Dysfunctional whole brain networks in mild cognitive impairment patients: an fMRI study

Zhenyu Liu[a], Lijun Bai[a], Ruwei Dai[a], Chongguang Zhong[a], Ting Xue[b], Youbo You[a], Jie Tian*[a,b]

[a]Intelligent Medical Research Center, Institute of Automation, Chinese Academy of Sciences, P. O . Box 2728, Beijing, 100190, China;

[b]Life Science Research Center, School of Electronic Engineering, Xidian University, Xi'an, Shaanxi, 710071, China

* Corresponding author, E-mail: tian@ieee.org, Tel.: 86-10-82618465; Fax: 86-10-62527995

ABSTRACT

Mild cognitive impairment (MCI) was recognized as the prodromal stage of Alzheimer's disease (AD). Recent researches have shown that cognitive and memory decline in AD patients is coupled with losses of small-world attributes. However, few studies pay attention to the characteristics of the whole brain networks in MCI patients. In the present study, we investigated the topological properties of the whole brain networks utilizing graph theoretical approaches in 16 MCI patients, compared with 18 age-matched healthy subjects as a control. Both MCI patients and normal controls showed small-world architectures, with large clustering coefficients and short characteristic path lengths. We detected significantly longer characteristic path length in MCI patients compared with normal controls at the low sparsity. The longer characteristic path lengths in MCI indicated disrupted information processing among distant brain regions. Compared with normal controls, MCI patients showed decreased nodal centrality in the brain areas of the angular gyrus, heschl gyrus, hippocampus and superior parietal gyrus, while increased nodal centrality in the calcarine, inferior occipital gyrus and superior frontal gyrus. These changes in nodal centrality suggested a widespread rewiring in MCI patients, which may be an integrated reflection of reorganization of the brain networks accompanied with the cognitive decline. Our findings may be helpful for further understanding the pathological mechanisms of MCI.

Keywords: mild cognitive impairment, functional MRI, small-world network, nodal centrality

1. INTRODUCTION

As the prodromal stage of Alzheimer's disease (AD), mild cognitive impairment (MCI) refers to the clinical condition between the normal aging and AD. MCI patients usually experience the memory loss to a greater extent than one would expect for age, while they do not meet the criteria for AD [1]. According to a previous study, nearly half of MCI patients will convert to AD in 5 years [2]. It is thus necessary and urgent to find out the neurological relations between AD and MCI, for it offers opportunities for relatively early diagnosis of AD. A pathological study [3] has shown that neurodegeneration in AD begins in the MTL (including the hippocampus, amygdala, and parahippocampal gyrus), while a neurological study [2] finds that the MTL exhibits abnormalities in MCI patients as well. Furthermore, Agosta et al [4] investigate the brain motor network during a simple motor task and find that the functional connectivity is altered between primary sensorimotor cortices in MCI patients, suggesting the occurrence of a widespread brain rewiring rather than a specific response of cognitive network. A recent study exploring the brain networks in MCI patients using structural MRI finds altered interregional correlations mainly in the MTL as well as the abnormal hub regions in the frontal lobe and the temporal lobe [5]. However, it is still unclear whether the global functional integrations of the whole brain networks are altered in MCI patients.

The small world, characterized by large clustering coefficients and short characteristic path lengths, is an attractive model to describe both local and global information processing within the complex brain networks [6]. Moreover it provides quantitative parameters to measure the connectivity of brain networks [7]. Recent studies using EEG [8], and MRI [5, 9] have found abnormal clustering coefficients and characteristic path lengths in the brain networks of AD patients, implicating a loss of small-world attributes and disrupted whole brain network architectures suffering from the diseases. However, few studies pay attention to the characteristics of the whole brain networks in MCI patients.

In this study, we attempted to investigate the topological properties of the whole brain networks in MCI patients compared with age-matched normal controls using graph theoretical approaches. The main hypotheses were as follows:

(1) Several previous studies have indicated losses of small-world attributes in AD patients. It is possible that such topological changes also exist in the functional brain networks in MCI patients. In this study, we hypothesized that MCI would accompany altered small-world parameters in the large-scale functional brain networks.

(2)Recent studies about MCI have shown that brain regions of MTL are the regions where the neurodegeneration starts [10]. We hypothesized that nodal centrality changes in these regions would be detected in MCI patients compared with normal controls.

2. METHOD AND MATERIALS

2.1. Subjects

From Beijing Tiantan Hospital, we recruited 16 right-handed subjects with MCI according to the MCI criteria [1, 2]. 18 healthy right-handed age-matched subjects recruited from a community served as controls. Prior to the experiment, the purpose of the study was briefly explained to the subjects. Each subject provided written informed consents approved by Institutional Review Board of the Tiantan Hospital Subcommittee on Human Studies. Subjects were excluded if they had any neurological illness, or they were taking medications or substances that would influence the central nervous system. Demographics and neuropsychological findings of MCI patients and healthy elderly were shown in Table 1.

Table 1 Subject characteristics

	MCI	Controls
N	16	18
Age range (year)	(54-81)	(49-78)
Age (mean ± SD)	68.5 ± 9.4	64.9 ± 8.4
Sex (M/F)	6/4	10/8
MMSE score (mean ± SD)	24.8 ± 1.3	29.5 ± 0.5
CDR	0.5	0

No significant differences ($p < 0.05$) were observed in age, sex between groups. Significant differences were noted in MMSE scores between groups ($p < 0.0001$). MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating.

2.2. Data acquisition and preprocessing

All experiments were performed on a Siemens Trio 3-Tesla MRI system at Tiantan Hospital. A custom-built head holder was used to prevent head movements. The resting state scan lasted for 500s. Functional MR images were obtained using a gradient echo T2*-weighted pulse sequence with TR = 2000 ms, TE = 30 ms, matrix = 64 × 64, FOV = 256 mm × 256 mm and FA = 85°. After the functional run, a high-resolution T1-weighted 3D MRI sequence was used (voxel size = 1 × 1 × 1 mm^3, no gap, TR = 2100 ms, TE = 3.25 ms, matrix = 256 × 256, FOV = 230 mm x 230 mm, and FA = 10°).

All preprocessing steps were carried out using Matlab 7.6.0 with Statistical Parametric Mapping software (SPM5). The first five volumes of each session were discarded to allow for equilibrations of the magnetic field. The following processing was applied to all the remaining volumes: motion correction using the least-squares minimization, spatial normalization based on the Montreal Neurological Institute (MNI) space, temporal band-pass filtering (0.01~ 0.08Hz), and spatial smoothing with FWHM of 6 mm.

2.3. Data analysis

After preprocessing, the fMRI data were segmented into 90 regions (45 for each hemisphere), using the anatomically labeled template [11]. For each subject, the representative time series of each region were estimated simply by averaging the fMRI time series over all voxels in the region.

Partial correlations between each pair of brain regions were calculated to reduce the indirect dependencies by other brain regions and get a partial correlation matrix R. Then, the Fisher's transform was applied to improve the normality of the partial correlation coefficients. Finally, a threshold (r) was related with the partial correlation coefficients (R_{ij}) to convert R to a binary graph. In this step, we set any R_{ij} whose absolute value was greater than r to 1 and others to 0. And a false discovery rate (FDR) procedure was performed at a q value of 0.05 to adjust the multiple comparisons. Because there is no golden standard to select a single threshold, we thresholded each correlation matrix repeatedly over a wide range of sparsity ($8\% \leq S \leq 36\%$) and calculated the parameters of the resulting graphs for with different threshold.

Small-world measures the functional connectivity of nervous systems briefly with clustering coefficients, C_p, and characteristic path length, L_p [12]. C_p is the averaged clustering coefficients over all the nodes in the graph. The clustering coefficient of a node is the ratio of the number of existing connections among the neighbors of the node to the number of all their possible connections. L_p is the average of the shortest path lengths between any pair of nodes in the graph.

A real network would be considered to have the small-world topology if it meets the criteria: $\gamma = C_p^{real} / C_p^{rand} > 1$ and $\lambda = L_p^{real} / L_p^{rand} \approx 1$.

In this study, we considered the "betweenness centrality" of the nodes to investigate nodal characteristics. The betweenness B_i of a node i was defined as the number of shortest paths between any pair of nodes that run through node i [13]. We considered the normalized betweenness $b_i = B_i / <B>$ ($<B>$ was the average betweenness of the network).

3. RESULTS

3.1. Small-world model and alterations related to MCI

As expected, both networks demonstrated small-world architectures as they had almost identical characteristic path length ($\lambda \approx 1$) but were more locally clustered ($\gamma > 1$) at a wide range of sparsity ($8\% \leq S \leq 36\%$), compared with the matched random networks. Clustering coefficient, C_p, and characteristic path length, L_p as the function of sparsity were shown in Figure 1. L_p in the MCI networks was significantly larger than that in the control networks at the low sparsity (two-sample t-test, $p < 0.05$), but C_p didn't show significant difference.
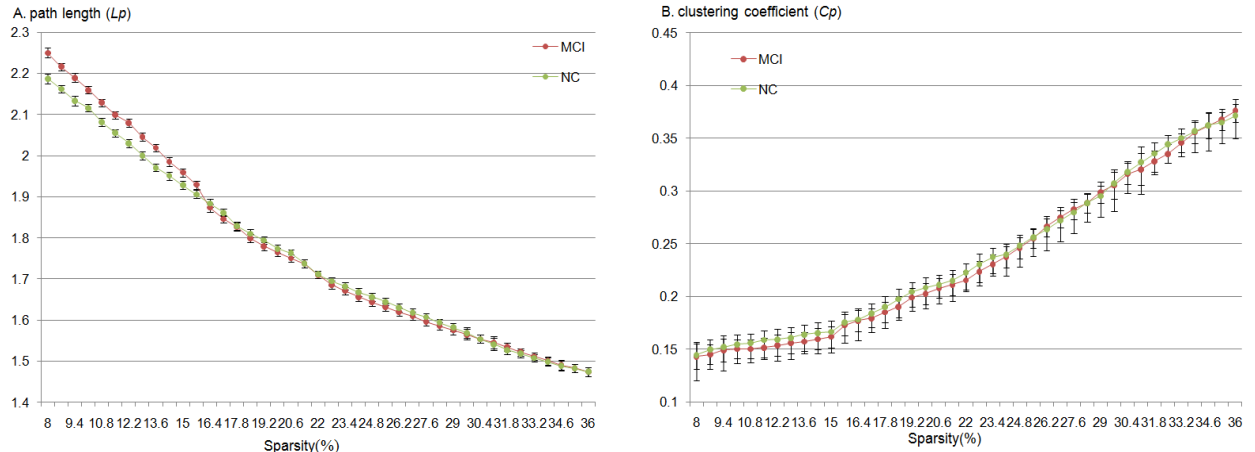

Figure 1. The graphs showed the characteristic path lengths and clustering coefficients in normal controls and MCI patients as a function of sparsity thresholds. L_p of MCI patients was significantly larger than that of normal controls ($p < 0.05$, two sample t-test) at the low sparsity, while C_p didn't show significant difference between the two groups.
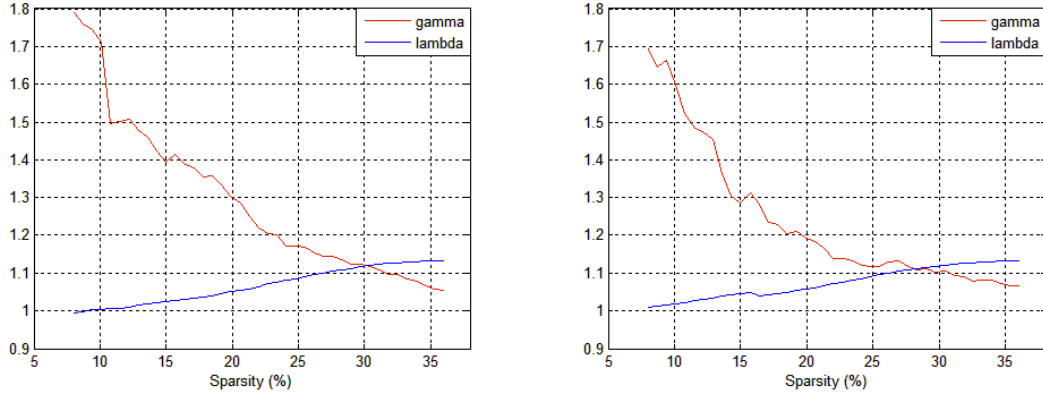
Figure. 2. Small-world properties of the two groups. The graphs show the γ (C_p^{real}/C_p^{rand} , red) and λ (L_p^{real}/L_p^{rand} , blue) in normal controls (left) and MCI patients (right) as a function of sparsity thresholds. At a wide range of sparsity, both networks have γ > 1 and λ ≈ 1, demonstrating prominent small-world properties.

3.2. Nodal characteristics and alterations related to MCI

The networks were constructed at the sparsity of 9%, which ensured all nodes included in the networks to present the nodal characteristics of the networks. The brain regions with b_i > 1.7 were identified as the hubs of the networks, symbolizing that the betweenness of the hubs was over 1.7 times larger than the average betweenness of the network. In this study, 14 brain regions were identified as hubs in both groups. At last we examined the changes of the betweenness centrality in MCI patients. Compared with normal controls, MCI patients showed decreased centrality in the brain areas of the angular gyrus, heschl gyrus, hippocampus and superior parietal gyrus, while increased centrality in the the calcarine, inferior occipital gyrus and superior frontal gyrus.
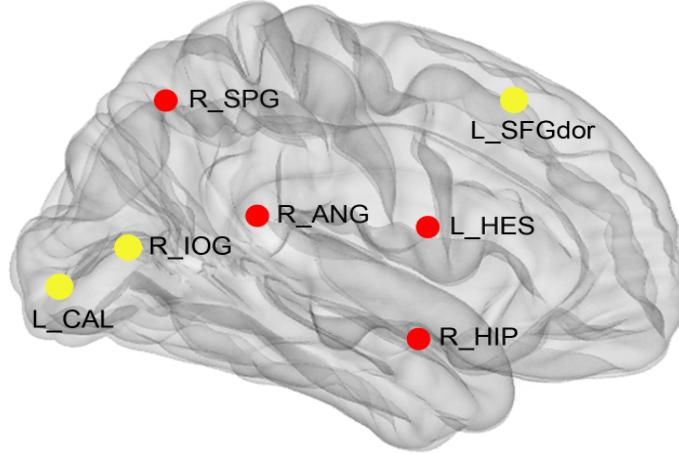

Figure 3. Regions showing decreased (red) and increased (yellow) nodal centrality in MCI patients compared with healthy control subjects. (L_HES—left heschl, R_ANG—right angular, R_HIP—right hippocampus, R_SPG—right superior parietal gyrus, L_CAL—left calcarine, R_IOG—right inferior occipital gyrus, L_SFGdor—left superior frontal gyrus dorsolateral)

4. DISCUSSION

In this study, we investigated the topological properties of the whole brain networks in MCI patients. We found that: (1) MCI patients exhibited losses of small-world attributes indicated by longer characteristic path lengths, and (2) abnormal nodal centrality changes were detected in the brain networks in MCI patients compared with normal controls.

The brain networks in MCI patients showed small-world attributes. However, we detected that MCI patients showed longer characteristic path lengths over a wide range of sparsity. The L_p and C_p indicated global and local functional integration of the whole brain networks, which constituted the basic cognitive processes [14].The increases of L_p in MCI patients may represent the disrupted information processing among distant brain regions across the whole brain.

In addition, we noted that MCI patients showed abnormal nodal centrality in several brain regions. The decreased nodal in the heschl gyrus could result from the development of MCI, because it has been demonstrated that the heschl gyrus would not degenerate in the normal aging [15]. Previous studies have observed reductions in the functional connectivity of the hippocampus to the regions of default mode network in the very early stage of AD [16]. Meanwhile, recent studies suggest that the hippocampus is likely to show abnormalities at the onset of AD before other brain regions are affected by the disease [17]. Hereafter, we speculated that the abnormalities in these brain regions may cause cognitive declines greater than one could expect for age, and disrupt the topology of the whole brain network. In a previous study, the frontal areas are found to show increased functional connectivity to the regions of default mode network in MCI [18], and this evidence is interpreted as the compensation for the loss of cognitive function in other brain regions [19]. Thereafter, the results identified significantly increased functional connectivity at resting state in frontal regions, providing new supports to the previous studies.

In conclusion, our study found that both networks of MCI patients and normal controls showed small-world attributes. It demonstrated that the human brain has evolved into a complex but efficient neural architecture to maximize the power of information processing. Though MCI patients experienced impairments in multiple cognitive domains, the disease did not change the basic topology of brain networks. However, we detected that MCI patients showed larger characteristic path length, L_p, than that of normal controls at the low sparsity. The clustering coefficient, C_p, did not show significant changes among the three groups. The loss of small-worldness may reflect disrupted neuronal integrations that were associated with impaired cognitive functions. Our findings may be helpful for further understanding the pathological mechanisms of MCI.

5. ACKNOWLEDGEMENT

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