Original Article

Frequency-specific Alterations of Large-scale Functional Brain Networks in Patients with Alzheimer's Disease

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Abstract

Background: Previous studies have indicated that the cognitive deficits in patients with Alzheimer's disease (AD) may be due to topological deteriorations of the brain network. However, whether the selection of a specific frequency band could impact the topological properties is still not clear. Our hypothesis is that the topological properties of AD patients are also frequency-specific.

Methods: Resting state functional magnetic resonance imaging data from 10 right-handed moderate AD patients (mean age: 64.3 years; mean mini mental state examination [MMSE]: 18.0) and 10 age and gender-matched healthy controls (mean age: 63.6 years; mean MMSE: 28.2) were enrolled in this study. The global efficiency, the clustering coefficient (CC), the characteristic path length (CpL), and "small-world" property were calculated in a wide range of thresholds and averaged within each group, at three different frequency bands (0.01–0.06 Hz, 0.06–0.11 Hz, and 0.11–0.25 Hz).

Results: At lower-frequency bands (0.01–0.06 Hz, 0.06–0.11 Hz), the global efficiency, the CC and the "small-world" properties of AD patients decreased compared to controls. While at higher-frequency bands (0.11–0.25 Hz), the CpL was much longer, and the "small-world" property was disrupted in AD, particularly at a higher threshold. The topological properties changed with different frequency bands, suggesting the existence of disrupted global and local functional organization associated with AD.

Conclusions: This study demonstrates that the topological alterations of large-scale functional brain networks in AD patients are frequency dependent, thus providing fundamental support for optimal frequency selection in future related research.

Key words: Alzheimer's Disease; Frequency; Network

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder clinically characterized by progressive dementia and neuropsychiatric symptoms. A breakdown in connectivity, both in the functional and structural system domain, is thought to contribute significantly to the onset of AD symptoms.[1] The human brain is organized as a complex network, allowing for segregation and integration of information processing.[2] By modeling the brain as a complex network, data from recent studies suggest that AD-associated brain network changes may be related to cognitive decline and neuropsychological impairment.[3] He *et al.* demonstrated the topological alterations in AD patients using interregional correlation of cortical thickness as a metric of the structural basis underlying brain dynamics in structural networks.[4] Sorg *et al.* reported diminished functional connectivity between the hippocampus and posterior cingulate cortex for functional networks that are prominently involved in the processes of episodic memory in patients at prodromal stages of AD.[5]

Two basic topological measurements of a complex network are clustering coefficient (CC) and characteristic path length (CpL).[2] The CC quantifies the local efficiency of information transfer while CpL quantifies the global efficiency of parallel information transmission.[6] Although previous studies have indicated that the cognitive deficits may be due to topological deteriorations of the brain network,[4,7-9] a consensus regarding the nature of the alteration pattern has not been reached.[10] A study by Stam *et al.* found that the network CC was unchanged in patients with AD although the average CpL was elongated.[3] Contradictorily, Supekar *et al.* indicated that AD patients had a lower CC, but no changes in CpL compared with healthy controls.[11] Using structural MRI data, He *et al*. demonstrated a higher CC and longer CpL in patients with AD.[4]

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To account for these discrepancies, several hypothetical suggestions have been proposed. One suggestion is to compare structural and functional networks simultaneously in the same group of people.[6,12,13] Another is to diminish the heterogeneity of the population.[10] To date, most studies just examined the large-scale brain network properties at a specific frequency band. It is not clear whether the selection of a specific frequency band could impact the topological properties in patients with AD. Recent studies have reported the frequency specificity of functional connectivity in multiple functional networks derived from resting-state functional magnetic resonance imaging (RS-fMRI) signals, as well as frequency-specific correlations between hemodynamic changes and electroencephalography oscillations in healthy people.[14,15] Frequency-specific alterations of neuronal oscillations were revealed in patients suffering from schizophrenia using RS-fMRI,[16] and Parkinson's disease by simultaneous magnetoencephalography (MEG) and local field potential recordings.[17]

In our study, we expected to find frequency-specific changes in the topological properties of AD patients. Focusing on RS-fMRI data only, large-scale topological properties of moderate AD patients and healthy controls were investigated at three distinct frequency bands (0.01–0.06 Hz, 0.06–0.11 Hz, and 0.11–0.25 Hz). The global efficiency, the CC, the CpL and the "small-world" property of the subjects were quantified to describe the alterations in each frequency band.

Methods

Subjects

All participants were screened and enrolled according to the procedure used in former studies of the same group.[18,19] Finally, according to the NINCDS-ADRDA criteria for probable AD, ten right-handed subjects were drawn from the outpatients. The patients were all clinically categorized as those at moderate stages of AD according to the Clinical Dementia Rating (CDR) scale of 2. Ten right-handed healthy controls with no history of neurological disorder or head trauma and normal neurologic examination findings (CDR = 0) were recruited from the local community. Global cognitive function of all subjects was evaluated using the mini-mental state examination. Detailed clinical and demographic data for all subjects are shown in Table 1.

Magnetic resonance imaging examination

A 3T MR scanner (Signa HDxt, GE Healthcare, USA) with 8-channel head array coil was used in this study. Each subject was scanned in a supine, head-first position with symmetrically placed cushions on both sides of the head to ensure stability. During the RS-fMRI scanning, the subjects were instructed to keep as still as possible, with eyes closed, and think of nothing in particular while maintaining wakefulness. A gradient-echo planar sequence was performed for the acquisition of RS-fMRI data, with the acquisition parameters as follows: Repetition time (TR)/echo time (TE) 2000/30 ms, field of view (FOV) 240 mm × 240 mm, phase FOV 1, matrix 64 × 64, slices 33, slice thickness 4.0 mm, slice gap 0.5 mm, scan time 8 min. A three-dimensional fast spoiled gradient recalled-echo sequence covering the whole brain was used for structural data acquisition with TR/TE/inversion time 6.5/2.1/400 ms, FOV 256 mm × 256 mm, phase FOV 1, matrix 256 × 256, slice thickness 1.0 mm, slice gap 0 mm, number of signal averages (NSA) 1, flip angle 15°, scan time 4 min 8 s.

Data preprocessing

SPM8 (*http://www.fil.ion.ucl.ac.uk/spm/*) was used for the preprocessing of fMRI datasets. After the first 10 time points were discarded, slice timing and head motion correction were performed. The remaining images of all subjects were then normalized to Montreal Neurological Institute 152 space. All images were then smoothed with a 4 mm × 4 mm × 4 mm Gaussian kernel. Datasets were then drifted and filtered in three distinct frequency bands: 0.01–0.06 Hz, 0.06–0.11 Hz, and 0.11–0.25 Hz. Nuisance covariates of whole brain, white matter, and cerebrospinal fluid signals were removed using regression.

Construction of brain functional network

The registered fMRI data were segmented into 90 regions using an automated anatomical labeling template. Time series of each region were then exacted. The Pearson correlation coefficients were calculated between any two functionally connected regions at three different frequency bands (0.01–0.06 Hz, 0.06–0.11 Hz and 0.11–0.25 Hz). Each subject was assigned a 90 × 90 correlation matrix at different filter bands. In order to detect the topological differences of functional brain network between AD patients and healthy controls, a wide range of thresholds were selected to establish binary networks. Specifically, if the Pearson correlation coefficient was greater than the threshold, the correlation coefficient was set to 1; otherwise, it was set to 0. The selected threshold ranged from 0.35 to 0.60 and increased by 0.01 at each step.

Topological properties of the functional brain network

In this study, the global efficiency, the CC, the CpL, and "small-world" property were calculated in a wide range of thresholds and averaged within each group. The definition of these parameters can be found in Bullmore and Sporns.[2] To compare the degree distributions of functional brain network between AD patients and healthy controls, a binary matrix was constructed at a threshold of 0.45 for each subject. The node degree was then calculated in each node and averaged within each group to generate the degree distribution curve. Brain regions that exhibited significant differences

Table 1: Subject characteristics

Items	AD	Controls	*P*
Age (years)	64.3 (52-81)	63.6 (56-82)	0.862
Male:female	6:4	5:5	0.673
MMSE	18.0 (13-25)	28.2 (27-30)	< 0.001

AD: Alzheimer's disease; MMSE: Mini-mental state examination.

between groups were displayed. A "small-world" network is characterized as a network with a shorter CpL than a regular network (high CC and long CpL) and a greater CC than a random network (low CC and short CpL).[6,20] To detect the differences of "small-world" properties between AD patients and healthy controls, the ratio of CC and CpL was quantified in each subject and averaged within each group.

Statistics

The differences of topological parameters between patients and controls were compared by two-sample *t*-test using SPSS 17.0 (SSPS Inc., Chicago, IL, USA) software. The results were considered statistically significant if the *P* value was below 0.05.

Results

Topological parameter comparisons at different frequency bands

The global efficiencies of AD patients and healthy controls at three different frequency bands are shown in Figure 1. The global efficiencies of AD patients were always lower than healthy controls at the frequency bands of 0.01–0.06 Hz and 0.06–0.11 Hz under all thresholds. No significant difference of global efficiency between groups at the frequency band of 0.11–0.25 Hz was found at smaller thresholds. However, within a higher threshold (more than 0.5), the global efficiency was still lower in AD patients than in healthy controls.

Figure 2 shows the CC of the functional brain network of AD patients and healthy controls at different frequency bands. The results indicate that the CC was always lower in AD patients than in controls at lower frequency bands of 0.01–0.06 Hz and 0.06–0.11 Hz. For higher frequency band (0.11–0.25 Hz), no significant difference was found between groups.

The statistical results of the average CpL are shown in Figure 3. The average CpL of the healthy controls was much shorter at the frequency band of 0.11–0.25 Hz if the threshold was greater than 0.5. There was no significant difference in the CpL at lower frequency bands (0.01–0.06 Hz, 0.06–0.11 Hz).

"Small-world" property is measured by the ratio of CC and CpL. Figure 4 shows the "small-world" property of the healthy controls was always higher than that of AD patients under all the thresholds at three distinct frequency bands.

Changes of the node degree

The degree of a node is the number of connections that link it to the rest of the network.[2] The degree of each node was calculated at the frequency band of 0.06–0.11 Hz with a threshold value of 0.45 in each subject and then averaged within each group. Table 2 shows the average node degrees in patient group and control group. Among all 90 nodes, the proportion of nodes with a node degree higher than 17 was just 5.56% in AD patient group while in healthy controls the proportion was as high as 28.89%.

Previous studies have shown that the degree distribution of the functional brain network is described by a Gauss function curve.[21] Figure 5 represents the degree distribution curve of AD patients and controls fitted with a Gaussian distribution. The probability distribution of node degree in the healthy group was higher than in the AD group when the node degree was >15.

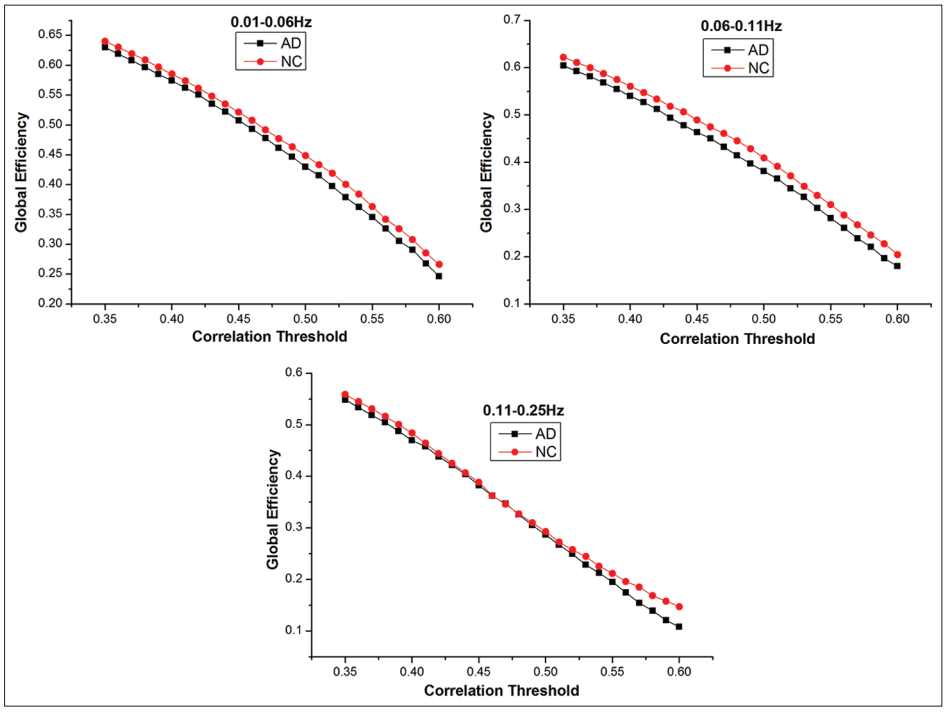

Figure 1: The global efficiencies of the functional brain networks in Alzheimer's disease patients (marked in black) and in healthy controls (marked in red) at the three different frequency bands.

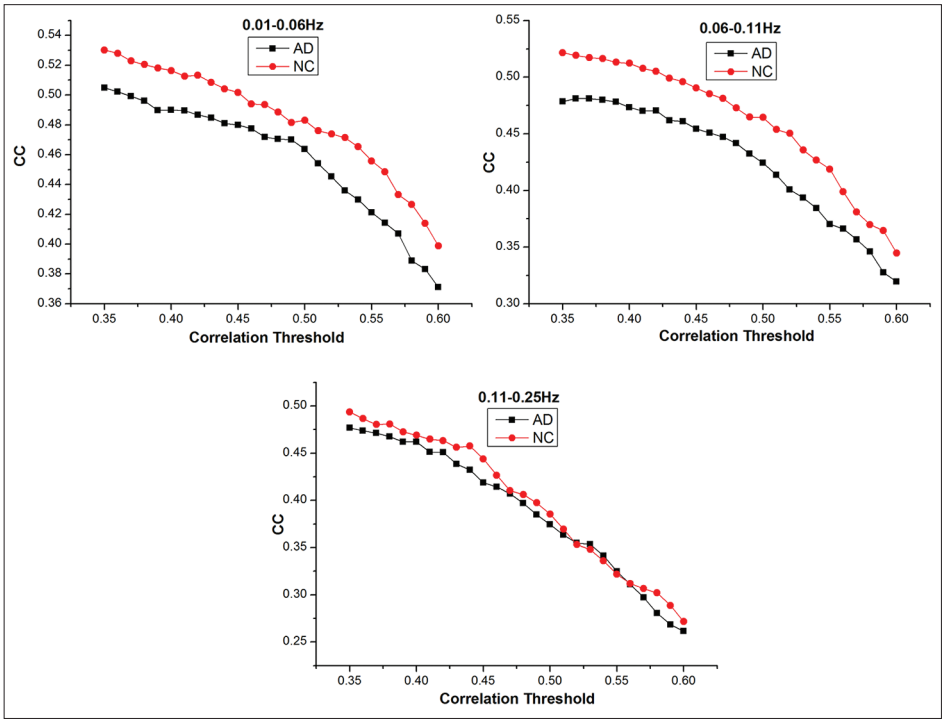

Figure 2: The clustering coefficients of the functional brain networks in Alzheimer's disease patients (marked in black) and in healthy controls (marked in red) at the three different frequency bands.

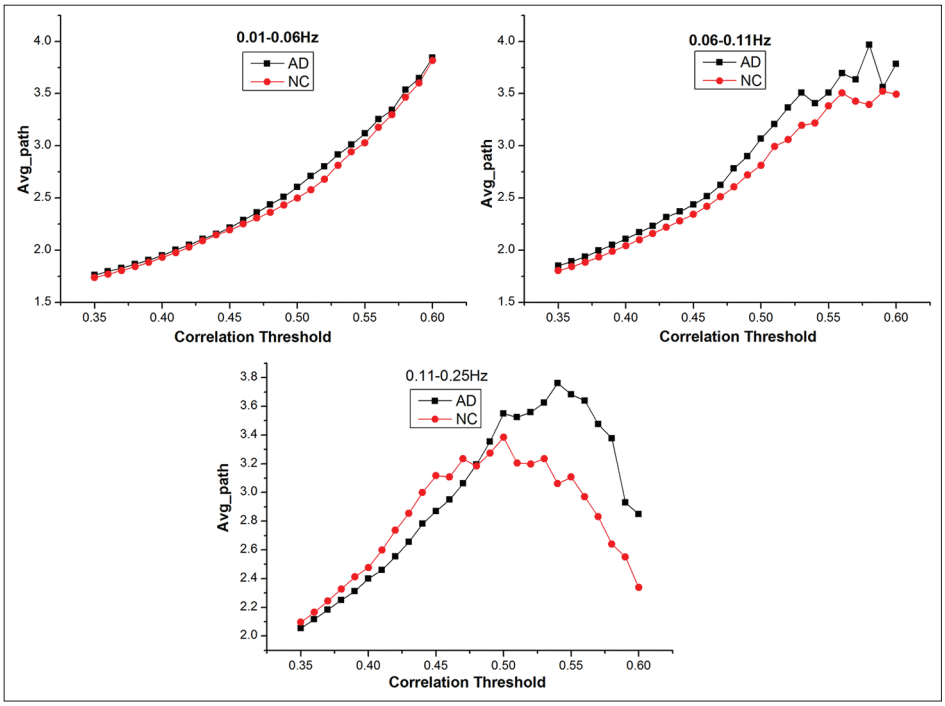

Figure 3: The average shortest path length of the functional brain networks in Alzheimer's disease patients (marked in black) and in healthy controls (marked in red) at the three different frequency bands.

The differences of node degree between AD patients and healthy controls are further investigated [Figure 6]. The results demonstrate that a reduction of node degree was distributed in the left postcentral gyrus (PoCG.L), the right hippocampus (HIP.R), the left middle temporal gyrus (MTG.L), the right middle occipital gyrus (MOG.R), the right orbital part of middle frontal gyrus (ORBsupmed.R), the right amygdala (AMYG.R), the left lingual gyrus (LING.L), the medial part of right superior frontal gyrus (SFGmed.R), and the medial part of left superior frontal gyrus (SFGmed.L). Only a few regions show increased node degree in AD patients: The left inferior temporal gyrus (ITG.L), the left

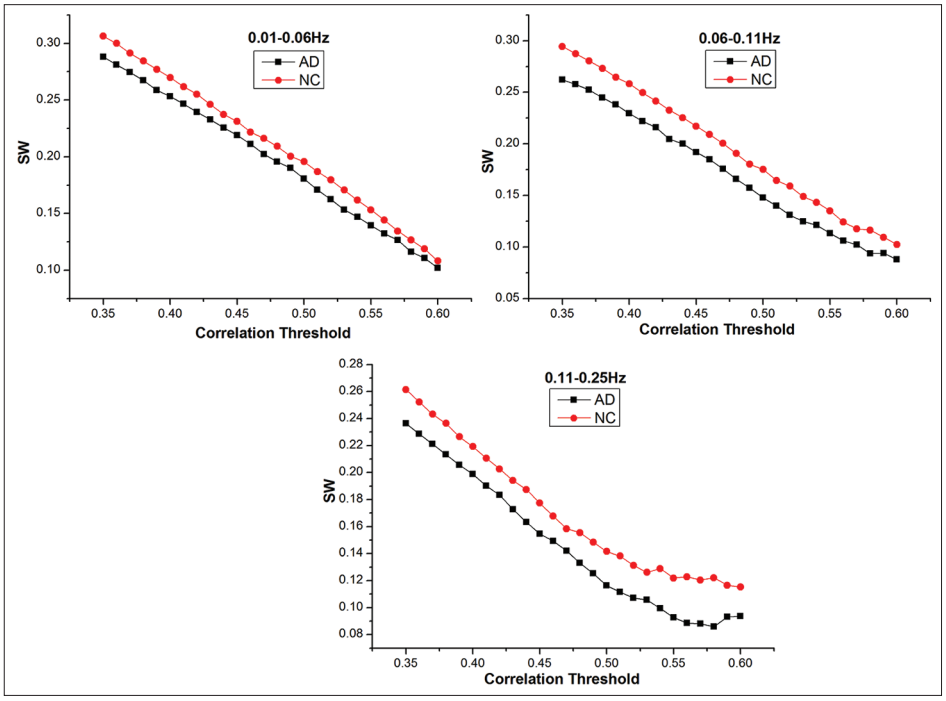

Figure 4: The "SW" properties of the functional brain networks in Alzheimer's disease patients (marked in black) and in healthy controls (marked in red) at the three different frequency bands. SW: Small-world.

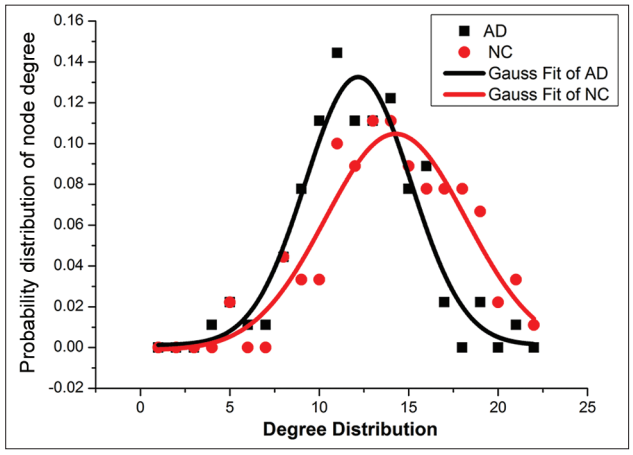

Figure 5: The degree distribution of Alzheimer's disease group (black curve) and control group (red curve) after Gaussian function curve-fitting.

orbital part of superior frontal gyrus (ORBsup.L), and the right MTG (MTG.R).

Discussion

The present study shows that the global efficiency, the CC, and the "small-world" properties in the AD patient group changes with different frequency bands, suggesting the existence of disrupted global and local functional organization associated with AD. Specifically, at lower-frequency bands (0.01–0.06 Hz, 0.06–0.11 Hz), the global efficiency, the CC and the "small-world" properties of AD patients decreased compared with healthy controls while the CpL elongated within a wide range of thresholds.

Table 2: The probability of node degree in AD patient group and healthy control group

Node degree	AD (%)	Normal controls (%)
1	0	0
2	0	0
3	0	0
4	1.11	0
5	2.22	2.22
6	1.11	0
7	1.11	0
8	4.44	4.44
9	7.78	3.33
10	11.11	3.33
11	14.44	10
12	11.11	8.89
13	11.11	11.11
14	12.22	11.11
15	7.78	8.89
16	8.89	7.78
17	2.22	7.78
18	0	7.78
19	2.22	6.67
20	0	2.22
21	1.11	3.33
22	0	1.11

AD: Alzheimer's disease.

However, at higher-frequency bands (0.11–0.25 Hz), the global efficiency and the CC showed no significant differences compared with healthy controls, while the "small-world" properties were lower and the CpL were much longer in AD than in controls, particularly at a higher

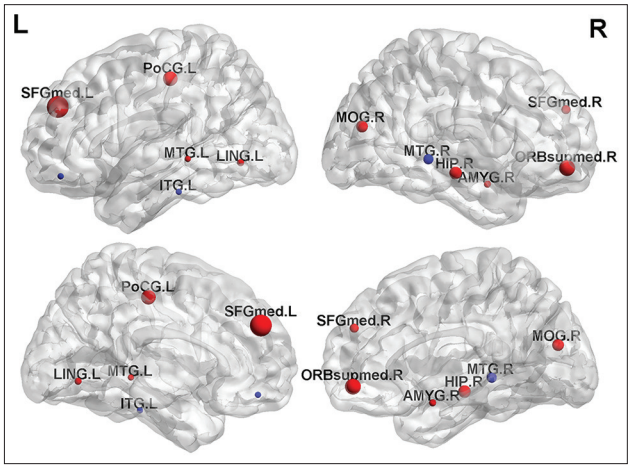

Figure 6: The structure-specific alterations of node degrees in AD patients. The red dots indicate increased node degrees in the AD group compared with healthy controls; the blue dots indicate reduced node degrees in the AD group. The size of the dot indicates the degree of alterations. AD: Alzheimer's disease; AMYG.R: Right amygdala; HIP.R: Right hippocampus; ITG.L: Inferior temporal gyrus; LING.L: Left lingual gyrus; MOG.R: Right middle occipital gyrus; MTG.L: Left middle temporal gyrus; MTG.R: Right middle temporal gyrus; ORBsupmed.R: Right orbital part of middle frontal gyrus; PoCG.L: Left postcentral gyrus; SFGmed.L: Medial part of left superior frontal gyrus; SFGmed.R: Medial part of right superior frontal gyrus.

threshold. Comparisons of node degree indicate that the probability distribution of node degree in healthy groups was higher than in AD group if the node degree exceeded 15. For structure-specific alterations, there was a significant reduction of node degree in brain regions of PoCG.L, HIP.R, MTG.L, MOG.R, ORBsupmed.R, AMYG.R, LING.L, SFGmed.R, and SFGmed.L; while in areas of ITG.L, ORBsup.L, and MTG.R, the node degree increased. The results of this study demonstrate that the topological property of large-scale functional brain networks in AD patients is frequency dependent.

Different topological properties at different frequency bands

Previous studies have suggested that the hemodynamic responses measured by RS-fMRI reflect spontaneous neural activity which largely fluctuates at a lower-frequency band.[2,22,23] It has been demonstrated that spontaneous low-frequency fluctuations (0.01–0.1 Hz) are physiologically meaningful. Higher-frequency fluctuations are usually affected by respiratory signal frequency (0.1–0.5 Hz) and cardiovascular signal frequency (0.1–0.5 Hz).[24] In this study, the topological properties of AD patients and healthy controls exhibited different properties at different frequency bands. One possibility is that topological properties are frequency-dependent, which contributed to the discrepancies observed in previous studies.

Stam *et al*. demonstrated that within an extensively wide range of thresholds, AD patients exhibited a longer CpL than healthy controls but no significant changes in the CC were found.[3] However, Supekar *et al*. showed a decline of CC in patients with AD.[11] Meanwhile, in 2009, using MEG data, Stam *et al*. demonstrated that AD patients had a lower CC and a longer CpL.[25] In 2010, using RS-fMRI data, Sanz-Arigita *et al*. reported no significant changes in CC in AD but with a shorter CpL.[9] The inconsistent results of these studies may be caused by the selection of different frequency bands. Our report agrees with reports from de Haan *et al*.,[26] which suggest that various frequency bands impact the topological properties of a functional brain network.

Topological organizations of large-scale functional brain network

Global efficiency is one of the most pertinent parameters for quantifying the parallel information propagation capability of a network.[27] In this study, the global efficiency of AD patients was always lower than healthy controls at lower-frequency bands (0.01–0.06 Hz, 0.06–0.11 Hz) [Figure 1], data which agrees with Zhao *et al*.'s research.[10] The decline of global efficiency in AD patients indicates that pathological changes in the brain have reduced connectivity strength and blocked information communication in remote functional regions. A wealth of studies has demonstrated that the global efficiency of the brain network declines if the brain is pathologically impaired.[6,28,29] This may be one major factor contributing to the cognitive decline of patients with AD. However, compared with healthy controls, there was no significant difference of the global efficiency at a higher frequency band (0.11–0.25 Hz). We suggest that higher-frequency fluctuations may result from coexisting noise during the acquisition of MRI signals in both AD patients and healthy controls. Therefore, the global efficiency of AD and healthy controls does not significantly differ.

The CC of a network quantifies the number of local connections that exist as a proportion of the maximum number of possible connections. It depicts the extent of local efficiency of information transfer in a network.[2] Our study demonstrates that at lower-frequency bands within a higher range of thresholds, the CC of AD patients is diminished compared with healthy controls, in line with previous studies.[10,11] This finding indicates a decline in coupling, robustness, as well as the local functional connectivity strength between nodes in patients with AD.

There was no significant difference in CpL between AD and controls, demonstrating that short-range connections are maintained in AD patients. Short paths promote effective interactions between neuronal elements within and across cortical regions, and are essential for functional integration.[30]

In 1998, Watts and Strogatz first explored the characteristic of a "small-world" network.[20] It has been suggested that hierarchical organizations of AD and controls differ with each other, resulting in a significant decline in CC among AD patients. A "small-world" network has a higher CC and a shorter CpL. It not only facilitates both modularized and distributed information processing but also maximizes the efficiency of information transfer at a relatively low

wiring cost.[6] In a "small-world" network, there are many clusters (small groups of nodes connected to each other) or node clusters of which the number of connections is less than the number of clusters. In addition, any two nodes are usually connected by at least one short path. Numerous studies have demonstrated that the "small-world" properties of AD patients suffer significantly deterioration.[3,8,10] Our study supports such a conclusion. The disruption of "small-world" properties indicates that the efficiency of information transfer within different brain regions has also declined, a factor which may play a major role in the cognitive decline observed in AD patients.

Regional alterations of node degree

At a threshold of 0.45, the structure-specific alterations of node degree in AD patients were further investigated at the frequency band of 0.06–0.11 Hz. The results indicate that areas with node degree reduction are located mostly in the temporal lobe and frontal lobe. Previous studies have demonstrated that Aβ deposition in AD occurs preferentially in locations of cortical hubs (nodes), accounting for the observed activity-dependent mechanism associated with connectional hubs.[31,32] Hubs are brain areas that act as critical way stations for information processing. The cortical components of the medial temporal lobe and the frontoparietal lobe of these hubs are especially vulnerable to AD.[33-35] Cortical topological organization may contribute to disease vulnerability in AD. Furthermore, three regions show an increased node degree in AD patients (ITG.L, ORBsup.L and MTG.R), indicating a coexisting functional compensation in the temporal lobe and frontal lobe.[4]

In conclusion, based on data analysis of resting-state functional networks, large-scale functional brain networks of AD patients and healthy controls were constructed and compared for a wide range of thresholds at different frequency bands. Compared with healthy controls, the patients with AD exhibited lower global efficiency, lower CC, and also lower "small-world" properties associated with functional brain networks. Furthermore, a decline in the node degree was observed in the large majority of pathologically attacked regions, with other areas increasing as functional compensations. Our study accurately depicts the frequency-specific topological alterations in AD-related large-scale functional brain networks, providing fundamental support for optimal frequency selection in future related research.

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