functional connectivity. Hence, these methods can't discriminate main changed functional connectivity between normal control and AD.

In addition, evaluating functional connectivity using SICE method relates to the parameter λ selection issues, the parameters λ has significant impact for functional connectivity. To tune the parameters of the SICE method, in this work we calculate the different values of λ, we selected parameters range between [.02–.80], when the $\lambda = 0.02$, the quantity of noise (weak connectivity) are kept in normal control and AD. As λ increasing, the noise would be reduced, when the $\lambda = 0.2$, the mainly connections are retained and the weak connectives are removed. Hence, in ideal case, $\lambda = 0.2$ was selected in this study.

3.2. *Functional connectivity changes in ECN and FPN*

In this section, we mainly investigate the functional connectivity changes in large-scale networks of ECN and FPN. As shown in Fig. 2, the left superior frontal gyrus (SFGmed.L) [Fig. 2(d)] and left thalamus (THA.L) regions [Fig. 2(f)] of ECN showed increased functional connectivity. In contrast, the left anterior cingulate (ACG.L) [Fig. 2(b)] region of ECN has shown decreased functional connectivity compared with NC [Fig. 2(a)]. ECN was typically composed of the anterior cingulate cortex (ACC), anterior prefrontal cortex (APFC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DPFC), left inferior parietal ((IPL.L), and the left fronto-insula were reported as brain regions of ECN in healthy subjects (Seeley et al., 2007; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Our results [Fig. 2(d)] show increased functional connectivity in the superior frontal gyrus and thalamus, the functional connectivity changes maybe indicate these regions occur to damages, which results in functional connectivity becomes increased. On the other hand, in this study the left anterior cingulate (ACG.L) [Fig. 2(b)] region of ECN has decreased functional connectivity.

Compared with normal controls, partial regions of FPN showed increased functional connectivity in AD patients. As show in Fig. 3, the results showed the Superior Parietal Gyrus (SPG) region [Fig. 3(b)] and left Inferior parietal (IPL.L) region [Fig. 3(d)] of FPN have increased functional connectivity (Fig. 3) in AD patients, however, the left supramarginal gyrus (SMG.L) regions [Fig. 3(f)] showed decreased functional connectivity compared with normal control [Fig. 3(e)]. More interestingly, compared with healthy controls, AD patient's left FPN showed a significantly increased connectivity of in the left IPL region.

3.3. *Reduced functional connectivity in large-scale functional connectivity networks*

Compared with normal control (NC), AD patients showed the reduced functional connectivity, the detailed results can be seen in Fig. 4. Fig. 4(a) show the NC functional connectome, Fig. 4(b) show the AD patients functional connectome figures. Here, we quantitative analysis the reduced functional connectivity, when the parameter $\lambda = 0.01$, the reduced functional connectivity not significantly. Fig. 4(c) and (d) show functional connectivity NC and AD respectively when the parameter $\lambda = 0.1$. It is notice that functional connectivity compared Fig. 4(c) with (a) didn't significant reduced, which suggesting these functional connectivity haven't significant reduced in NC with the parameters changes. Conversely, Fig. 4(d) show reduced functional connectivity. These reduced functional connectivity included left posterior cingulate gyrus (PCG.L), hippocampus (HIP.L), left anterior cingulate (ACG.L), middle frontal gyrus (MFG.R), supramarginal gyrus (SMG.L), middle temporal gyrus (TPOmid.L, TPOmid.R), superior temporal gyrus (TPOsup.L, TPOsup.R), thalamus (THA.L), paracentral lobule (PCL.L, PCL.R), precuneus (PCUN.L), left inferior parietal (IPL.L), middle temporal gyrus (MTG.L), middle frontal gyrus (ORBmid.L), precentral gyrus(PreCG.L) and superior frontal gyrus (ORBsup.L). The reduced functional connectivity of PCG.L, PCUN.L, IPL.L and HIP.L were mainly cover the area of DMN. The, ACG.L regions is located on anterior cingulate

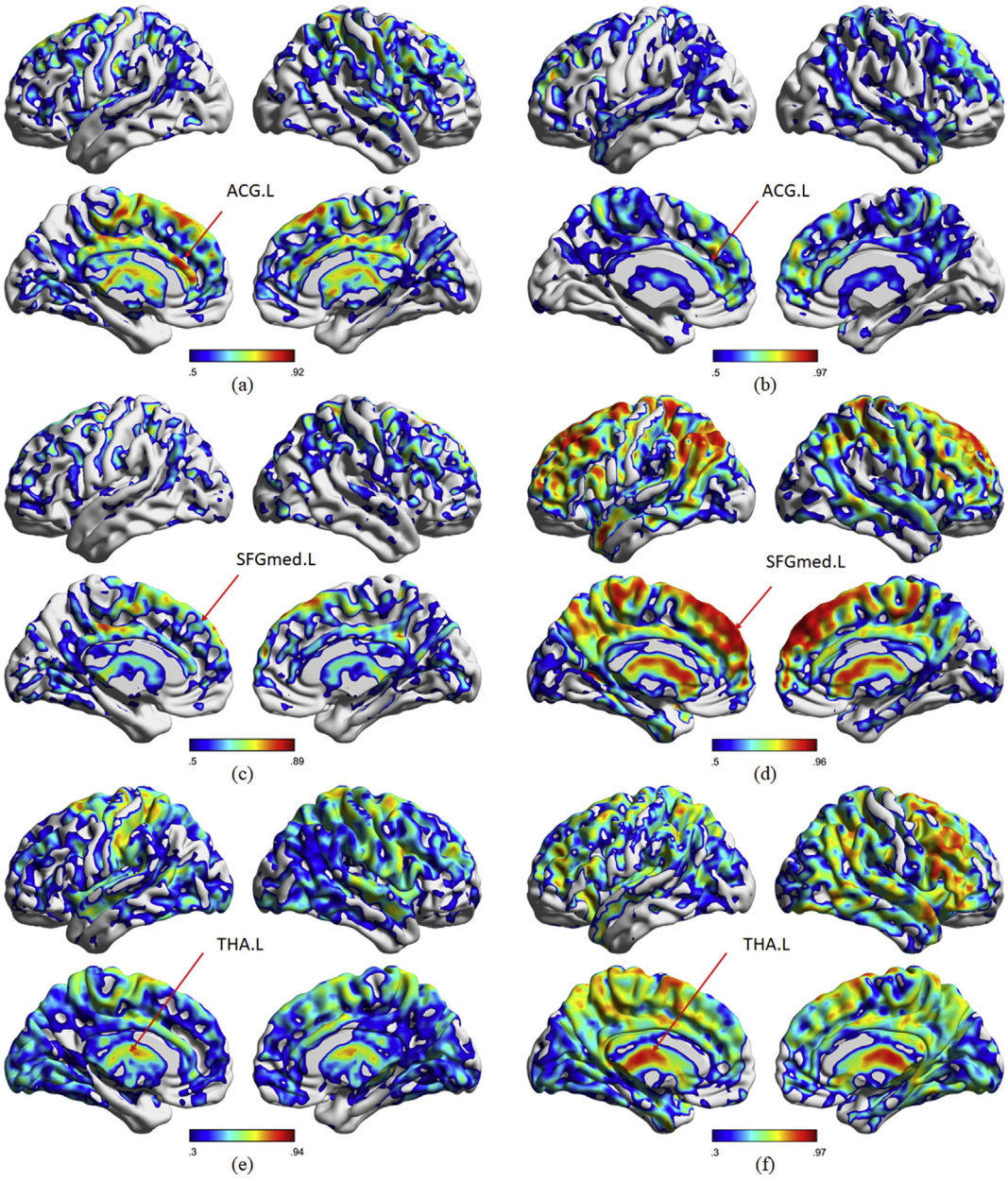


Fig. 2 – The changed functional connectivity of ACG.L, SFGmed.L and THA.L regions in the ECN, (a) is the ACG.L region of Normal subject, (b) is the ACG.L region of AD, (c) is the SFGmed.L region of Normal subject, (d) is the SFGmed.L region of AD, (e) is the THA.L region of normal subject and (f) is the THA.L regions of AD.

cortex, this cortex is the main areas of ECN, SMG.L and IPL.L (overlap with DMN) are the main areas of FPN. Furthermore, the reduced functional connectivity also found in TPOmid.L, TPOsup.L, TPOsup.R, ORBmid.L PreCG.L and ORBsup.L areas in Fig. 4(d).

To quantitative analysis changed functional connectivity, Fig. 5 shows reduced and preserved functional connectivity. Fig. 5(b) shows AD patient preserved functional connectivity when the parameter $\lambda = 0.5$, these functional connectivity also can be found in Fig. 5(a), that suggesting these functional connectivity are common connections are preserved. Conversely, comparison Fig. 5(a) and (b), we found the AD patients have reduced functional connectivity included PCL.L, PCUN.L, PCUN.R, SMG.L, SMG.R, SFGdor.L, ORBsup.L, ORBsup.R, ACG.L, and ACG.R. Most interesting, we found these reduced regions are mainly cover the DMN, ECN and FPN networks. The functional connectivity of posterior cingulate cortex (PCC) and parahippocampal gyrus reduced in AD patients. In summary, we found reduced functional connectivity not only in DMN, but also found both SFGmed.L and ACG.R in ECN, and the reduced connections of SMG.L in FPN.

4. Discussion

In this study, we adopt SICE approach to investigate the functional connectivity of large-scale functional connectivity networks of ECN and FPN. Our experimental results have shown

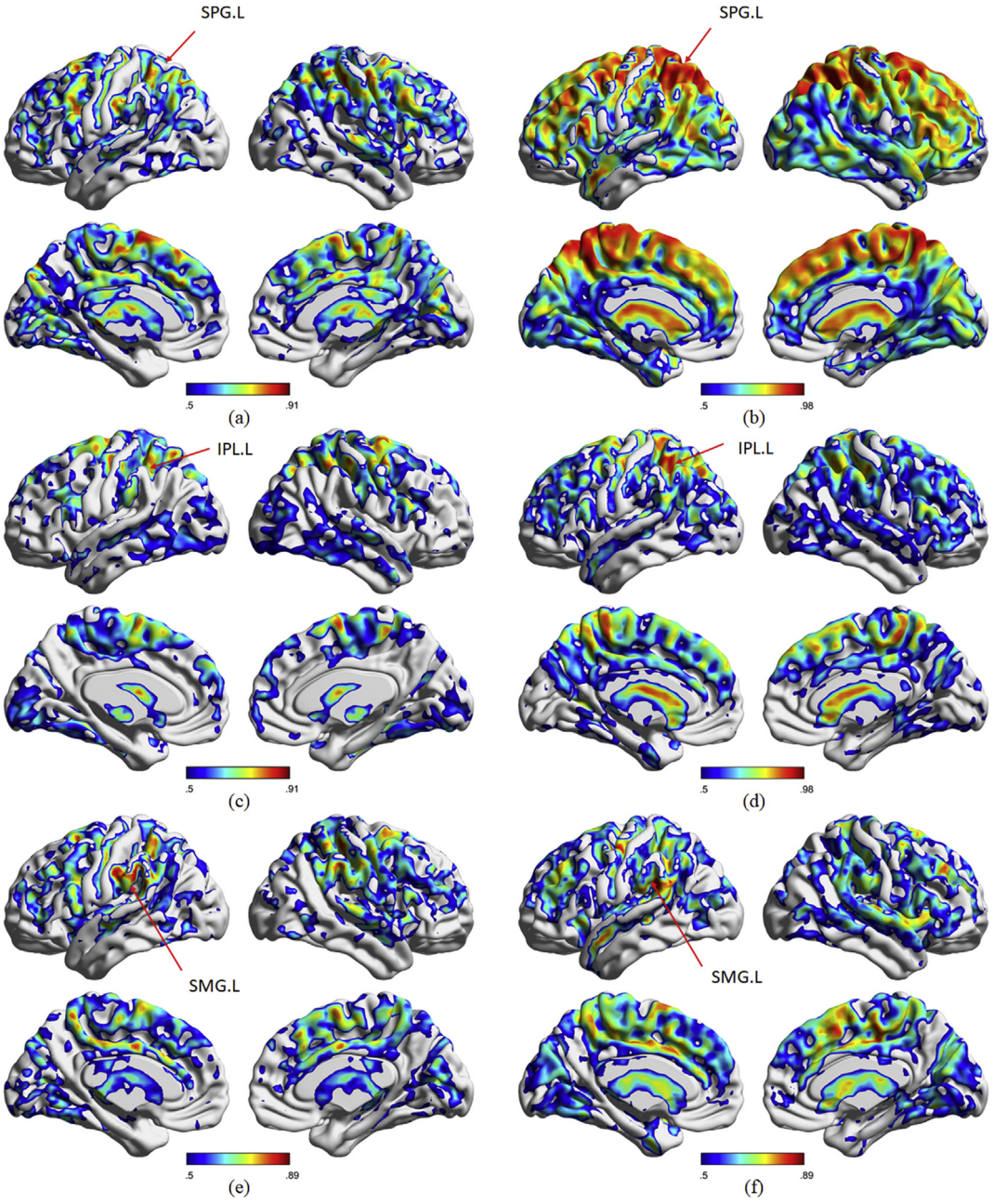


Fig. 3 – The changed functional connectivity of SPG.L, IPL.L and SMG.L regions in the FPN, (a) is the SPG.L region of Normal subject, (b) is the ACG.L region of AD, (c) is the IPL.L region of Normal subject, (d) is the IPL.L region of AD, (e) is the SMG.L region of normal subject and (f) is the SMG.L regions of AD.

except for DMN, AD is also associated with altered functional connectivity networks of ECN and FPN, and these networks demonstrate increased/decreased and reduced functional connectivity. The reduced functional connectivity included PCG.L, HIP.L, ACG.L, MFG.L, MFG.R, SMG.L, TPOmid.L, TPOmid.R, TPOsup.L, TPOsup.R, THA.L, PCL.L, PCL.R, PCUN.L, IPL.L, MTG.L, ORBmid.L, PreCG.L and ORBsup.L. These reduced functional connectivity regions cover DMN, ECN and FPN. Furthermore, the left superior frontal gyrus (SFGmed.L) and thalamus (THA.L) regions of ECN showed increased functional connectivity, the left anterior cingulate (ACG.L) region of ECN showed decreased functional connectivity compared with NC. On the other hand, compared with normal controls, the Superior Parietal Gyrus (SPG) regions and part paracentral Lobule (PCL.L) showed increased functional connectivity, the SMG.L regions has shown decreased functional connectivity within the FPN. These changed functional connectivity possibly as a potential noninvasive biomarker to diagnose incipient Alzheimer's disease.

4.1. *The increased/decreased functional connectivity of ECN and FPN*

The large-scale functional networks have reported which include Visual network, Default Mode Network (DMN),

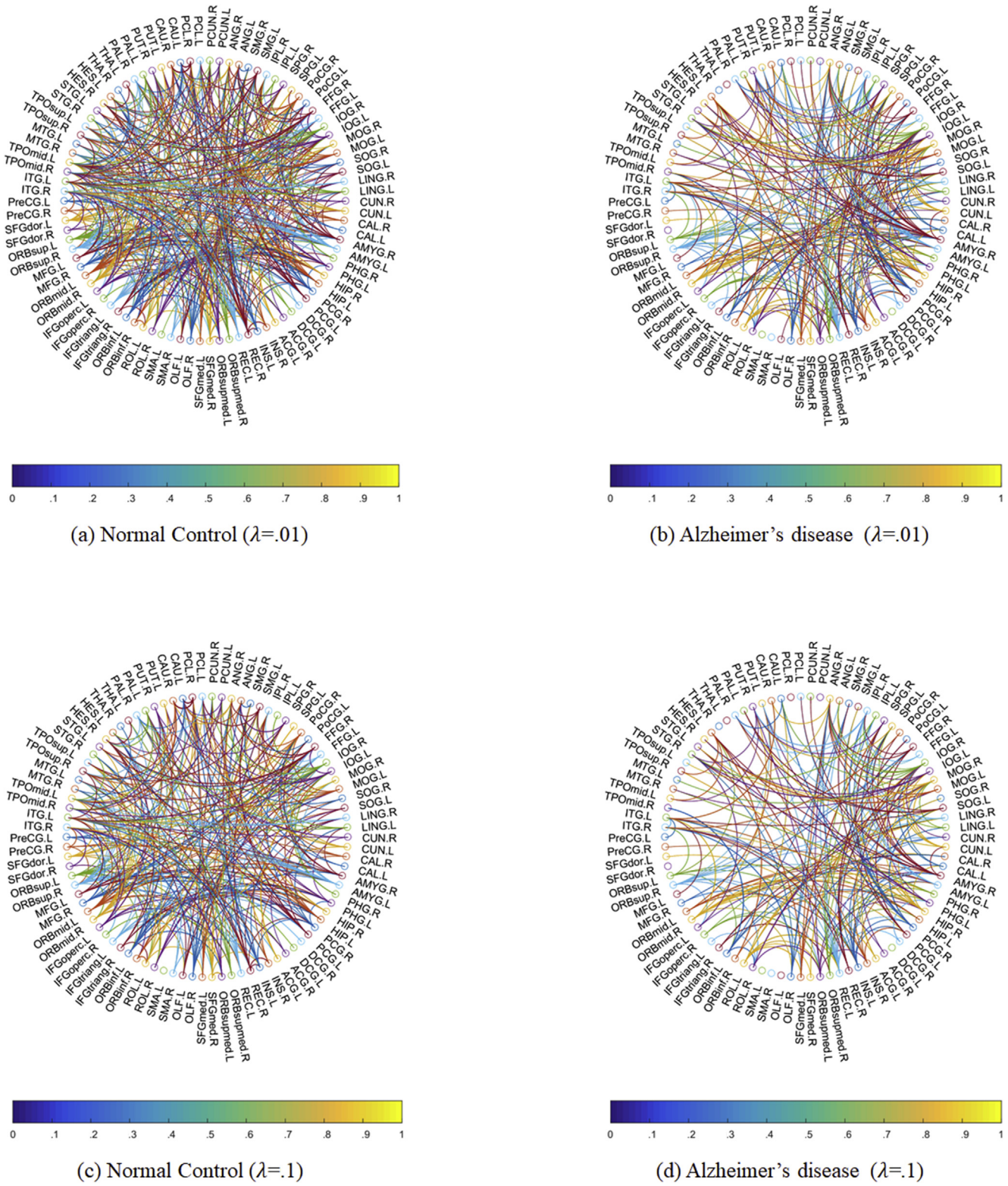
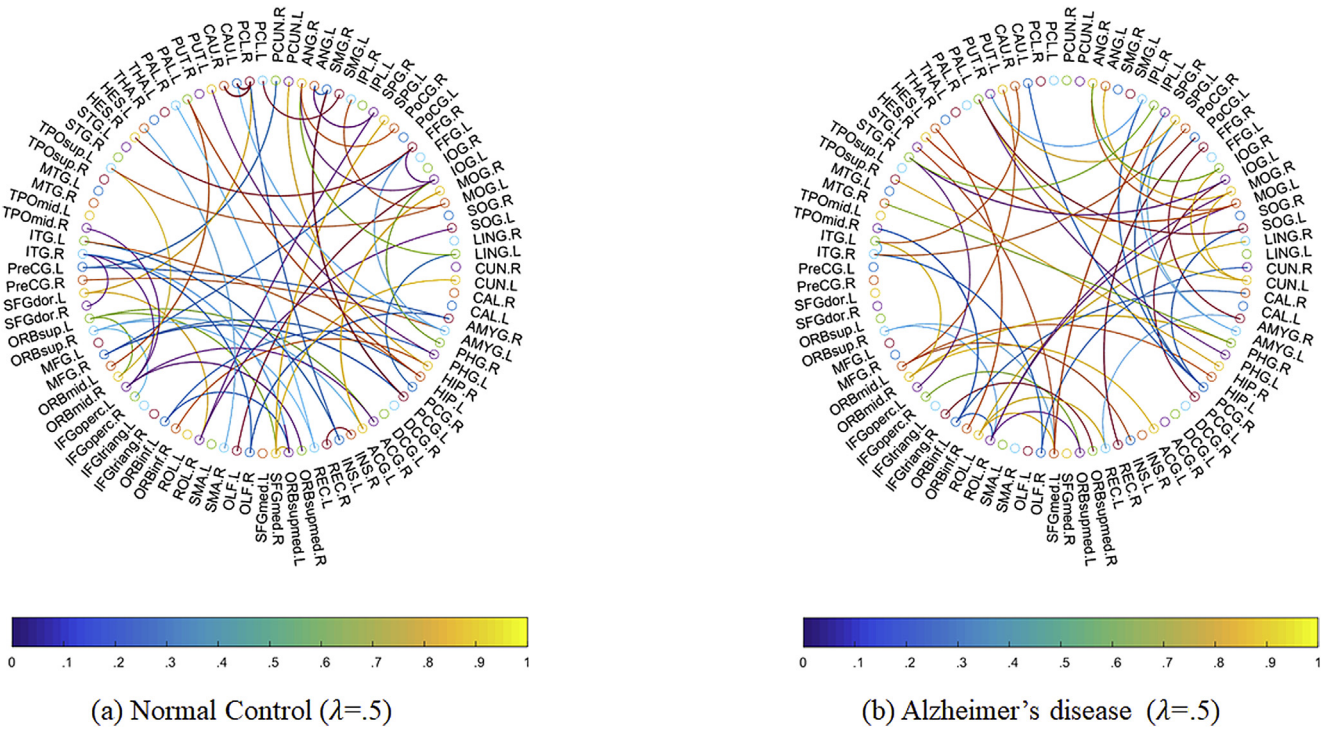


Fig. 4 – Functional Connectivity of Normal Subject and AD based on SICE method.

Cerebellum, Sensorimotor, Auditory, Executive Control Network (ECN) and frontoparietal Network (FPN). In this study, the increased functional connectivity were observed in the left superior frontal gyrus (SFGmed.L) and left thalamus (THA.L) regions of ECN. In contrast, the decreased functional connectivity were observed in the left anterior cingulate (ACG.L) region of ECN in AD, which are coincided with Andrews–Hanna report (Andrews-Hanna et al., 2007). Previous studies showed the anterior cingulate cortex (ACG) was engaged in regulating emotional and cognitive behavior. The damaged ACG region can



(a) Normal Control (λ=.5) (b) Alzheimer's disease (λ=.5)

Fig. 5 – (a) Preserved functional connectivity of Normal Subject based on SICE, (b) Preserved functional connectivity of AD based on SICE.

lead to personality changes, impulsivity and impaired social behavior. The ACG atrophy was a feature of certain neurodegenerative diseases, such as frontotemporal dementia (FTD) and Parkinson's disease dementia (PDD). Furthermore, these regions have several cognition paradigms, action–inhibition, emotion, and perception function. Although these regions have an increased/decreased connectivity, the pathology was still not clear, these changed functional connectivity could be indicate these regions occur to damage. The ECN mainly includes the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC) (Damoiseaux et al., 2006). The frontal lobe is responsible for logic, regulating behavior, complex planning, and learning. Alzheimer's disease could be damaged the frontal lobe with the disease progresses. As such, complex tasks such as driving, cooking, or multi-step planning may become severely impaired by Alzheimer's disease. Moreover, the damaged of the frontal lobe could be results in the loss of motivation and sluggishness. It plays a key role in active maintenance and manipulation of information in working memory, and decision-making in the context of goal-directed behavior (Petrides, 2005).The previous researches showed that DMN and ECN were affected and associated with AD. For example, Agosta et al. (2012) reported AD patients showed a significant increased mean connectivity of the executive control network compared with NC. Specifically, Agosta et al., used voxel-based analysis showed that AD patients had an increased executive control network connectivity in the dorsomedial and bilateral dorsolateral PFC relative to NC; when compared with amnestic Mild Cognitive Impairment (aMCI) patients, these regions of increased connectivity were more extensive. Moreover, Balachandar et al. (2015) also reported increased connectivity of ECN in mild AD patients. In our study, we also found similar results that the left superior frontal gyrus (SFGmed.L) [Fig. 2(d)] and thalamus (THA.L) regions [Fig. 2(f)] of ECN in AD patient. Our results in Fig. 2 also confirmed that enhanced connection phenomena occurs in the medial parietal cortex, dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC) regions.

In this study, the Superior Parietal Gyrus (SPG) regions and part paracentral Lobule (PCL.L) of FPN has shown increased functional connectivity (Fig. 3), and the SMG.L region has shown decreased functional connectivity in AD patients. These results are consistent with the previous results (Agosta et al., 2012). In the FPN, AD compared with NC also showed an increased connectivity in the right supramarginal gyrus. The detailed frontoparietal network (FPN) (Vincent et al., 2008) is composed of the anterior prefrontal cortex (aPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), anterior insula, anterior inferior parietal lobule (aIPL), and caudate (Vincent et al., 2008), which these areas correspond several cognition/language paradigms. Previous works (Agosta et al., 2012) shown that the left FPN showed a significantly increased connectivity in the left IPL in AD patients compared with NC. On the other hand, compared with healthy controls, AD experienced a decreased mean connectivity in the left frontoparietal network, particularly at the level of the left inferior temporal gyrus (Agosta et al., 2012). In addition, experimental results indicated that in the SMG.L region of frontoparietal networks have decreased function connectivity in AD patients, this result is in line with Anne Hafkemeijer et al. report, which released results showed decreased connectivity between precuneus and right frontoparietal network in AD patient (Hafkemeijer et al., 2017). Furthermore, although

Agosta et al. report that the mean connectivity in the right frontoparietal network did not changes, the SMG.L region has shown decreased functional connectivity in AD patients were found in our study.

4.2. *The reduced functional connectivity of ECN and FPN*

In our present study, we specifically examine reduced functional connectivity of ECN and FPN in AD patients. The ACG.L region of ECN, SMG.L and IPL.L (overlap with DMN) areas of FPN were found significantly reduced functional connectivity. The executive control network (ECN) is critical for guidance of thought and behavior. Most previous studies (Agosta et al., 2012; Anor et al., 2016, pp. P1068–P1069; Seeley et al., 2007; Sorg et al., 2007) found reduced connectivity of the left executive control network (Left ECN) in AD patients, these results suggest that altered connectivity may have an effect on the executive control network in AD patients. Our study also found that ACG.L region of executive control network (ECN) has obvious reduced connectivity in AD patients. Previous studies also showed reduced connectivity in the DMN and central executive control network (ECN) hubs of MCI patients (Agosta et al., 2012; Sorg et al., 2007). Agosta et al., used voxel-based analysis of the FPN, the results shown AD patients had a significantly reduced connectivity in the right middle frontal gyrus compared with NC, right orbitofrontal gyrus, inferior frontal gyrus, and middle frontal gyrus compared with aMCI. Furthermore, ROI-based analysis also detected a significantly reduced connectivity in left inferior temporal gyrus of frontoparietal network (FPN) in AD patients. In summary, our found reduced functional connectivity are in line with the previous studies.

In this study, our experimental results showed significantly reduced functional connectivity both SMG.L and IPL.L (overlap with DMN) areas in FPN. The left Supramarginal gyrus (SMG.L) is part of the somatosensory association cortex, which interprets tactile sensory data and is involved in perception of space and limbs location. It is also involved in identifying postures and gestures of other people, and is a part of the mirror neuron system. The right portion of the supramarginal gyrus plays a central role in controlling our empathy towards other people. When this structure isn't working properly or we have to make very quick judgments, our empathy becomes severely limited. The changed functional connectivity may result in the loss of motivation or drive, sluggishness and the gradual loss of inhibition and impulsive behavior, the reduced functional connectivity may cause the loss of partly regular function for AD patients. Moreover, Inferior parietal lobule (IPL) has been involved in the perception of emotions in facial stimuli, and interpretation of sensory information. The Inferior parietal lobule is concerned with language, mathematical operations, and body image, particularly the supramarginal gyrus and the angular gyrus (Radua et al., 2010). In this study, frontoparietal networks (FPN) showed reduced connectivity may lead to dysfunction of logic, regulating behavior, complex planning, and learning.

In addition to the reduced functional connectivity of ECN and FPN, we also found other regions exectience reduced functional connectivity, e.g., PCG.L, HIP.L, MFG.L MFG.R, TPOmid.L TPOmid.R,TPOsup.L TPOsup.R, THA.L, PCUN.L, MTG.L, ORBmid.L, PreCG.L and ORBsup.L. In these regions, the PCG.L, HIP.L and PCUN.L compose the default mode network (DMN). The posterior and precuneus of the DMN, which have reduced connectivity and lack of deactivation during cognitive tasks in the early phases of the disease (Buckner et al. 2008; Greicius, Srivastava, Reiss, & Menon, 2004), our experimental results proved this characteristic. Furthermore, Andrews–Hanna et al. (Andrews-Hanna et al., 2007) also found a significantly reduced functional connectivity between anterior and posterior hubs of the DMN (medial prefrontal cortex and PCC). Previous study showed that AD reduced functional connectivity within a specific network of regions that includes the posterior cingulate and lateral temporoparietal cortices. For example, Greicius et al. demonstrated that AD patients performed a simple motor task had reduced intra-subject functional connectivity within the default-mode network(DMN)—that includes posterior cingulate cortex, temporoparietal junction, and hippocampus(Greicius et al., 2004). Moreover, Wang et al. (2006) showed altered hippocampal connectivity to several neocortical regions in the early stages of AD. In our current study, we achieved results shown except for DMN, ECN and FPN that other regions have reduced connectivity.

4.3. *The limitations and in future directions*

In this work, our results demonstrated the changed functional connectivity in DMN, ECN and FPN. However, there are also some challenges associated with the current study. First, the current study only adopts resting-state data and relatively short sample of patients. As a consequence, there is still a need for more subjects to be performed, which will also take into account factors that may have influenced our results. Secondly, although our results indicate these changed functional connectivity association with the DMN, ECN and FPN, we must acknowledge that pathological mechanism of the functional connectivity reduction and change for AD is still unknown. Finally, besides ADNI2 dataset, other fMRI datasets should be applied to examine the results of current study. Anyway, the results presented here inspired us to further study those changed functional connectivity and other larger scale functional networks. Moreover, these are changed functional connectivity networks may help us better understand and diagnoses AD disease.

5. Conclusion

In this paper, we employ SICE approach to investigate the changed functional connectivity of large-scale functional connectivity networks (ECN, FPN). Based on the Alzheimer's disease Neuroimaging Initiative (ADNI 2) database, our experimental results show besides DMN, several other functional networks. e.g., frontoparietal network (FPN), executive control network (ECN) also have demonstrated increased/decreased functional connectivity. Moreover, our experimental results the AD patients have significantly reduced connectivity in the FPN, DMN and ECN. These conclusions suggest AD is not only associated with DMN, but also associated with other functional networks, and the results also validate these functional networks may sometimes work

together to perform tasks. These changed functional connectivity in disease progression and investigating the very early stage of AD may be helpful to understand changes that take place during the entire disease trajectory, and improve our ability to appropriately classify normal subjects and AD. Ultimately, allow us to use those changed functional connectivity as a potential noninvasive biomarker to diagnose incipient Alzheimer's disease.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author declaration

No part of the study procedures or analyses was preregistered in a time-stamped, institutional registry prior to the research being conducted.

Data and matlab source codes

The data are available from ADNI (http://adni.loni.usc.edu/adni-go-adni-2-clinical-data-available), Matlab source codes are available on (https://osf.io/hgsn4/quickfiles).

Conflicts of interest

The authors declared no conflict of interest.

Open Practices

The study in this article earned an Open Materials badge for transparent practices. Materials and data for the study are available at http://adni.loni.usc.edu/adni-go-adni-2-clinical-data-available/.

CRediT authorship contribution statement

Qinghua Zhao: Methodology, Software, Visualization, Writing - original draft. **Xiaoshuang Sang:** Data curation, Investigation. **Hichem Metmer:** Validation. **Zar nawab N.K. Swati:** Formal analysis, Resources. **Jianfeng Lu:** Conceptualization, Funding acquisition, Writing - review & editing, Supervision, Project administration.

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Appendix

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. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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