Exploring the effective connectivity of resting state networks in Mild Cognitive Impairment: an fMRI study combining ICA and multivariate Granger causality analysis

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***Abstract*—Mild cognitive impairment (MCI) was recognized as the prodromal stage of Alzheimer's disease (AD). Recent neuroimaging studies have shown that the cognitive and memory decline in AD and MCI patients is coupled with abnormal functions of focal brain regions and disrupted functional connectivity between distinct brain regions, as well as losses of small-world attributes. However, the causal interactions among the spatially isolated but function-related resting state networks (RSNs) are still largely unexplored in MCI patients. In this study, we first identified eight RSNs by independent components analysis (ICA) from resting state functional MRI data of 16 MCI patients and 18 age-matched healthy subjects respectively. Then, we performed a multivariate Granger causality analysis (mGCA) to evaluate the effective connectivity among the RSNs. We found that MCI patients exhibited decreased causal interactions among the RSNs in both intensity and quantity compared with normal controls. Results from mGCA indicated that the causal interactions involving the default mode network (DMN) became weaker in MCI patients, while stronger causal connectivity emerged related to the memory network and executive control network. Our findings suggested that the DMN played a less important role in MCI patients. Increased causal connectivity of the memory network and executive control network may elucidate the dysfunctional and compensatory processes in the brain networks of MCI patients. These preliminary findings may be helpful for further understanding the pathological mechanisms of MCI and provide a new clue to explore the neurophysiological mechanisms of MCI.**

I. 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 altered global functional integrations of the whole brain networks [5]. However, the causal interactions among the spatially isolated but function-related resting state networks (RSNs) are still largely unexplored in MCI patients.

Resting state fMRI reflects the neuronal baseline activity of the brain, representing the state of the human brain without goal-directed neuronal action and external input [6], and the resting state functional connectivity in the blood oxygenation level-dependent (BOLD) signal during rest corresponds to consistent functionally relevant resting state networks (RSNs) [7]. Resting state fMRI has been used to evaluate brain function by measuring functional connectivity between brain regions [8]. However, there are still few studies evaluating the relationship of one large network of brain regions with another in MCI patients. Functional network connectivity (FNC) has recently been used to measure the relationships among the RSNs separated using ICA [9]. The data-driven method ICA is an effective method to examine functional connectivity of brain activity, for it can spatially isolate the spatial patterns of function-related neural networks from the spatial patterns of activity related to the artifacts, such as subtle movements, machine noise, and cardiac and respiratory pulsations. Each RSN detected using ICA consists of a spatial map and an associated time course. The temporal dependencies among the time courses describe the integrity and intervention of brain areas across large neural networks [9]. In the classic FNC analysis, lag-shift correlation has been used. But this method ignores that the interactions among RSNs are complex, possibly dynamic and directional. In this paper, we proposed an alternative causality analysis based on Granger causality analysis to evaluate the effective connectivity within the RSNs of MCI patients and normal controls.

* This paper is supported by the knowledge innovation program of the Chinese academy of sciences under grant No.KGCX2-YW-129, the National Natural Science Foundation of China under Grant Nos. 81071137, 81071217, the Fundamental Research Funds for the Central University, the Beijing Nova program, the Project for the National Key Basic Research and Development Program (973) under Grant No. 2011CB707700, 2007CB512500, 2007CB512503, 2009CB521905.

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In the present study, we attempted to investigate the causal interactions among the RSNs in MCI patients and normal controls combining the ICA and mGCA. We identified consistent RSNs from the two groups using ICA. These RSNs have been proved to be highly reproducible and stable across subjects and sessions [7]. Then, mGCA was applied to evaluate the effective connectivity between these RSNs. We hypothesized that MCI patients would exhibit weaker and less causal interactions among the RSNs and we expected that the RSNs would play abnormal roles in MCI patients compared with that in normal controls.

II. Methods

A. 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 I. 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

B. 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.

C. Data Analysis

We performed a group spatial ICA operation on the preprocessed resting state fMRI data of AD patients and normal controls using the fMRI Toolbox respectively (GIFT, http://icatb.sourceforge.net/). The images were reduced to 40 dimensions using principal component analysis, and the number of independent components (ICs) was estimated to be 25 using the MDL criteria [10]. The mean ICs of all the subjects, the corresponding mean time courses and ICs for each subject were obtained from group ICA separation and back-reconstruction [11]. The maps of these ICs across all subjects were generated for a random effect analysis using a one-sample t-test ($P < 0.05$, correction using the false discovery rate (FDR) criterion). The intensity values in each spatial map were converted to Z-scores to indicate the voxels that contributed most strongly to a particular IC. Voxels with absolute Z-values greater than 1.5 are considered as active voxels of the IC in this study [12]. According to the previous studies [9, 13], a selection of the components to be retained for further analysis among the 25 estimated ICs was performed using anatomic information. The classification of the ICs in terms of RSNs was performed according to the fMRI networks during rest consistently shown in previous ICA studies. Our selected RSNs corresponded to the cerebral components with the largest spatial correlations with the network templates, which contained the main components of the RSNs.

The mGCA has been proved to be effective to investigate the causal networks according to previous neuroimaging studies. We performed mGCA on the ICA time courses of the eight detected ICs in both groups. The mGCA detected causal interactions among ICs by computing DTF from a multivariate autoregressive model of the ICA time courses. The direct directed transfer function (dDTF) was included in the mGCA process which could be interpreted in terms of Granger causality [14]. We also adopted the weighted DTF with partial coherence in order to emphasize direct connections and de-emphasize mediated influences. More details may be available on the study from Deshpande et al. [15]. To assess the significance of path weights, a null distribution was obtained by generating 2500 sets of surrogate data and calculating the DTF from these data sets. The DTF value was compared with the null distribution for a one-tailed test of significance with a p-value of 0.05 (FDR corrected).

In order to better extract information on the temporal relations among these RSNs obtained from mGCA, a node interaction analysis was performed. In the current study, we analyzed the measures of In degree and Out degree of the two directed networks. A general definition of In degree and Out degree, as provided by previous studies [16, 17], was as follows:

- In degree: Number of Granger causal efferent connections to a node (one of the RSNs) from any other node. This casual flow profile identified nodes that were the central targets of the network.

- Out degree: Number of Granger causal afferent connections from a node (one of the RSNs) to any other node. This casual flow profile identified nodes that were the central sources of the network.

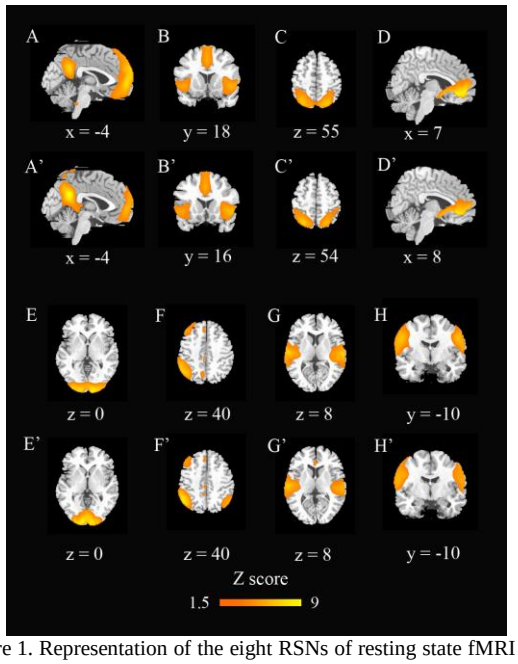

Figure 1. Representation of the eight RSNs of resting state fMRI data of MCI patients and normal controls. A-H images are DMN, SN, DAN, ECN, VN, MeN, AN and MoN in MCI patients, while A'-H' show the eight RSNs in normal controls, Imanges are Z statistics overlaid on the average high-resolution scan transformed into standard (MNI 152)

III. RESULTS

Eight ICs, including default mode network (DMN), salience network (SN), dorsal attention network (DAN), executive control network (ECN), visual network (VN), memory network (MeN), auditory network (AN), and motor network (MoN), were selected in the present study. Then we explored the causal interactions using mGCA among the RSNs detected via ICA in MCI patients and normal controls. The effective connectivity patterns of brain networks were described as directed graphs. The thickness of connecting lines and the directions of arrows indicate strength and directions of the causal influences. Figure 2 showed the Granger casual connectivity measures within the eight RSNs. Only significant effective connectivity ($p < 0.01$) was divided into four levels (25%, 50%, 75%, and 100%) relative to the maximum significant dDTF value and presented in the graphs.

In normal controls (Figure 2A), the DMN was mostly connected with other RSNs. We detected that the DMN was intensely connected with the DAN, SN, MoN and AN. Strong causal interactions were also observed between the AN and SN, DAN, respectively. Compared with normal controls, MCI patients (Figure 2B) exhibited decreased Granger causal interactions within the RSNs in both the intensity and quantity ($p < 0.01$). It was particularly noteworthy that the intensity of interactions of the DMN decreased while a strong bidirectional regulation was forged between the MeN and

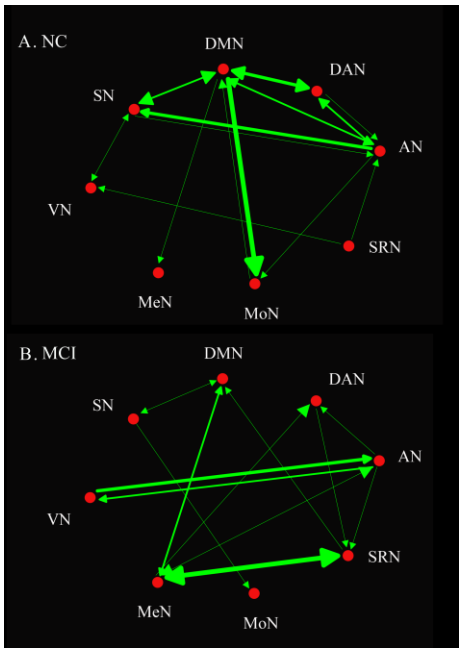

Figure 2. Effective connectivity patterns of MCI patients and normal controls from the mGCA results. The red dots refer to the eight RSNs. The relative causal influence strength was divided into four levels relative to the maximum significant dDTF value and represented by the thickness of the green line..

ECN.

In order to better evaluate the causal interactions among the RSNs, we showed the In degree, Our degree and In + Out degree for every RSN in the two networks in Figure 3. In normal controls, the mean of in + out degree for every RSN was 4.5 and the SD was 2.88. The DMN and AN served as hubs according to the standard, and they were not only central targets but also central sources according to the standards. In MCI patients, the mean of in + out degree for every RSN was 3.25 and the SD was 1.83. The MeN was identified as the hub in MCI patients. Meanwhile, the MeN and AN served as central sources while the ECN and MeN served as central targets in the network in MCI patients.

IV. DISCUSSION AND CONCLUSION

In the present study, we combined ICA with mGCA to evaluate the effective connectivity among the RSNs of the MCI patients and normal controls. The main findings of this paper were as follows: (1) Compared to normal controls, MCI patients exhibited abnormal effective connectivity patterns; (2) the causal influence involving the DMN became weaker in MCI, while stronger causal connectivity emerged related to MeN and ECN.

ICA was successfully used to indentify resting state components in MCI patients and normal controls in this paper. We were able to examine the causality interactions between these RSNs and to identify the effective connectivity among them using mGCA. We separated and characterized the activity of eight RSNs, which overlapped with DMN, SN,

DAN, ECN, VN, MeN, AN, and MoN, as previously defined in neuroimaging studies on active behavior tasks and resting state studies.

Apart from just identifying the RSNs, the primary purpose of this paper was to evaluate the effective connectivity patterns among these RSNs. To date, there were still few studies pay attention to the causal interactions among the RSNs in MCI patients. We found that in normal controls, the DMN had strong causal interactions with DAN, SN, MoN and AN. But the effective connectivity between the DMN and other RSNs in MCI patients decreased in both intensity and quantity. Functional connectivity was found decreased in the DMN regions in early stage of AD [18]. The abnormal connectivity within the DMN and with other regions have been suggested to be directly related to MCI [19], and proposed as potential biomarkers to detect AD [20, 21]. Our findings from mGCA may provide further support for the conclusion that the activity and connectivity in the DMN became weaker in MCI patients.

Furthermore, we found that the DMN and AN were central targets and central sources in normal controls. A recent fMRI study on DMN has demonstrated that a causal target in the neuronal activity propagation process tend to have a stronger BOLD activity, suggesting that causal influences may predict the neuronal activity levels [22]. Our results suggested that the DMN was fundamental in the resting state in normal controls, as it can integrate information from other RSNs. While in MCI patients, the DMN was never the hub in the network. We argued that the DMN played a less important role, as the DMN showed decreased connectivity. In addition, we identified that the MeN and AN emerged as central sources and the ECN and MeN served as central targets. The ECN and DMN have been found to play distinct roles in the human brain functional structure [12]. So we suggested that when the DMN showed decreased activity and connectivity in MCI patients, the ECN may compensate for the impairments of DMN. Patients with AD and MCI patients usually showed degeneration in basic cognitive domains like memory and auditory [23]. Our results indicated that the MeN and AN became more connected in MCI patients, which may reflect the compensatory processes for the two RSNs.

In conclusion, the current investigation focused on the effective connectivity patterns within RSNs in MCI patients and normal controls. We adopted ICA to identify RSNs from resting state fMRI data, and then mGCA to evaluate the causal interactions among these RSNs. We found that the DMN and AN showed decreased causal interactions with other RSNs in MCI patients, while the causal connectivity of MeN and ECN increased. This suggested that MeN and ECN may compensate for the impairment of DMN and AN. These preliminary findings may provide a new clue to explore the neurophysiological mechanisms of MCI.

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