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Impaired Functional Connectivity of the Thalamus in Alzheimer's Disease and Mild Cognitive Impairment: A Resting-State fMRI Study

Bo Zhou[1], Yong Liu[2,3,*], Zengqiang Zhang[1], Ningyu An[4], HongxiangYao[4], Pan Wang[1], Luning Wang[1], Xi Zhang[1,*] and Tianzi Jiang[2,3,5,6]

[1]Department of Neurology, Institute of Geriatrics and Gerontology, Chinese PLA General Hospital, Beijing, 100853, China; [2]Brainnetome Center, Institute of Automation, Chinese Academy of Sciences, Beijing, 100190, China; [3]National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing, 100190, China; [4]Department of Radiology, Chinese PLA General Hospital, Beijing, 100853, China; [5]Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, 610054, China; [6]The Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia

Abstract: *Objectives:* The current study evaluated whether the functional connectivity pattern of the thalamo-cortical network in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) would show disease severity-related alterations.

Methods: Resting-state functional magnetic resonance imaging (MRI) data were obtained from 35 patients with AD, 27 patients with MCI and 27 subjects with normal cognition (NC). First, the altered functional connectivity pattern in AD patients was evaluated in comparison to NC subjects. Second, the MCI subjects were included to evaluate how different stages of disease affect the functional connectivity pattern of the thalamus. Finally, a correlation analysis was performed between the strength of the functional connectivity of the identified regions and various clinical variables to evaluate the relationship between the strength of functional connectivity and the cognitive abilities of MCI and AD patients.

Results: When compared to NC subjects, AD patients showed decreased functional connectivity between the left thalamus and brain regions including the precuneus/posterior cingulate cortex, right middle frontal gyrus and left inferior frontal gyrus. Decreased functional connectivity was also found between the right thalamus and right middle frontal gyrus and left inferior parietal lobule/angular gyrus. In addition, increased functional connectivity was observed between the bilateral thalamus and brain regions including the middle frontal gyrus, middle temporal gyrus, inferior temporal gyrus, superior parietal lobule, postcentral gyrus and precuneus. Functional connectivity between the bilateral thalamus and the identified brain regions of MCI subjects was intermediate in comparison to the functional connectivity of AD and NC subjects. A significant correlation between the fitted functional connectivity strength and the clinical variables was also detected.

Conclusion: Our results revealed disease severity-related alterations of the thalamo-default mode network and thalamo-cortical connectivity in AD and MCI patients. These results support the hypothesis of network disconnection in AD.

Keywords: Alzheimer's disease, mild cognitive impairment, thalamic connectivity, resting-state, functional magnetic resonance imaging.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder in the geriatric population and has received considerable interest from clinicians and researchers because of its insidious disease course and lack of available drug treatments. As a well-accepted transitional phase between elderly individuals with normal cognition and AD, mild cognitive impairment (MCI) is associated with a high risk for the clinical acquisition of dementia, especially AD [1-3]. Currently, MCI is recognized as representative of the early symptomatic stages of AD [4, 5], although it remains unclear whether MCI may progress to other types of dementia [3]. In contrast to the classical physiopathological changes found in AD, several converging pieces of evidence indicate that disrupted connectivity between different brain regions is prevalent and may play a prominent role in the cognitive/mental dysfunction associated with AD/MCI [5-9].

Functional connectivity represents the synchronized neural activity between brain regions and has been widely used in the brain imaging community to study the functional integration of the brain [10-12]. Functional connectivity analysis

*Address correspondence to these authors at the Brainnetome Center, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, P.R. China; Tel: 86-10-8254 4768; Fax: 86-10-8254 4777; Email: yliu@nlpr.ia.ac.cn (Yong Liu) and Department of Neurology, Institute of Geriatrics and Gerontology, Chinese PLA General Hospital, Beijing, 100853, P.R. China; Tel: 86-10-6693 7693; Fax: 86-10-6693 9693; Email: zhangxi@301hospital.com.cn (Xi Zhang)

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based on a region of interest (ROI) is the most common method for investigating functionality in the brain, especially in studies of AD and MCI [13-17].

The thalamus is the main region that receives inputs from primary sensory brain regions, such as the basal ganglia, the cerebellum and the limbic system, and it then processes this information before passing it on to the cerebral cortex [18]. Previous studies based on multimodal brain imaging have demonstrated significant connectivity between the thalamus and different functional brain regions, such as the frontal, temporal, parietal and occipital lobes [18-22]. Some of these connections, such as the thalamo-hippocampus connection, are considered to be important pathways for memory [23], and memory dysfunction is often the earliest and most prominent symptom in AD and MCI [2, 24]. Using diffusion tensor imaging (DTI), Damoiseaux *et al.* [25] found an impaired connection between the medial temporal cortex and the thalamus in AD. Furthermore, by combining structural magnetic resonance imaging (MRI) and DTI, Zarei *et al.* [26] also found altered white matter and structural atrophy in the thalamus of AD patients, and these atrophic regions of the thalamus were connected with the temporal cortex, hippocampus and prefrontal cortex. Using electroencephalographic measurements, Cantero *et al.* [27] found that functional dynamics of thalamo-cortical networks could differentiate individuals with MCI from healthy elderly subjects. In a resting-state functional MRI(fMRI) study, Wang *et al.* [17]observed disrupted functional connectivity between the bilateral thalamus and brain regions that comprise the default mode network in MCI patients. However, no studies have compared the functional connectivity pattern of the thalamus between AD and MCI populations, and it also remains unclear whether the pattern of functional connectivity correlates with disease severity.

In this study, resting-state functional MRI data were obtained from 35 patients with AD, 27 subjects with MCI and 27 age- and gender-matched normal controls (NC). First, the functional connectivity patterns of the bilateral thalamus were evaluated according to the correlation coefficients between the thalamus and other brain regions at a voxel level. Second, altered functional connectivity in AD group was identified by comparing the correlation coefficients of functional connectivity to those of the NC group using a two-sample, two-tailed t-test. The MCI subjects were then evaluated to determine how different stages of the illness (MCI and AD) affect the functional connectivity pattern of the thalamus. Finally, a correlation analysis was performed between the functional connectivity strength of the identified regions and the various clinical variables (Mini-Mental State Examination (MMSE) and Auditory Verbal Learning Test (AVLT) immediate/delayed recall scores) to evaluate the relationship between the strength of functional connectivity and the cognitive abilities of the MCI and AD subjects (Fig. **1**).

2. MATERIALS AND METHODS

2.1. Subjects

All of the participants were recruited by an advertisement (http://www.301ad.com.cn, Chinese version). Written consent forms were obtained from all of the subjects or their legal guardians under protocols approved by the ethics committee of the Chinese PLA General Hospital. Prior to selection for this study, all of the participants were given free physical, psychological and laboratory examinations. All of the subjects were right-handed and underwent a battery of neuropsychological tests, including the MMSE, AVLT, Geriatric Depression Scale (GDS) [28], Clinical Dementia Rating (CDR) [29] and Activities of Daily Living (ADL) scale. In brief, the AVLT consisted of 1 learning trial in which a list of 10 Chinese double-character words was read, and the subject was asked to immediately recall as many items as possible. The trial was repeated twice, and the immediate recall score was the average of 3 accurate recalls. After a 5-minute delay, each subject was asked to recall the words from the initial list (AVLT-delayed recall). The subjects were then told to identify the 10 studied words that were inter-mixed with 10 novel words (AVLT-recognition).

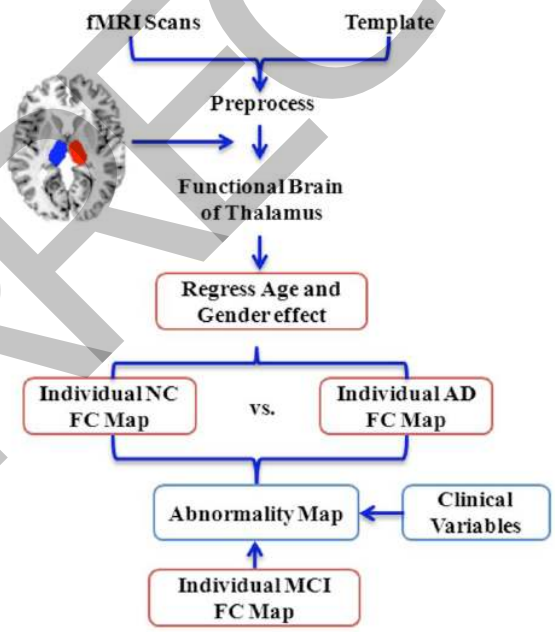

Fig. (1). Design of the present study. First, the functional connectivity patterns of the bilateral thalamus were evaluated using the correlation coefficients between the thalamus and other brain regions at a voxel level. Second, altered functional connectivity in AD was identified by comparing the functional connectivity to that in NCs. Finally, a correlation analysis was performed between functional connectivity strength in the identified regions and the various clinical variables (MMSE and AVLT immediate/delayed recall scores) to evaluate the relationship between the strength of functional connectivity and the cognitive abilities of the MCI and AD subjects.

The recruited AD patients fulfilled the following inclusion criteria: (1) diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease's and Related Disorders Association criteria for probable AD; (2) CDR = 1 or 2; (3) currently receiving no nootropic drugs, such as cholinesterase inhibitors; and (4) able to perform the neuropsychological test and tolerate MR scanning. The diagnostic criteria for MCI were determined as previously described [1] and included the following: (1) memory complaints lasting at least 6 months; (2)

CDR = 0.5; (3) intact functional status and ADL< 26; and (4) lack of dementia. The criteria for NC included the following: (1) normal physical status; (2) CDR = 0; and (3) without memory complaints.

Exclusion conditions for participants of this study included the following: (1) metabolic conditions such as hypothyroidism or vitamin B12/folic acid deficiencies; (2) psychiatric disorders such as schizophrenia or depression; (3) infarction or brain hemorrhaging, as indicated by MR/CT imaging; and (4) Parkinsonian syndrome, epilepsy and other nervous system diseases that can influence cognitive function. In addition, patients with a metallic foreign body, such as a cochlear implant, heart stent or other relevant MR scanning contraindications, were excluded from the study.

2.2. Data Acquisition

During the fMRI scans, all of the subjects were instructed to keep their eyes closed, relax and move as little as possible. MR images were acquired with a 3.0 T GE MR system using a standard head coil. Tight but comfortable foam padding was used to minimize head motion, and a pair of earplugs was used to reduce scanner noise. Resting-state fMRI scans were performed using an echo planar imaging (EPI) sequence with scan parameters of repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90^{o}, matrix = 64 × 64, field of view (FOV) = 220 ×220 mm^2, slice thickness = 3 mm and slice gap = 1 mm. Each brain volume was comprised of 30 axial slices, and each functional run contained 200 volumes.

2.3. Data Preprocessing

The data were preprocessed using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). To allow magnetization equilibrium, the first 10 volumes of each functional time series were discarded. The remaining 190 volumes were corrected for slice timing and realignment. All of the data were then spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template and re-sampled to 2×2×2 mm cubic voxels. To further reduce the effects of confounding factors, six motion parameters, linear drift and the mean time series of all voxels within the white matter and cerebrospinal fluid were removed from the data by linear regression. Temporal filtering (0.01-0.08 Hz) was then performed to reduce the effect of low-frequency drift and high-frequency signals. Finally, the regressed images were smoothed with a 6-mm full width and half maximum kernel to reduce spatial noise.

It has recently been suggested that small head motion during scanning may have a substantial impact on certain resting-state fMRI measurements, such as network measures and strength of functional connectivity[30-32]. Therefore, we evaluated group differences in head motion among the three groups according to the criteria of Van Dijk *et al.* [32]. The results showed that the three groups had no significant differences in head motion (one-way ANOVAs P = 0.084) (Table **1**). Any subject who exhibited a maximum displacement in any of the cardinal directions (x, y, z) larger than 3 mm (smaller than one voxel) or a maximum rotation (x, y, z) greater than 3° was excluded [9, 33-35]. As a result, 13 of 102 subjects (2 NC, 3 MCI and 8 AD) who exhibited large amounts of head motion during scanning were excluded [33]. The demographic and neuropsychological details for the remaining 89 subjects are shown in Table **1**.

2.4. Definition of the Thalamus

The WFU_PickAtlas toolkit (www.ansir.wfubmc.edu) [36] was used to identify the bilateral thalamus as the region of interest (ROI). To guarantee that the selected voxels were located in the thalamus, we intersected the bilateral thalamic regions using an automated anatomical labeling (AAL) tool and the SPM brain template in the WFU_PickAtlas. The volume of the left thalamus was 823 voxels and the right thalamus was 844 voxels, with a voxel size of 8 mm^3 (Fig. **1**).

2.5. Functional Connectivity and Statistical Analysis of the Bilateral Thalamus

A voxel-wise functional connectivity analysis of each ROI was separately performed for each seed region. The seed reference time series for each ROI was obtained by averaging the fMRI time series of all of the voxels within the

Table 1. Demographic, Clinical and Neuropsychological Data for Normal Control (NC), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) Patients.

	NC(n=27)	MCI(n=27)	AD(n=35)	*p* value
Gender (M/F)	16/11	13/14	12/23	0.143
Age (year)	69.2±6.5	73.8±7.8	72.4±8.5	0.09
MMSE	28.9±1.0	26.8±1.8[a]	19.7±4.1[a,b]	<0.001
CDR	0	0.5	1.3±0.5[a,b]	<0.001
AVLT-Immediate Recall [c]	5.9±1.1	4.6±1.5	2.6±1.6[a,b]	<0.001
AVLT-Delay Recall [c]	5.8±2.0	3.1±2.0 [a]	0.6±1.2[a,b]	<0.001
Head Motion	0.25±0.27	0.16±0.10	0.30±0.27	0.084

The chi-square test was used for gender comparisons. One-way ANOVA with the Bonferroni post-hoc test was used for age and neuropsychological test comparisons.
[a]Significant compared to NC. [b]Significant compared to MCI. [c]Three AD subjects refused to complete this test.
MMSE, mini-mental state examination; CDR, clinical dementia rating; AVLT, auditory verbal learning test.

ROI and then computing the Pearson's correlation coefficient between the average time series for that seed and those from each voxel in the brain. For further statistical analysis, the correlation coefficients were transformed to z-values using the Fisher r-to-z transformation to improve the normality of the correlation coefficients [37]. This transformation yielded a map that presented the strength of the functional connectivity with the seed region in terms of z-values for each subject. To reduce the effect of age and gender on functional connectivity, a regression analysis was performed on the z-values for age and gender using a general linear method.

Within each group, the individual z-values were entered into a one-sample, two-tailed *t*-test in a voxel-wise manner to determine the brain regions that showed significant functional connectivity with the left thalamus. The combined threshold for the contrast maps was set according to clusters with a minimum volume of 100 voxels at an uncorrected individual voxel height threshold of $p< 0.001$ using SPM8 software.

A two-sample, two-tailed *t*-test was performed between NC and AD patients to create an abnormality map. The threshold for the resultant *T*-value map was determined using $p < 0.01$ [T = 2.39, df = (1,60)] for each voxel and a cluster size of at least 100 voxels, which resulted in a corrected threshold of $p_{alpha}< 0.05$, as determined by a Monte Carlo simulation (see AlphaSim in AFNI http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). The parameters were FWHM = 6 mm, with an AAL template in MRIcro as a mask. Subsequently, the regions that showed significant differences were extracted as ROIs, and the mean functional connectivity values of the MCI subjects were used to evaluate altered functional connectivity at different stages of disease severity (Fig. **1**). Statistical comparisons of the mean functional connectivity between each pair of groups were performed using a two-sample, two-tailed *t*-test at a threshold of $p< 0.05$ (FDR corrected; 3 groups (between NC and AD, NC and MCI, MCI and AD) multiplied by the number of identified regions).

The same functional connectivity and statistical analyses were performed on the right thalamus.

2.6. Relationship Between Functional Connectivity and Clinical Variables

Correlation analyses between functional connectivity strength and the clinical variables (MMSE, AVLT-immediate/delayed recall scores) were performed to investigate whether the functional connectivity varied with disease progression in MCI and AD patients. Because these analyses were exploratory, we used a statistical significance level of $p < 0.05$ (uncorrected). To evaluate the relationship between the severity of illness and the clinical variables, we also performed a correlation analysis within the MCI or AD groups at $p <0.05$ (uncorrected).

3. RESULTS

3.1. Thalamic Connectivity Analyses within Groups

In each group, we found significant functional connectivity between the bilateral thalamus and itself, as well as with brain regions including the frontal, parietal, temporal and occipital lobe, using a one-sample, two-tailed *t*-test in a voxel-wise manner and combining threshold clusters with 100 voxels at an uncorrected level of $p< 0.001$ (Fig. **S1**).

3.2. Altered Functional Connectivity Patterns of the Thalamus in AD and MCI

When compared to the NC group, the AD group demonstrated decreased functional connectivity between the bilateral thalamus and brain regions in the default mode network, such as precuneus/posterior cingulate cortex(PCu/PCC), middle frontal gyrus (BA 10), inferior frontal gyrus (BA 47) and inferior parietal lobule/ angular gyrus (Table **2**-**3**, Figs. **2**-**3**). In comparison, increased functional connectivity was observed between the bilateral thalamus and several brain regions, including the middle temporal gyrus and some motor-sensory brain regions (Table **2**-**3**, Figs. **2**-**3**).

To evaluate disease severity-related alterations of functional connectivity in MCI, we next investigated the functional connectivity pattern in MCI for all of the regions that were identified as altered in the AD group. We found that in the bilateral thalamus, the mean strength of functional connectivity in MCI subjects was about the median value of functional connectivity in AD and NC subjects (Fig. **4**). Specifically, the strength of functional connectivity between the left thalamus and the right middle frontal gyrus, PCu/PCC and left inferior frontal gyrus was significantly decreased in MCI patients in comparison to normal controls after FDR correction ($p<0.05$). Functional connectivity between the right thalamus and the left inferior partial lobe/angular lobe was also significantly decreased (Fig. **4**).

3.3. Relationship Between Functional Connectivity and Clinical Variables

Functional connectivity between the bilateral thalamus and regions that showed deceased functional connectivity in AD was significantly and positively correlated with the clinical scores (MMSE, AVLT immediate/delayed recall) of the MCI and AD populations ($p < 0.05$). In other words, increased severity of the illness was correlated with lower functional connectivity (Table **4**, Figs. **5**-**6**).

Additionally, the strength of functional connectivity between the bilateral thalamus and some of the regions exhibiting increased functional connectivity in AD showed significant negative correlations with clinical scores in the MCI and AD populations ($p < 0.05$) (Table **4**, Figs. **5**-**6**).

4. DISCUSSION

In this study, we investigated the alteration of functional connectivity patterns in the thalamus in patients with AD and MCI using resting-state fMRI. Impaired functional connectivity between the thalamus and various functional brain regions was identified by comparing the differences between AD and NC subjects. Specifically, functional connectivity was mainly decreased in regions constituting the default mode network, whereas increased functional connectivity was observed in brain regions involved in short-term/working memory and sensory-motor function. The functional connectivity pattern of MCI subjects and the relationship between the strength of functional connectivity and

Table 2. Altered Functional Connectivity Using the Left Thalamus as the ROI in the AD Group Compared to the Control Group (Cluster Size > 100 Voxels, p_{alpha}< 0.05, AlphaSim Corrected).

Brain Area	BA	Cluster size	T-value	Z-value	MNI Coordinates (x, y, z)
Decreased functional connectivity of the Tha.L in AD					
MFG.R(-)	10	200	4.09	3.82	10 66 16
			3.01	2.89	20 60 22
			2.81	2.71	10 56 28
PCu/PCC(+)	7	219	3.78	3.57	-2 -56 38
			3.38	3.22	6 -52 34
			3.10	2.98	-2 -66 44
IFG.L(-)	47	123	3.75	3.54	-48 30 -14
			2.99	2.88	-40 22 -10
Increased functional connectivity of the Tha.L in AD					
MTG/ITG.R(-)	37	346	-4.60	-4.24	46 -56 2
			-4.29	-3.99	34 -74-4
			-3.64	-3.44	20 -84-8
PCu.L(-)		126	-3.96	-3.71	-22 -480
			-3.45	-3.29	-32 -68 -6
			-3.20	-3.07	-28 -54 -2
SPL.L(-)	7	137	-3.93	-3.69	-22 -64 60
			-2.91	-2.81	-28 -50 64
			-2.69	-2.61	-22 -56 66
PostCG/SPL.R(-)	5/7	145	-3.73	-3.52	34 -48 64
			-3.38	-3.22	22 -50 62
			-3.28	-3.13	16 -44 72

Abbreviations: MFG: middle frontal gyrus; PCu: precuneus; PCC: posterior cingulate gyrus; IFG: inferior frontal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus; SPL: superior parietal lobule; PostCG: postcentral gyrus.
L: left; R: right; +: positive functional connectivity, -: negative functional connectivity.

clinical variables suggests that MCI is a transitional stage between NC and AD. To the best of our knowledge, this is the first report concerning the alteration of functional connectivity in the thalamus in AD and MCI subjects.

4.1. Functional Connectivity Pattern of the Thalamus in Normal Controls

The thalamus is an important region that receives multiple inputs from different brain regions and then processes this information before passing it on to other functional regions [18]. Almost every sensory system (with the exception of the olfactory system) projects into the thalamic nucleus, which receives sensory signals and subsequently sends them to the associated primary cortical region. Thus, the thalamus is an important region with complex functions that can act as an informational relay station between subcortical areas and the cerebral cortex. We consistently found significant functional connectivity between the thalamus and brain regions distributed in the frontal, temporal, parietal and occipital lobes in the diseased patient and control groups (Fig. **S1**).

Note that altered functional connectivity of the bilateral thalamus included positive and negative connectivity. The correct interpretation of positive or negative functional connectivity remains unclear, although some studies have speculated that negative functional connectivity may represent an anti-correlation effect that intrinsically exists between two opposed networks [11, 38-41]. Given that the synaptic connections in the thalamus may play more of a modulatory than a relaying role[18], we inferred that the thalamus may play an important role in shifting between different networks in healthy controls. Additionally, this function may be disturbed in AD patients.

Table 3. Altered Functional Connectivity Using the Right Thalamus as the ROI in the AD Group Compared to the Control Group (Cluster Size > 100 voxels, p_{alpha}< 0.05, AlphaSim Corrected).

Brain Area	BA	Cluster size	T-value	Z-value	MNI Coordinates (x, y, z)
Decreased functional connectivity of the Tha.R in AD					
MFG.R(-)	10	244	3.92	3.68	12 66 16
			3.30	3.15	22 62 6
			3.16	3.03	22 58 22
IPL/ANG.L(+)		101	3.49	3.31	-44 -62 32
			2.71	2.62	-40 -58 40
			2.61	2.53	-54 -66 30
Increased functional connectivity of the Tha.R in AD					
MFG.L (-)	11	101	-3.67	-3.47	-6 32 -10
			-3.25	-3.10	-20 34 -14
PostCG/SPL.R(-)	7/5	273	-3.57	-3.38	16 -42 72
			-3.46	-3.29	24 -50 64
			-3.05	-2.93	36 -48 64
ITG.R(-)		119	-3.55	-3.37	34 -74 -4
			-3.15	-3.02	20 -84 -6
			-3.04	-2.92	44 -70 -4
PCu/PostCG/SPL.L(-)	7	283	-3.48	-3.30	-20 -46 72
			-3.26	-3.11	-14 -40 72
			-3.21	-3.08	-12 -58 56

Abbreviations: MFG: middle frontal gyrus; IPL: inferior parietal lobule; ANG: angular gyrus; IFG: inferior frontal gyrus; PostCG: postcentral gyrus; SPL: superior parietal lobule; ITG: inferior temporal gyrus; PCu: precuneus.
L: left; R: right; +: positive functional connectivity, -: negative functional connectivity.

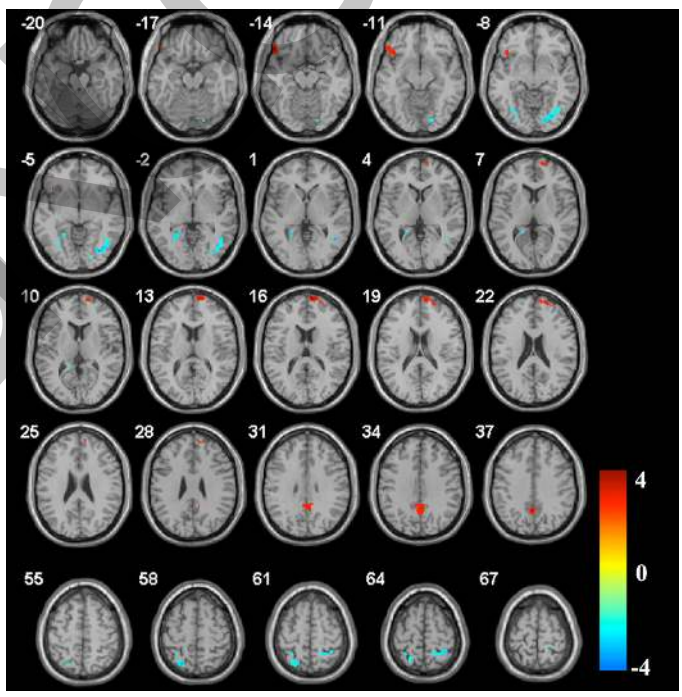

Fig. (2). The brain areas exhibiting significant differences in functional connectivity of the left thalamus in AD patients when compared to the NC group. Red and blue colors represent decreased and increased functional connectivity, respectively (p<0.01, 100 voxels, AlphaSim corrected).

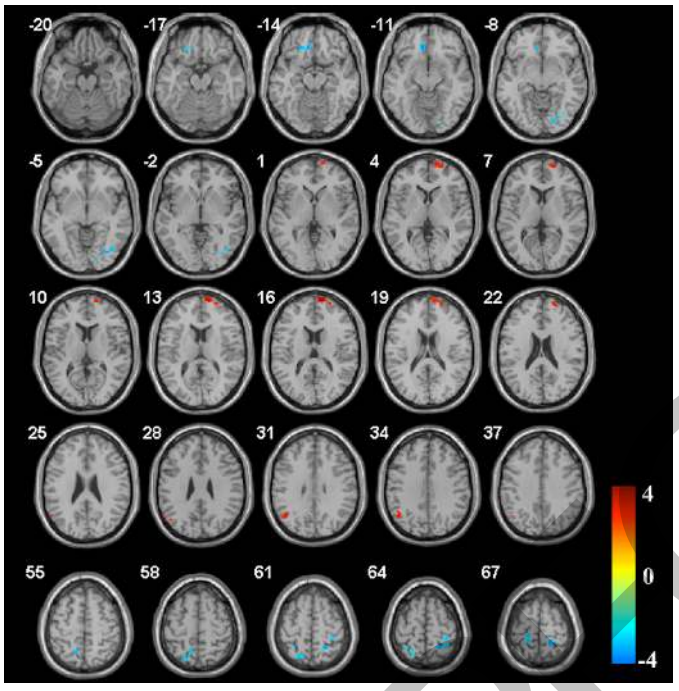

Fig. (3). The brain areas exhibiting significant differences in functional connectivity of the right thalamus in AD patients when compared to the NC group. Red and blue colors represent decreased and increased functional connectivity, respectively (p< 0.01, 100 voxels, AlphaSim corrected).

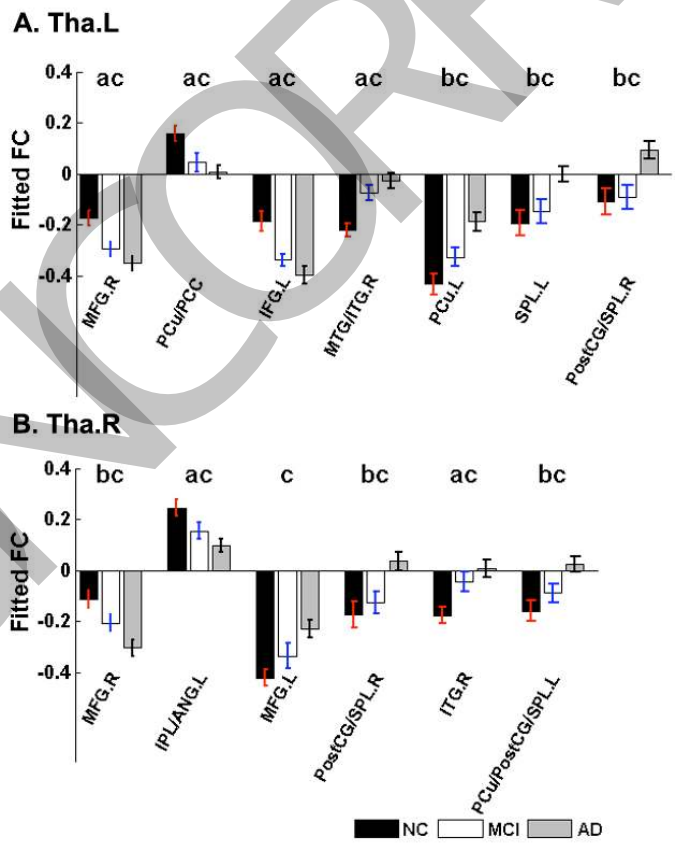

Fig. (4). The strength of functional connectivity in the NC (black), MCI (white) and AD (grey) groups in the identified brain regions (p < 0.05, FDR corrected). a: the strength of functional connectivity was significantly different between the NC and MCI groups; b: the strength of functional connectivity was significantly different between the MCI and AD groups; c: the strength of functional connectivity was significantly different between the NC and the AD groups. Bars represent the mean functional connectivity after correction for age and gender effects. Error bars represent the standard error of functional connectivity. Fitted FC is the strength of functional connectivity after correction for age and gender effects.

Table 4. Summary of the Correlations Between the Mean-Fitted Strength of the Functional Connectivity Between the Bilateral Thalamus, Identified Regions and Various Clinical Variables (MMSE, AVLT Immediate Recall/Delay Recall) in MCI and AD Patients ($p < 0.05$).

	Brain Area	Brain Area	AD&MCI		MCI		AD	
			CC	*p*	*CC*	*p*	*CC*	*p*
MMSE	Tha.L	MTG/ITG.R	**-0.270**	**0.034**	-0.125	0.536	-0.303	0.077
	Tha.L	PCu.L	**-0.286**	**0.024**	-0.177	0.377	-0.047	0.787
	Tha.L	PostCG/SPL.R	**-0.264**	**0.038**	0.144	0.475	-0.017	0.923
	Tha.R	ITG.R	**-0.283**	**0.026**	-0.100	0.621	**-0.368**	**0.030**
AVLT Immediate Recall	Tha.L	SPL.L	-0.177	0.180	**-0.448**	**0.019**	-0.098	0.595
AVLT Delay Recall	Tha.L	MFG.R	0.187	0.157	-0.233	0.242	**0.457**	**0.009**
	Tha.L	IFG.L	**0.256**	**0.050**	-0.065	0.748	**0.444**	**0.011**
	Tha.L	PostCG/SPL.R	**-0.310**	**0.017**	-0.145	0.470	0.004	0.983
	Tha.R	PostCG/SPL.R	**-0.299**	**0.021**	-0.262	0.187	0.120	0.512

Abbreviations: MTG: middle temporal gyrus; ITG: inferior temporal gyrus; PCu: precuneus; PostCG: postcentral gyrus; SPL: superior parietal lobule; MFG: middle frontal gyrus; IFG: inferior frontal gyrus;
L: left; R: right; CC: correlation coefficient, the results for a threshold of $p<0.05$ are shown in bold.

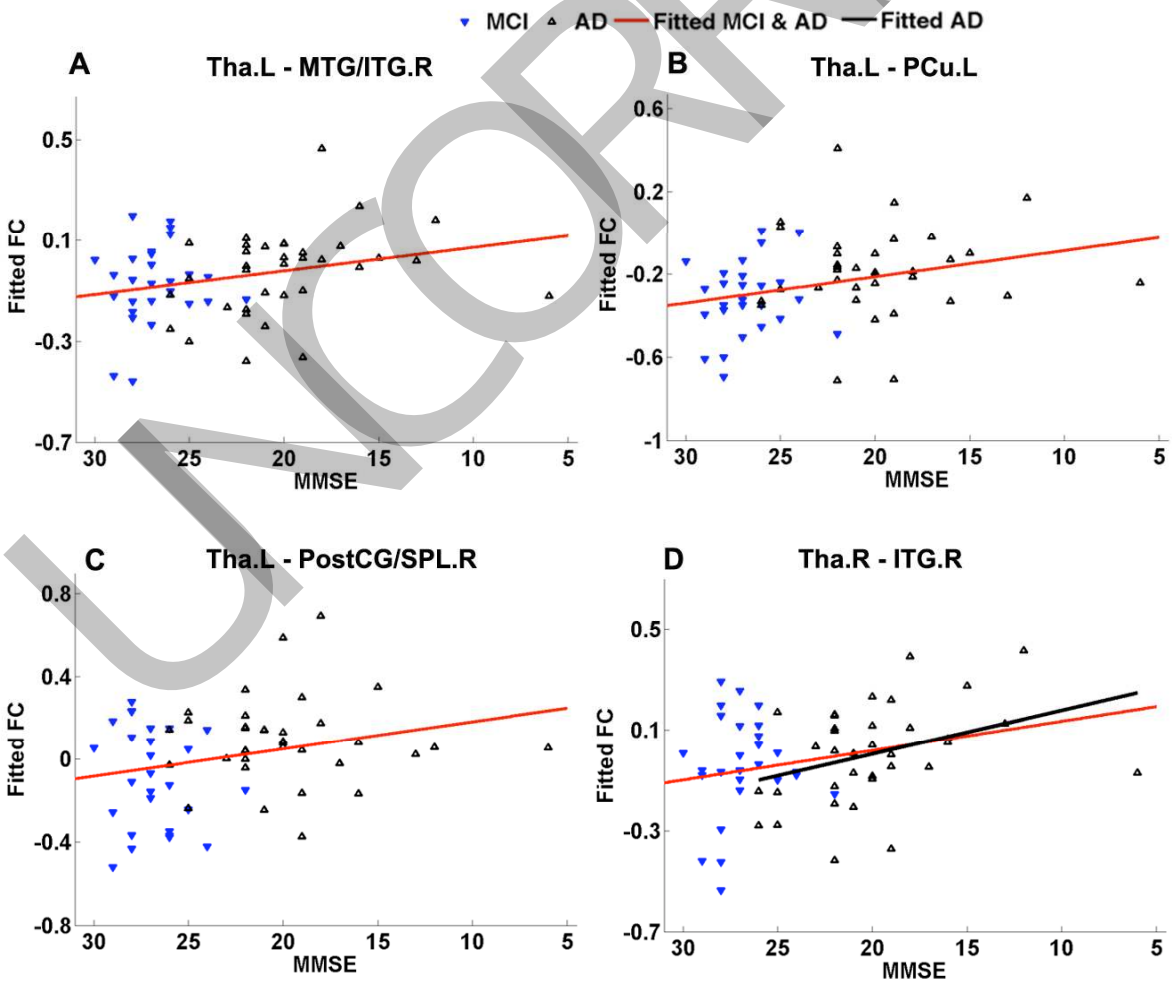

Fig. (5). The correlation between the mean strength of functional connectivity of the thalamus and MMSE scores in both MCI and AD patients ($p< 0.05$). For details, please see Table 4. Fitted FC is the strength of functional connectivity after correction for age and gender effects.

4.2. Altered Functional Connectivity Pattern of the Thalamus in AD and MCI

4.2.1. Decreased Functional Connectivity of the Thalamus in AD and MCI

In this study, a significant decrease in functional connectivity between various brain regions (PCu/PCC, middle frontal gyrus (BA 10), the inferior frontal gyrus (BA 47) and inferior parietal lobule/angular gyrus) and the bilateral thalamus was identified in AD subjects compared to normal control subjects (Tables **2**, **3** and Figs. **2**-**4**). Notably, all of these regions overlap with brain regions that underlie the default mode network [42, 43]. The default mode network concept has been well established and accepted in the last decade. This network demonstrates a consistent pattern of "deactivation" in the tasks-state across some remarkable brain regions, which includes the PCC, PCu, medial prefrontal cortex, inferior parietal lobe (IPL) and hippocampus [13, 42, 43]. Among these brain regions, the PCC coupled with the PCu constitutes a hub-like region at the posterior midline of brain and plays a critical role in this network [7, 42, 43]. Functionally, the default mode network is involved in episodic memory processing, emotional processing and the monitoring of the internal and external environment [13, 44, 45]. Accumulating evidence has revealed that normal cognition depends on the integrity of the default mode network, which has been consistently found to be disrupted in AD [7, 13, 15, 46-48] as well as MCI [14, 49]. Interestingly, decreased functional connectivity was found between the middle frontal gyrus (BA 10) and the bilateral thalamus (Figs. **2**, **3**). The BA 10 area (also called the rostral prefrontal cortex, anterior PFC or fronto-polar cortex) is an extensive region in the human brain and an important component of the default mode network. It has been proposed that this area is involved in episodic memory retrieval, emotion processing and executive function, and it plays a prominent role in the integration of information from multiple cognitive domains [50, 51] and sits at the top of the frontal processing hierarchy [52, 53]. Specifically, when subjects performed an episodic memory retrieval task, robust activation was found in the rostral PFC [54, 55]. For the thalamus, the anterior and dorsal medial nuclei [56] and the mammillo-thalamic tract [57] have been reported to be involved in episodic memory, which is specifically impaired in AD [24].

Functional imaging tools have been used to show the disruption of functional connectivity between the thalamus and PCC/PCu in AD patients [47]. Furthermore, decreased functional connectivity between the bilateral thalamus and various brain regions, including the superior frontal gyrus, medial prefrontal cortex, inferior frontal gyrus and PCu, was also found in the MCI population [17]. Consistent with these previous studies, we also found disruption of functional connectivity between the thalamus and the default mode network regions in AD. Furthermore, we found that the strength of functional connectivity in MCI subjects was intermediate between that of the AD and NC groups (Fig. **4**). More importantly, the strength of functional connectivity between the thalamus and the identified brain regions, particularly the default mode network regions, was positively correlated with the MMSE (Fig. **5**) and the AVLT-immediate/delayed recall scores (Fig. **6**), which indicates that cognitive ability is significantly correlated with the functional connectivity index of these regions. Considering the importance of the default mode network in episodic memory, attention and alertness functions [7, 13, 43, 44], these results may explain some of the symptoms exhibited in AD, such as impaired cognition and decreased attention. In this context, our findings demonstrate the importance of the default mode network in human cognitive function and provide further evidence that disrupted thalamo-default mode network functional connectivity patterns may underlie the impaired cognitive ability of AD and MCI patients.

4.2.2. Increased Functional Connectivity of the Thalamus in AD and MCI

The inferior temporal gyrus (ITG) is the final visual processing region of the ventral visual pathway and is involved in visual working memory [58]. The middle temporal gyrus (MTG) is associated with verbal and visual semantic knowledge [59] and is also involved in verbal short-term memory [60]. Previous functional imaging studies showed compensatory increased activation in the MTG of AD patients during a working memory task [61]. Significant activation in the MTG has also been observed in AD patients during the encoding of tasks, which indicates that access to semantic knowledge was relatively preserved [62]. Thus, our finding of increased functional connectivity between the thalamus and temporal lobe may reflect a compensatory reallocation of functional connectivity. It is noteworthy that the regions of the temporal lobe that show increased functional connectivity with the thalamus are all related to working/short-term memory, which is relatively preserved in the early stages of AD [63, 64]. Thus, we inferred that AD patients may effectively utilize this preserved working/short-term memory capacity to partially compensate for the disruption in long-term memory.

We also found increased functional connectivity between the thalamus and the prefrontal cortex, and it could be argued that both decreases and increases in functional connectivity were present between the middle frontal gyrus and the thalamus (Figs. **2**-**4**, Tables **2**-**3**). Note that decreased functional connectivity was found within the BA 10 area, whereas increased functional connectivity was found within the BA 11 area. As previously discussed, many studies have shown that the rostral PFC (BA 10) is an important component of the default mode network and is involved in the retrieval of episodic memory [42, 44], which is specifically impaired in AD/MCI. Our result is consistent with these previous studies and suggests that decreased functional connectivity between this region and the thalamus may subserve the impaired episodic memory characteristic of AD/MCI. In comparison, increased prefrontal activity during cognitive tasks [65, 66] and increased functional connectivity between the prefrontal regions and other areas of the brain have been repeatedly reported in AD patients [16, 67], and these findings were often interpreted as a compensatory re-allocation. The BA 11area belongs to the orbital frontal cortex (OFC) and is among the least understood regions of the human brain. Previous studies have suggested that the OFC has reciprocal connections with the mediodorsal nucleus of the thalamus and is involved in emotion, sensory integration,

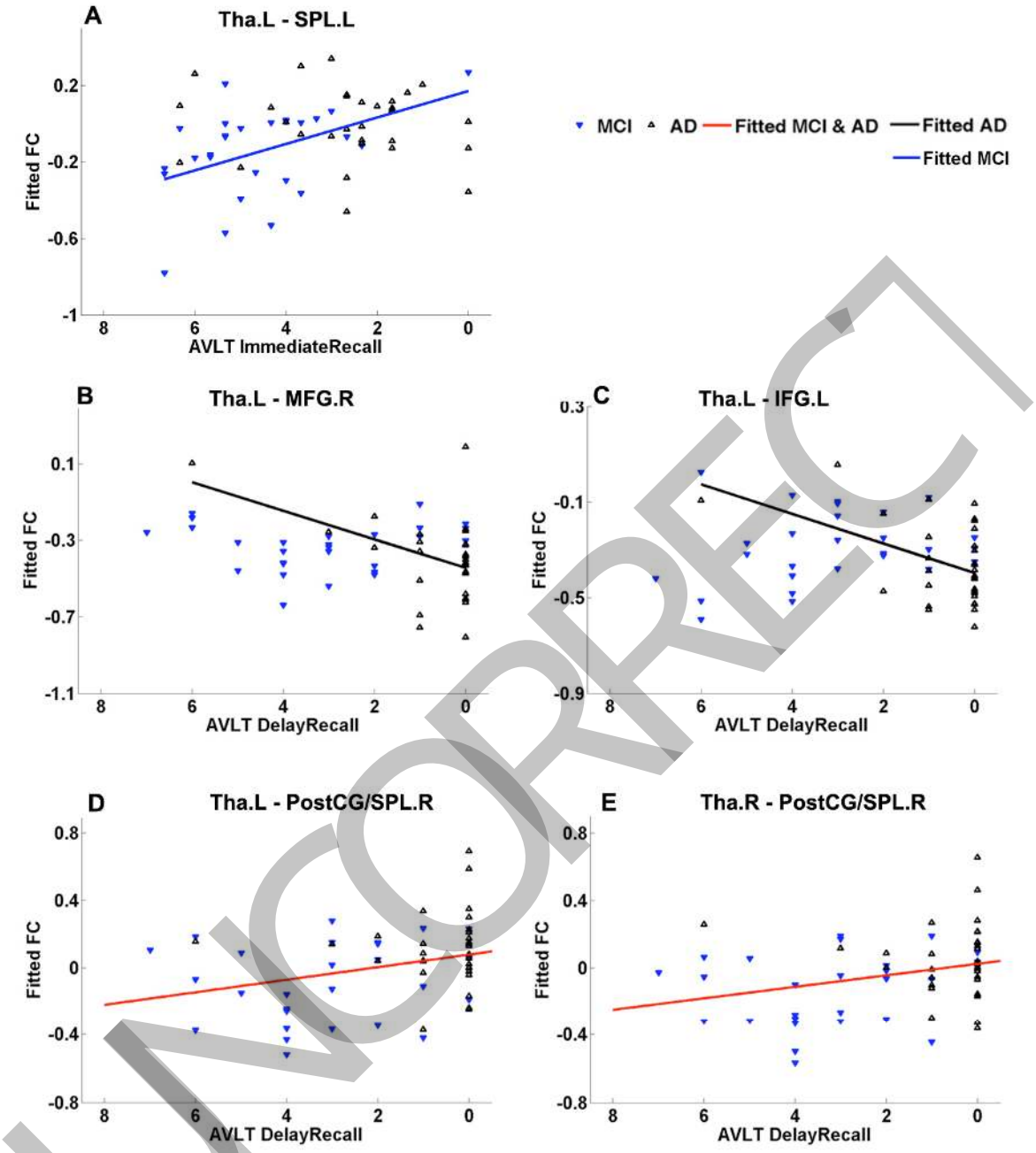

Fig. (6). The correlation between the mean strength of functional connectivity of the thalamus and the AVLT immediate recall scores in MCI and AD patients ($p < 0.05$). For details, please see Table 4. Fitted FC is the strength of functional connectivity corrected for age and gender effects.

complex reward processing, visual recognition, decision making and working memory [68, 69]. It has further been proposed that the hippocampus works together with the anterior thalamic nuclei, the mammillary bodies and the retrosplenial cortex to support episodic memory and recollective recognition [70, 71]. In contrast, the parahippocampal region has extensive interconnections with the thalamus and the prefrontal cortices, including the OFC, and forms an independent network that subserves familiarity-based recognition [69]. When performing some cognitive tasks, AD/MCI patients show impaired recollective recognition but preserved familiarity-based recognition [72, 73]. Therefore, a speculative explanation could be that increased functional connectivity between the OFC and thalamus may reflect the increased activity of the OFC-parahippocampal system, which sustains familiarity-based recognition, although we did not find increased functional connectivity between the thalamus and parahippocampal area. Thus, this result may also explain the relatively preserved familiarity-based recognition in the AD/MCI population.

In addition, we also found increased functional connectivity between the sensory-motor cortex (including the con-

junction area of the superior parietal lobule (SPL) and the postcentral gyrus (PostCG) (BA5/7)) and the thalamus in the AD group. Previous studies showed that the primary sensorimotor cortex is not typically involved until very late in the disease progression of AD [74], which suggests that the sensory-discriminative function would be preserved. Thus, the enhanced interaction between the sensory-motor cortex and the thalamus may be regarded as compensation for the loss of functional connectivity elsewhere. As expected, we also found that functional connectivity between the thalamus and various regions of the cortex (e.g., MTG/ITG.R, PCu.L, PostCG/SPL.L) were significantly correlated with the MMSE (Fig. **5**) and AVLT-immediate/delayed recall scores (Fig. **6**). Taken together, our data suggest that AD patients may recruit other brain regions involved in working/short-term memory and use different cognitive mechanisms to compensate for impaired episodic memory. In the thalamus, we infer that enhanced functional connectivity may represent enhanced modulation, given that the synaptic connections in the thalamus may play more of a modulatory than a relaying role [18]. Alternatively, increased functional connectivity may reflect increased, but unnecessary, connections and metabolic costs following the disruption of global information processing in AD patients [7].

4.3. MCI is a Transitional Stage Between NC and AD

In this study, the functional connectivity of MCI patients was intermediate in comparison to that of the AD and NC groups (Fig. **4**). Clinically, MCI has been proposed to be a transitional stage between normal aging and the earliest clinical manifestation of AD [1, 2, 4] and is correlated with a high risk of progression into AD [3, 35].In accordance with the clinical features and prior functional imaging studies [27, 75], our results showed altered functional connectivity patterns that correspond to disease progression (Fig. **4**). Therefore, this study provides new functional evidence that MCI is a transitional stage between normal aging and early AD, and the relationship between the strength of functional connectivity of the thalamus and the identified regions and clinical variables provides supplemental evidence for this conclusion (Figs. **5**-**6**, Table **4**).

4.4. Methodological Issues

In agreement with previous findings regarding thalamic functional connectivity in MCI [17], we found decreased thalamic connectivity in the default mode network regions. However, we found less decreased functional connectivity in our AD population than previous studies conducted by Wang *et al.* [17]. This discrepancy may have arisen because the voxel cluster that we defined was larger (the minimum cluster size was 800 mm^3in our study versus 270 mm^3 in the report of Wang *et al.*). Furthermore, it has been proposed that the pattern of degeneration is mainly driven by disruptions in connectivity [26]. In this regard, our results, together with those of Wang *et al.* [17], support the hypothesis of functional disconnection in AD/MCI and also support the hypothesis that the symptoms of AD/MCI are caused by changes in neuronal circuitry at early disease stages. However, further neurobiological and modeling studies are needed to test this hypothesis. As a noninvasive tool, the evaluation of functional connectivity deserves additional attention and may become an objective diagnostic and monitoring approach in future AD/MCI studies.

In the present study, we evaluated the relationship between the strength of functional connectivity and various clinical variables (i.e., the MMSE) in the combined MCI and AD groups to discover relationships between the strength of functional connectivity and cognitive ability, given that MCI may represent an early symptomatic stage of AD [4, 5]. As suggested by our previous studies [9, 33, 35], these types of correlations indicate a general relationship between abnormal functional connectivity and cognitive function in the AD and MCI patient groups. Because the discriminatory ability of the clinical variables was relatively low, the variability among patients was relatively high and the severity of AD in our patient sample was mild (35 subjects, 25 with CDR=1, 10 with CDR =2), we found lower correlations for the AD or MCI group than when we took the MCI and AD patients together (Table **4**, Figs. **5**-**6**). However, this type of correlation analysis could be affected by group effects, as not all MCI subjects will develop AD, and this could be the reason why we did not find a consistent significant correlation between the MMSE and strength of functional connectivity in the AD or MCI groups. Hence, a larger number of subjects with more detailed clinical variables are needed for future studies.

Note that our AD and MCI patients also met the core clinical criteria listed in the new diagnostic criteria for probable AD dementia and MCI due to AD [76, 77]. In future studies, it will be necessary to follow this recommendation, which incorporates new imaging biomarkers, to raise the probability of correct diagnosis and ensure that the pathophysiological substrate in patients in the AD/MCI groups is AD.

The thalamus is a complex region that can be divided into several distinct subdivisions according to the historical cytoarchitectonic atlas [19, 20]. To precisely elucidates the complex functional impairments of AD/MCI, we should explore the functional connectivity in each subdivided region of the thalamus. However, until now, we did not have a standard template for sub-dividing the thalamus. For example, there were obvious discrepancies between the historical cytoarchitectonic atlas and the parcellation atlas obtained from a functional MRI dataset [19, 20, 22]. We have evaluated the correlation between the representative time series and the time series of other voxels in the bilateral thalamus, and our results showed that the mean correlation coefficients were larger than 0.6 for the bilateral thalamus (Fig. **S2**). Furthermore, there was a very high correlation value, with a p-value less than 10^{-6} for 190 time points. These data demonstrate that it is suitable to take the mean time series of the bilateral thalamus as a representative signal. However, we would like to devise a new method to divide the thalamus into subregions and investigate altered functional connectivity in AD/MCI subjects.

In summary, we have demonstrated that functional connectivity between the thalamo-default mode network and the thalamo-cortical network is significantly impaired in AD. More importantly, this altered functional connectivity index was significantly correlated with clinical variables in MCI

and AD subjects. Our results also provide evidence that MCI should be regarded as a transitional stage between NC and AD. The changes in functional connectivity in AD/MCI warrant further investigation to test the hypothesis of functional disconnection in this disease.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary material is available on the publishers web site along with the published article.

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