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Functional Activity and Connectivity Differences of Five Resting-State Networks in Patients with Alzheimer's Disease or Mild Cognitive Impairment

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Abstract: We aimed to investigate the activity within and the connectivity between resting state networks (RSNs) in healthy subjects and patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI). Magnetic resonance imaging (MRI) and resting-state MRI were performed on patients diagnosed with AD (n=18) or MCI (n=16) and on healthy subjects (n=18) with matching demographic characteristics (age, sex, and education level). Independent component analysis and Granger causality analysis (GCA) were used during image post-processing. We calculated 'In + Out degree' for each RSN. Then, we investigated the relationships between "In + Out degree" of each brain network and the cognitive behavioural data. RSNs were obtained using the optimal matching method. The core areas of the five RSNs were similar between the AD, MCI, and healthy control groups, but the activity within these five RSNs was significantly lower in the AD and MCI groups than in the healthy control group ($P<0.01$, false discovery rate corrected). The GCA results showed that the connectivity between the five RSNs, particularly the connectivity from the default mode network (DMN) to the other RSNs, was slightly lower in MCI patients and was significantly lower in AD patients than in healthy subjects. In contrast, increased connectivity was evident between the memory network and the executive control network in the AD and MCI patients. The "In + Out degree" of the DMN negatively correlated with the Montreal Cognitive Assessment score in AD patients ($R=-0.43$, $P<0.05$). In conclusion, the activity within RSNs and the connectivity between RSNs differed between AD patients, MCI patients, and normal individuals; these results provide an imaging reference for the diagnosis of AD and the measurement of disease progression and reveal insight into the pathogenesis of AD.

Keywords: Alzheimer's disease (AD), mild cognitive impairment (MCI), dementia, resting-state networks (RSNs), resting state functional magnetic resonance imaging (rs-fMRI), independent component analysis (ICA), granger causality analysis (GCA).

1. INTRODUCTION

Alzheimer's disease (AD), a primary neurodegenerative disorder characterized by progressive dementia, predominantly occurs in aged individuals [1]. The morbidity of AD is 4–7% in populations aged 65 years or older and 43% in populations aged 85 years or older [2]. AD exhibits an insidious onset, as it can take decades for AD symptoms and signs to manifest. Nonspecific premonitory symptoms such as memory impairment and visual-spatial perception syndrome develop during the premorbid stage of AD but cannot be differentiated from other forms of dementia [1]. Using common imaging techniques such as CT and MRI, structural changes are generally not evident during the early stage of AD (e.g., no atrophy is apparent); thus, the diagnosis of early-stage AD is difficult. Recently, improved functional magnetic resonance imaging (fMRI) and post-processing methods have been increasingly used to study cognition [3]. Therein, investigating early and progressive neuroimaging changes in AD would assist with understanding the pathogenesis of AD and the disease early diagnosis.

Biomarkers have become centrally important for the diagnosis of early and preclinical AD [1]. A growing consensus indicates that sufficient amounts of amyloid-beta (Aβ) plaques and neurofibrillary tangles in autopsied brains are

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definitive diagnostic criteria for AD [4]. Recently, the development of a positron emission tomography (PET) tracer, Pittsburgh Compound-B (PiB), has enabled the acquisition of *in vivo* images of amyloid species. Longitudinal studies have suggested that patients with mild cognitive impairment (MCI) and increased PiB retention much more frequently convert to AD [5-8]. Thus, PiB PET appears to display prognostic value for the clinical evaluation of MCI in subjects who exhibit underlying AD pathophysiology and are at high risk for further clinical decline [9, 10]. However, 10–30% of normal elderly subjects display significant PiB retention, depending on the region of interest [10, 11]. This wide range of PiB retention is assumed to depend on factors such as age, the presence of the ApoE ε4 allele (a genotype associated with increased PiB retention in cognitively normal elderly people [12-15]), the definition of 'cognitively normal', and the threshold for defining amyloid positivity [10]. Given these limitations, an objective imaging method that is negligibly affected by such factors and that can directly assess neural activity rather than neural metabolic changes is needed.

Resting-state networks (RSNs) are defined as regions of synchronized basal activity in the brain while at rest [16, 17]. The resting state in the living human brain is never complete. 'Resting' here refers to basic thinking activities, such as self-reflection. The pattern of RSN function appears to reflect the pattern of structural white matter connections, suggesting the existence of an underlying structural core of functional connect networks in the human brain [18]. For this reason, several RSNs have been regularly studied, including the five classic networks (i.e., the default-mode network [DMN] [19-23], the anterior temporal memory network [MeN] [24], the motor network [MoN] [21, 25], the auditory network [AN] [21, 25], and the executive control network [ECN] [21-23]). Because of their prominent roles in information processing and their widespread connections involving the entire brain, RSNs, particularly the DMN, have been extensively studied in patients with AD or MCI and in at-risk subjects [19-25]. The DMN is unique among the RSNs because (according to fMRI studies) patients with AD or amnestic MCI (aMCI) exhibit reduced activation of the DMN when performing cognitive tasks but increased activation of the DMN at rest [26, 27]. Thus, the basal activity of this network is related to cognition [28, 29]. fMRI studies have indicated that patients with MCI exhibit deficient DMN function [30-34].

Resting-state fMRI (rs-fMRI) can be used to evaluate regional brain functions based on changes in blood flow when a subject is not performing an explicit task. The undulation of resting-state blood oxygenation level-dependent (BOLD) signal is consistent with RSN functionality [35]. Cognitive functions are easier and more feasible to study using rs-fMRI than using fMRI. This non-invasive and relatively inexpensive neuroimaging method, which can directly detect neural activity related to cognitive performance, is more acceptable to subjects than PiB PET. With the development and improvement of resting-state imaging technology and post-processing methodologies, rs-fMRI is attracting increasing attention. During the resting state, the medial prefrontal cortex, the posterior cingulate cortex and parietal lobe display lower activity in patients with MCI than in healthy people [32]. Changes in the fMRI signals of certain areas during the resting state might serve as a significant indicator of MCI diagnosis and disease progression [36]. Warren *et al.* demonstrated the importance of neural network deficiencies in neurodegenerative diseases from a molecular perspective by suggesting that neural networks provide candidate substrates for the spread of proteinopathies that cause neurodegeneration and by proposing "the molecular nexopathy paradigm" to interpret the role of protein abnormalities in network signatures [37]. Many studies have investigated the connectivity within specific RSNs, but few studies have investigated the connectivity between RSNs. Here, the study of RSNs for the early detection of AD was examined. Independent component (IC) analysis (ICA) and Granger causality analysis (GCA) were used to explore differences in RSN connectivity, especially between AD patients and healthy controls. Previous studies have shown that MCI and AD induce dysfunction in multiple brain networks [38]. However, few studies in patients with AD and patients with MCI focused on the correlation between different brain networks. It is assumed that patients with AD and MCI might exhibit dysfunctional connectivity among distinct brain regions and that these cognitive deficits might be related to the dysfunction of entire networks that fail to properly communicate with one another [39]. Therefore, the current study aimed to explore the interactions between resting-state brain networks and to provide insight into the pathogenesis of AD.

2. MATERIALS AND METHODS

2.1. Subjects

From March 2010 to March 2011, patients with AD or MCI (who met the clinical diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] [1]) and healthy volunteers who were matched with respect to age, sex, and education level were recruited at the Department of Neurology of Beijing Tiantan Hospital, Beijing, China. Among these individuals, 18 AD patients, 16 aMCI patients (patients without a history of cerebrovascular disease, hyperlipidaemia or any other disease that leads to vascular dementia) and 18 control subjects were selected after confirming the absence of cerebral infarction, intracerebral space-occupying lesions, and demyelination based on conventional brain MRI. The control subjects had no previous history of neurological or psychiatric disorders, substance abuse, or severe internal organ involvement. All subjects were aged between 52 and 77 years. The Mini-Mental Score Examination (MMSE), the Hachinski Ischemic Scale, the Hamilton Anxiety Depression Scale, the Clinical Dementia Rating Scale (CDR), and the Montreal Cognitive Assessment (MoCA) were used to assess all subjects.

2.2. Methods

2.2.1. Cognitive Function Assessment

Cognitive function was assessed by qualified professionals who had prior training on neuropsychological testing and who were certified by the China Rehabilitation Centre. The patients and their families voluntarily provided informed consent to participate in this study. The tests were given to

the enrolled patients in a strict order in accordance with the protocol and were administered in quiet rooms, generally between 5 pm and 9 pm. Most patients completed the tests in one session. Patients in poor general health who were unable to complete the tests were excluded.

2.2.2. MRI Scan Protocol

No subjects carried implanted metal medical devices or had any contraindications for MRI. A Siemens Trio 3.0T scanner equipped with a standard quadrature head coil was used to perform MRI; the patients were placed in the supine position on a scanning bed, and their heads were comfortably fixed in position using a foam pad. The subjects were told to relax, close their eyes, not move their head, and avoid thinking. The scanning parameters were as follows: TR=2000 ms, TE=30 ms, flip angle (FA) =–90°, no. of layers=31, thickness of each layer=3.0 mm, interlayer spacing=–0.6 mm, field of vision (FOV)=24 cm×24 cm, and matrix size=64×64.

2.2.3. rs-fMRI Data Pre-Processing

Considering the relatively low signal-to-noise ratio and low sensitivity-to-motion fMRI artefact, pre-processing was necessary before statistical analysis.

fMRI image pre-processing and analysis were conducted using the SPM software package. The first five functional images were excluded to attenuate the magnetic field in each subject. Preprocessing included realignment, normalization, smoothing, and filtering. The functional images were motion-corrected using the realign function. Head movement was not excessive in any subject (i.e., fewer than three translational displacements > 2.0 mm or three rotational displacements > 2°). Subsequently, the functional images were spatially normalized using the SPM software package, and a technique for generating region of interest (ROI) masks based on the Talairach brain atlas was performed. Finally, the functional images were smoothed using a Gaussian kernel.

2.2.4. ICA

ICA was performed after smoothing the data using the software tool platform Group ICA of the fMRI Toolbox (GIFT, http://icatb.sourceforge.net/). The rs-fMRI data were reduced to a 40-dimensional space using principal component analysis. Maximum information entropy (Infomax) was used to estimate 25 independent components according to the minimum description length principle. We identified the RSNs based on visual inspection as described in previous studies [40-42]. The components, the group average composition, and the associated average time series of each subject from each group were obtained via ICA separation and re-establishment. Z values were used to quantify each subject's time courses and spatial maps, and a one-sample *t*-test and a two-sample *t*-test was performed to determine the statistical significance of within-group and between-group differences, respectively. The Z values in the IC map indicated the strengths of the observed functional connectivity (i.e., the ratios of a specific voxel time course to the group-averaged time course for the given component) [43].

2.2.5. GCA

Resting-state time series of the five RSNs were examined using GCA of multivariate autoregressive models [44] to describe the 'causal' influence between sets of fMRI series [45-51]. If the past values of a time series x(t) could be used as a prediction of the future values of another time series y(t), it means x(t) has a causal influence on y(t) [52]. This method is most commonly employed in neuroscientific studies [46, 53]. In this analysis, we included five RSNs (the DMN, the MeN, the MoN, the AN, and the ECN) as ROIs. The time series for each ROI represented the time component of each IC. We defined the effective connectivity networks of the ICs using multivariate GCA as previously described [39]. Using a multidimensional vector autoregressive model [49, 54, 55], the Granger causality (G-causality) between the time series was applied to evaluate the significance of the effective connectivity for the five ROIs.

We conducted a node interaction analysis to extract information about the temporal relationships between the RSNs obtained from GCA [56]. "In degree" and "Out degree" were used to evaluate the connectivity between different networks. "In degree" is defined as the number of Granger causal connections that are input to a node from any other nodes. The node here is the central target of the networks. "Out degree" means the number of Granger causal connections that are output from a node to any other nodes. The node here is the central source of the networks [57, 58].

Nodes with high degrees were considered to be the hubs of the network [59]. Then, we calculated "In + Out degree" for every RSN and investigated the relationship between "In + Out degree" of each brain network and the cognitive behavioural data.

2.2.6. Statistical Analysis

A single-sample *t*-test was used to assess the activity maps of the ICA data, which were generated via random effect analysis of all subjects in each group ($P<0.05$, false discovery rate corrected). We conducted multiple comparisons with the G-causalities of the five time series for each subject ($P<0.05$), and used a binomial test to analyse the significance of the effective connectivity for the entire sample. Correlation analysis was conducted to evaluate the relationships between the "In + Out degree" of each brain network and the cognitive behavioural data.

3. RESULTS

3.1. Cognitive Function in this Cohort

Based on the Hachinski Ischemic Scale and the Hamilton Anxiety Depression Scale, patients with pseudo-cognitive impairment resulting from anxiety/depression and patients with vascular dementia were excluded. Eighteen patients with AD (7 males and 11 females; age (mean ± SD), 64.83 ± 7.80 years [range 55–77]; MMSE score (mean ± SD), 11.94 ± 5.98; MoCA score (mean ± SD), 11.56±5.30), 16 patients with MCI (7 males and 9 females; age (mean ± SD), 63.25 ± 7.18 years [range 52–75]; MMSE score (mean ± SD), 20.25 ± 1.64; MoCA score (mean ± SD), 20.06±2.38) and 18 healthy subjects (8 males and 10 females; age (mean ± SD), 66.06 ± 7.23 years [range 53–77]; MMSE score (mean ±

SD), 28.11 ± 1.79; MoCA score (mean ± SD), 29.22±2.62) were enrolled. Number of years of education was not significant between the groups (P<0.05).

Two independent-sample *t* tests showed significant between-group differences in MMSE score and other cognition scale scores (P<0.001; Table **1**) but not in age (P=0.96), educational level (P=0.94), or sex (P>0.05).

3.2. RSNs

Five RSNs were detected based on ICA. RSN1 (the DMN) , which gets involved in internal processing, primarily includes the posterior cingulate cortex/precuneus (PCC/P), the bilateral inferior parietal gyrus, the angular gyrus, the middle temporal gyrus, and the superior temporal gyrus. RSN2 (the MeN), which is correlated with memory functions, primarily includes the middle frontal gyrus, the middle temporal gyrus, and the superior parietal gyrus. RSN3 (the MoN), which is related to motor function, includes the structures of the precentral gyrus, the postcentral gyrus, the middle frontal gyrus, and the middle temporal gyrus. RSN4 (the AN) includes structures that are responsible for auditory processing (i.e., the insular cortex and the middle and superior temporal gyri). RSN5 (putatively the ECN) primarily includes structures that are responsible for executive control and working memory (i.e., the superior and middle prefrontal cortices, the anterior cingulate cortex, and the ventrolateral prefrontal cortex).

Comparative analysis of the post-processed data revealed that the core areas of the five RSNs were similar between the three groups but that the activity within these five RSNs was significantly lower in the AD and MCI groups than in the healthy control group (P<0.01, false discovery rate corrected). In the AD group, the areas exhibiting decreased activity were the PCC/P in the DMN, the middle temporal gyrus and the middle frontal gyrus in the MeN, the middle temporal gyrus in the AN, the postcentral gyrus in the MoN, and the anterior cingulate cortex and the inferior frontal gyrus in the ECN. In the MCI group, the areas with decreased activity were the bilateral precuneus and the posterior cingulate cortex (PreCN/PCC, BA 7/31), the bilateral fusiform gyrus (FG, BA 37), the right hippocampus (HC, BA 35), the bilateral inferior parietal lobule (IPL, BA 40), the superior temporal gyri, and the middle temporal gyrus (Fig. **1**).

3.3. GCA of Effective Connectivity

GCA was performed on the multivariate autoregressive models to depict the "causal" interaction between sets of fMRI series. In addition to the decreased activity within the five RSNs in the AD and MCI patients, the connectivity between the five RSNs was slightly lower in MCI patients but was significantly lower in AD patients than in the healthy controls. Compared with the healthy controls, the connectivity from the DMN to the other RSNs was significantly lower in both AD and MCI patients. In contrast, the connectivity between the MeN and the ECN was increased in AD and MCI patients compared to the healthy subjects (Table **2** & Fig. **2**). By analysing the relationships between the "In + Out degree" of each brain network and the cognitive behavioural data, a significant negative relationship was found between the "In + Out degree" of the DMN and the MoCA score in the AD patients (R=-0.43, P<0.05).

4. DISCUSSION

Our study showed that the activity within and between different RSNs differed between patients with AD, patients with MCI, and healthy controls. The activity within the five RSNs was significantly lower in the AD and MCI groups than in the healthy control group, although the core areas of the RSNs were similar between these groups. The connectivity between the five RSNs was slightly lower in the MCI patients and was significantly lower in the AD patients than in the healthy subjects. However, the connectivity between the MeN and the ECN was increased in the AD and MCI patients compared to the healthy subjects. These differences might serve as an imaging reference for the diagnosis of AD and the measurement of disease progression and as a potential imaging signature to distinguish AD from other neurodegenerative disorders.

In 2004, Greicius *et al.* [31] found that the resting-state activity of the PCC and the hippocampus were decreased in AD patients and that these pathological changes serve as diagnostic markers for AD. A few rs-fMRI studies of AD patients have confirmed these findings [60-66]. Using correlation analysis to study the bilateral hippocampus, Wang *et al.* [61] found impaired connections between the right hippocampus and other regions, such as the interior prefrontal cortex, the right temporal lobe, the right precuneus, the right upper and middle temporal lobes, and the PCC. These findings were in line with those of previous studies, in which

Table 1. Cognitive characteristics.

	AD	MCI	Control group
N	18	16	18
Age (mean value ± SD)	64.83±7.80	63.25±7.18	66.06±7.23
MMSE (mean value ± SD)*	11.94±5.98	20.25±1.64	28.11±1.79
MoCA (mean value ± SD)*	11.56±5.30	20.06±2.38	29.22±2.62
CDR	1	0.5	0

MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment ; CDR: Clinical Dementia Rating Scale; *P <0.001

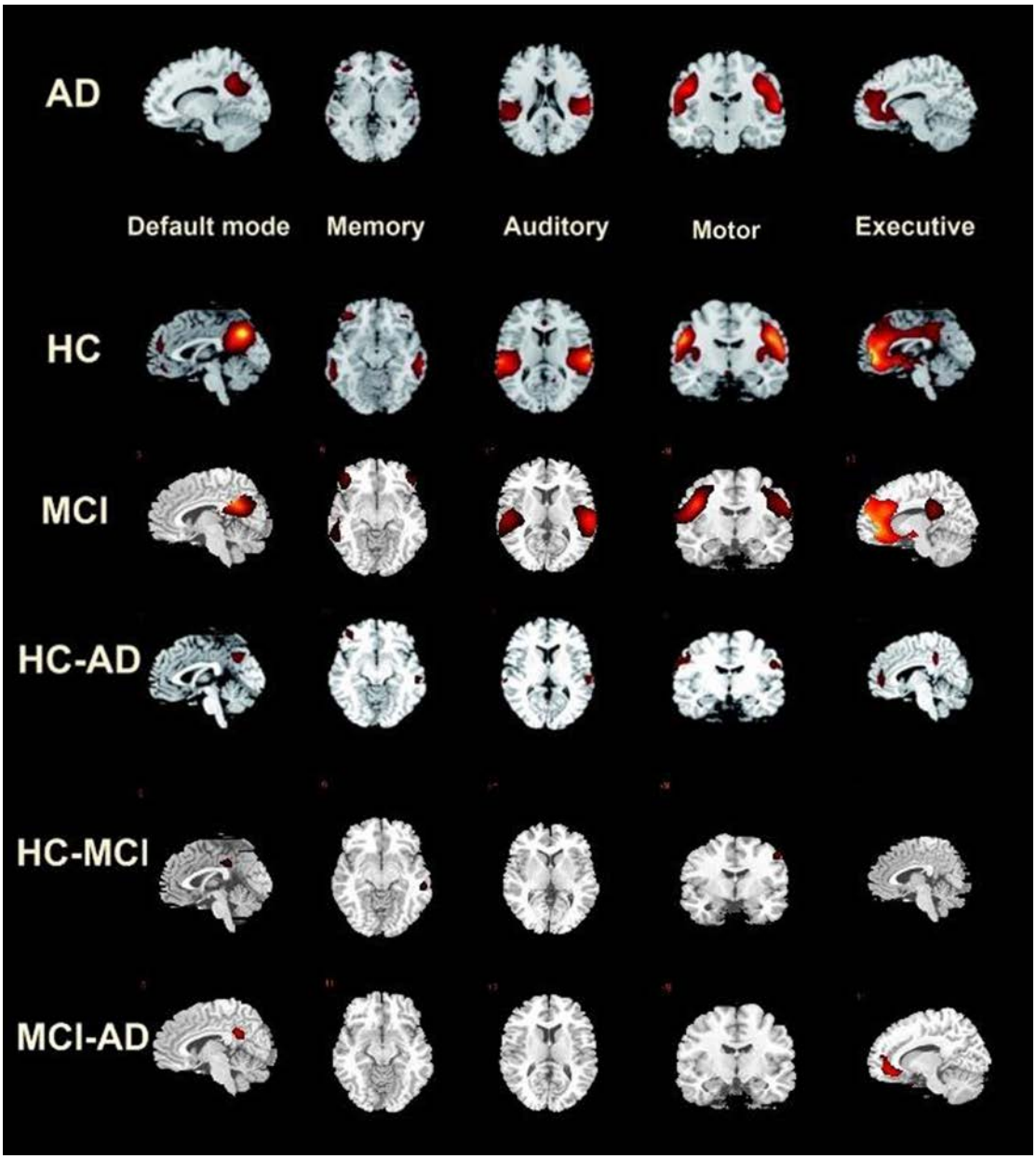

Fig. (1). Independent component analysis of RSNs in the AD and healthy control groups.

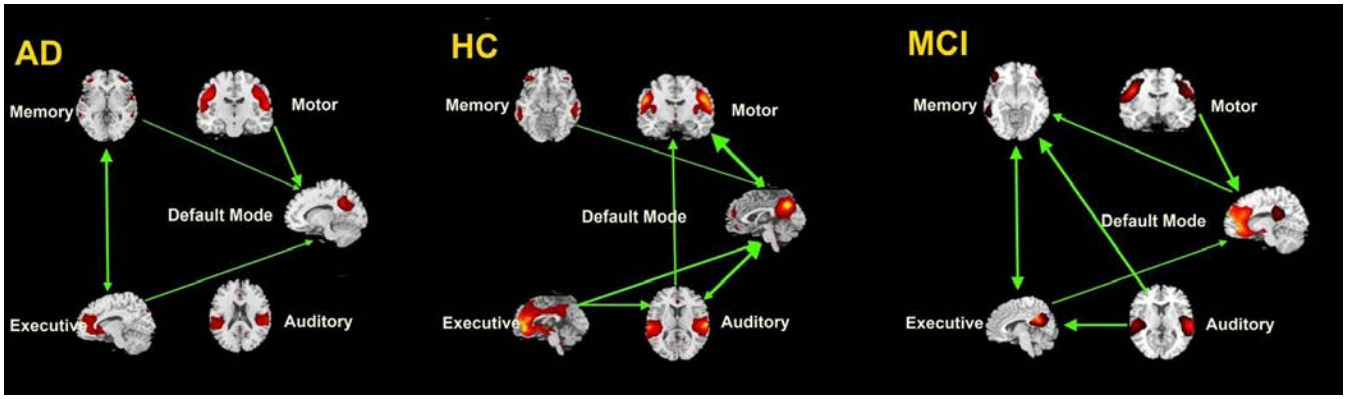

Fig. (2). Granger causality analysis of connectivity between RSNs. The arrows indicate the direction of information flow. And the width of the arrows show the relative path weight (any unit).

Table 2. Path weights from multivariate GCA for the HC, MCI and AD condition (P < 0.01, corrected for multiple comparisons).

	Default Mode			Memory			Executive			Motor			Auditory		
	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD
Default Mode	—	—	—	16 ↓	×	18 ↓	19 ↑	18 ↑	17 ↑	22 ↓	37 ↓	20 ↓	26 ↑	×	×
Memory	×	20 ↑	×	—	—	—	×	31 ↑	27 ↑	×	×	×	×	35 ↑	×
Executive	×	×	×	×	30 ↑	25 ↑	—	—	—	×	×	×	×	32 ↑	×
Motor	45 ↓	×	×	×	×	×	×	×	×	—	—	—	21 ↑	×	×
Auditory	24 ↑	×	×	×	×	×	20 ↑	×	×	×	×	×	—	—	—

GCA=granger causality analyses; HC=healthy control; MCI=mild cognitive impairment; AD=Alzheimer's disease
Only the significant paths are listed. Influences are from column ROI to row ROI. ↑ indicates co-varying, ↓ indicates anti- varying paths and × indicates the weights below the significance.

ICA demonstrated reduced activity in the posterior DMN [67] and the hippocampus [31] and increased connectivity within the frontal executive networks of AD patients [68]. Collectively, these findings suggested that disrupted connectivity in the DMN led to compensatory increases in anterior connectivity. We performed GCA on multivariate autoregressive models [44] to further examine the connectivity between the five classic RSNs; this method has widely been used to describe the 'causal' interaction between sets of EEG or fMRI time series [45-51]. The decrease in overall connectivity between the posterior DMN and the other RSNs and the lack of connectivity between the AN and the other RSNs (including the insular cortex and the middle and superior temporal gyri) in AD and MCI patients compared to healthy subjects suggest potential auditory impairment in AD and MCI patients. Although previous studies have demonstrated increased activity in frontal networks in AD patients [31], the connectivity changes between the ECN and the other RSNs remain unclear. Although the connectivity was decreased between the ECN, the AN, and the DMN, the connectivity between the ECN and the MeN was definitely increased, representing an additive effect of increased activity in the frontal executive networks of AD patients, in contrast to healthy subjects.

The most prominent symptom of AD is memory impairment. Based on how information is stored, memory can be divided into episodic and semantic memory. Many studies have shown that episodic memory, especially memory involving episodic speech, is commonly affected during the early stage of AD [69-71]. Connection areas in the interior temporal lobe (including the entorhinal cortex, the hippocampus, the parahippocampal gyrus, and the nasal cortex), the prefrontal lobe, the cingulate cortex, the precuneus, the temporal lobe, and the parietal lobe are key domains of episodic memory [72]. Inconsistent with the findings of previous studies [73], our study found higher connectivity between the MeN and the other RSNs, particularly between the MeN and the ECN, in AD and MCI patients compared to healthy subjects. These differences were even greater in aMCI patients. The increased connectivity observed between the MeN and the ECN indicates that AD and aMCI patients might experience difficulty in recruiting additional neural resources within the MeN (manifesting as decreased activity within the MeN) because these patients (in contrast to healthy individuals) are unable to separate the functions of the MeN. For this reason, the MeN must mobilize other RSNs to compensate for its abnormal function. Our study showed decreased connectivity among the five RSNs and significantly increased connectivity between the MeN and the ECN in AD and aMCI patients compared to healthy subjects. According to the compensatory hypothesis, this increase in connectivity indicates a salient abnormal function of the MeN. Consequently, AD patients exhibit prominent memory deficits, prolonged reaction times on cognitive tasks, and impaired information processing. This compensation was also observed in the DMN. By analysing the relationships between the "In + Out degree" of each brain network and the cognitive behavioural data, we found a significant negative relationship between the "In + Out degree" of the DMN and the MoCA score in AD patients. That is, the more severe the cognitive impairment, the greater the connectivity between the DMN and the other RSNs. Alternatively, it has been hypothesized that as connectivity increases, an increase in metabolism increases the susceptibility of the MeN to amyloid deposition [27, 74]. We propose that the connectivity increases between the MeN and the other RSNs during the preclinical and early clinical stages (the period of aMCI) in AD patients and the progressive decrease in this connectivity at advanced AD stages indicates amyloid accumulation in the MeN that leads to impairments in memory function. We found that the increased connectivity between the MeN and other RSNs was less significant in AD patients than in aMCI patients but that the decreases in the activity within the RSNs and in the connectivity between different RSNs were much more pronounced in AD patients than in aMCI patients, suggesting that the network characteristics of aMCI patients are intermediate between those of AD patients and healthy controls. We hypothesize that neural function in memory-related areas was masked by bypass connectivity, which partially compensated for the reduction in neurological function during the preclinical and early clinical stages of AD (the period of aMCI). These connectivity changes in the RSNs of aMCI patients were intermediate between those in the RSNs of AD patients and those of healthy controls. As the disease progresses, the amyloid burden in the MeN increases and results in greater memory impairment.

The cognition scale results from our study showed that AD and aMCI patients exhibited amnesia that was more severe than other cognitive deficits. Based on ICA, differences between the three examined groups were found, especially in locations that are related to memory, such as the interior prefrontal lobe, the PCC, and the ventral anterior cingulate cortex. Therefore, we suggest that the changes in the RSNs are associated with clinically significant cognitive impairment, particularly in the regions related to amnesia. This type of change might be due to a compensatory mechanism, as mentioned above. In our study, ICA was used to locate the RSNs, test intergroup differences, and describe the correlations between cognitive impairment and the changes in the RSNs in AD and aMCI patients. ICA enabled us to meaningfully examine the RSNs, thereby helping us to understand the pathogenesis of AD and to diagnose early-stage AD.

The limitations of this study include its small sample size, which limited the further classification of MCI, and the use of techniques that are restricted to assessing network differences that are associated with episodic memory deficits between AD and aMCI patients. However, our results suggested that the connectivity changes observed in the RSNs of aMCI patients are intermediate between those in AD patients and healthy controls. The results from this study indicate a need to examine such network changes in a larger population in conjunction with episodic memory-related fMRI studies and experiments using other techniques that provide physiological information about the MeN and the ECN. In future studies, we will use a larger sample size and compare the differences in memory deficits between patients with aMCI and AD using neuro-imaging techniques.

In summary, RSN changes that had been demonstrated in previous studies were confirmed, and the connectivity between the five classic RSNs was assessed for the first time. The altered brain connectivity pattern of RSNs might be a tool to distinguish AD from other neurodegenerative disorders such as frontotemporal dementia, and advance our knowledge in the progression of AD.

ABBREVIATIONS

Aβ	=	amyloid-beta
AD	=	Alzheimer's disease
ADAS-Cog	=	Alzheimer's Disease Assessment Scale-Cognition
BOLD	=	blood oxygenation level-dependent
aMCI	=	amnestic mild cognitive impairment
AN	=	auditory network
CDR	=	Clinical Dementia Ranking Scale
DMN	=	default mode network
ECN	=	executive network
FA	=	flip angle
FOV	=	field of vision
GCA	=	Granger causality analysis
GIFT	=	Group ICA of the fMRI Toolbox
fMRI	=	functional magnetic resonance imaging
IC	=	independent component
ICA	=	independent component analysis
MCI	=	mild cognitive impairment
MeN	=	memory network
MMSE	=	Mini-Mental State Examination
MoCA	=	Montreal Cognitive Assessment
MoN	=	motor network
NINCDS-ADRDA	=	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PCC/P	=	posterior cingulate cortex/precuneus
PET	=	positron emission tomography
PiB	=	Pittsburgh Compound-B
ROI	=	region of interest
RSNs	=	resting state networks
rs-fMRI	=	resting-state functional MRI
SPECT	=	single photon emission computed tomography

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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