Alterations in Resting-State Functional Connectivity Between the Hippocampus, Thalamus, Amygdala and the Whole Brain in Patients with Amnestic Mild Cognitive Impairment

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Research Article

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Abstract

Background

Amnesic mild cognitive impairment (aMCI) refers to a transitional stage between normal aging and Alzheimer's disease (AD). At present, numerous studies have reported that the functional connectivity between the hippocampus, thalamus, amygdala and other brain regions is abnormal in patients with MCI and AD. However, few studies have investigated hippocampal, thalamic, amygdalar and whole-brain functional connectivity abnormalities.

Methods

Here, we recruited 33 patients with amnesic mild cognitive impairment (aMCI) and 33 age- and sex-matched healthy controls (HCs) and chose the hippocampus, amygdala, and thalamus as regions of interest to explore the functional connectivity between the hippocampus, amygdala, thalamus and the whole brain in patients with aMCI.

Results

Using the hippocampus as region of interest, the whole brain functional connectivity analysis showed that the functional connectivity with the left precuneus, the right precuneus, and the parahippocampal gyrus was increased, and the functional connectivity with left anterior cingulate gyrus was reduced compared with the HC group. Using the thalamus as a region of interest, the whole-brain functional connectivity analysis showed that functional connectivity with the fusiform gyrus, left/right inferior occipital gyrus and left middle occipital gyrus was increased. Using the amygdala as a region of interest, whole-brain functional connectivity analysis showed reduced functional connectivity with the right frontal apex, the right central gyrus and left thalamus and the right supplementary motor area.

Conclusions

We found abnormal functional connectivity in patients with aMCI, indicating that it may provide a reliable imaging index for the early recognition and intervention of AD.

Background

Amnesic type mild cognitive impairment (aMCI) refers to a transitional stage between normal aging and Alzheimer's disease (AD)^[1] and it has a high probability of evolving toward AD at a rate of 10–15% per year^[2]. The main feature of patients with aMCI is deficits in the individual's memory, language, thinking judgment, emotion recognition, and executive function due to damage in multiple cognitive regions^[3]

[4]. In severe cases, it will lead to loss of social function and even an inability to care for themselves [5]. Therefore, the precise identification of high-risk patients with aMCI is very important for prevention and intervention in the early stages of AD.

The hippocampus is a part of the default mode network and closely related to individual learning, language and memory [6][7]. Studies reported reduced functional connectivity between the hippocampus and the prefrontal lobe, temporal lobe, parietal lobe, and cerebellum in patients with aMCI; in other brain regions, functional connectivity is increased and is negatively correlated with episodic memory performance, suggesting functional enhancement to compensate for cognitive impairment caused by the functional impairment [8][9][10]. The cognitive impairment associated with AD may have occurred in the aMCI stage [11]. These findings that abnormal hippocampal functional connectivity may be an early manifestation of AD in patients with aMCI may have important practical significance for the early identification and intervention of AD. Therefore, our work attempts to explore abnormalities in hippocampal function, which may have important practical significance for the in-depth study of AD.

The thalamus is the center of subcortical information transmission and processing, and it has extensive connections with the cerebral cortex and subcortical structures [12][13]. Previous studies have confirmed significant connectivity between the thalamus and different brain regions (such as the frontal, temporal, parietal and occipital lobes); for example, thalamus-hippocampus connectivity is an important pathway for memory [14]. Some studies have also provided evidence of impaired connectivity between the medial temporal cortex and thalamus in patients with AD [15]. Zhou Bo and Zhang Xi et al. (2014) [16] hypothesized that compared with baseline, the functional connectivity of the thalamus with the left inferior parietal cortex, putamen, and right posterior cerebellar lobe was decreased in patients with MCI. Based on the previous studies described above, the thalamus is damaged in patients with MCI, but researchers have not clearly determined whether abnormal thalamic function in patients with mild cognitive impairment is related to the onset of AD. Hence, an in-depth exploration of thalamic dysfunction must be conducted in patients with aMCI through brain imaging, which may provide a critical window for the early recognition and intervention of AD.

The amygdala is one of the key regions in the default network and is the basis of the emotion regulation process [17][18] and is related to emotion and cognitive function [19][20]. Studies have documented altered functional connectivity of the amygdala in patients with MCI and AD [21][22], and some researchers have also reported decreased functional activity of the amygdala in patients with AD [23]. The literature described above not only highlights a key role for the amygdala in emotion regulation but also indicates a certain relationship between changes in the function of the amygdala and cognitive impairment in patients with AD. However, few studies have examined the functional connectivity between the hippocampus, thalamus, amygdala and the whole brain in patients with aMCI, and different research methods have produced different research results. Therefore, this study used functional magnetic resonance imaging (fMRI) to further explore this issue, which may have practical clinical value.

Methods

Participants

From April 2018 to November 2019, 33 individuals with aMCI and 32 age- and sex-matched healthy controls (HCs) with no physical diseases or history of psychiatric or neurological disorders were recruited from the local community to participate in this study through advertising. All participants ranged in age from 60 to 80 years, and each subject was a right-handed Han Chinese individual with normal who provided written informed consent for inclusion before this study began. The study was approved by the Ethics Committee of the Wuxi Mental Health Center of Jiangsu Province. The diagnosis of aMCI was determined by the consensus of all experienced neurologists according to the published criteria in the study by Petersen^[24] and the National Institute on Aging-Alzheimer's Association.

Inclusion and exclusion criteria

All participants underwent a broad battery of neuropsychological tests: (a) Hachinski score (HIS) to exclude objects with vascular dementia; (b) activities of daily living (ADL) scale to assess the subjects' daily living abilities, including basic daily living abilities and relatively complex instrumental activities related to daily living; (c) Hamilton depression scale (HAMD) to exclude patients with a cognitive impairment caused by depression; and (d) Alzheimer's disease assessment scale (ADAS-Cog) to assess the severity of cognitive impairment. All subjects were right-handed.

Inclusion criteria for the aMCI group are described below. According to the diagnostic criteria of Petersen: (i) memory complaint, preferably corroborated by an informant; (ii) objective memory impairment for age; (iii) relatively preserved general cognition for age; (iv) essentially intact activities of daily living; (v) no diagnosis of dementia. The following cutoff values were established for the neuropsychiatric tests described above: (1) $HIS < 4$; (2) $14 \leq ADL \leq 19$; (3) $HAMD < 16$; (4) $10 < ADAS-Cog < 16$, and (5) $MoCA-B < 26$.

The normal participants were included based on the following criteria: (1) $HIS < 4$; (2) $14 \leq ADL < 16$; (3) $HAMD < 16$; and (4) $ADAS-Cog < 10$, $MoCA-B \geq 26$. The exclusion criteria for both groups were an age < 60 years and a history of psychiatric, neurological, cerebrovascular, or cognitive illness, stroke or other dementia diagnoses to ensure that they were cognitively normal.

Neuropsychological assessment

All subjects underwent clinical interviews, laboratory examinations, and activities of daily living (ADL) tests to assess functional impairment, and the ADAS-Cog was used to assess the severity of cognitive impairment. The Hamilton depression scale (HAMD) was used to exclude patients with a cognitive impairment caused by depression, and the Hachinski ischemic scale (HIS) was used to exclude people with vascular dementia.

MRI Data Acquisition

An MRI examination of participants was performed with a 3.0 T scanner (General Electric Medical Systems, 750 W, [America](#)) using a standard eight-channel phased-array head coil to obtain whole brain images of each subject. For the resting-state scan, the heads of all subjects were fixed with sponge padding and subjects were instructed to rest with their eyes closed, not fall asleep, think of nothing particular during the scan time, and continue to breathe normally during scanning. A structural T1-weighted image was acquired using a 3D SPGR sequence with the following parameters: repetition time (TR)=7.7 ms, echo time (TE)=minimum value, flip angle (FA)=11°, field of view (FOV)=256×256 mm², matrix=256×256, slices=186, slice thickness=1.2 mm, and voxel size of 1×1×1 mm³. Functional data were collected using a gradient-echo echo-planar imaging (EPI) sequence in axial slices parallel to the line through the anterior and posterior commissures with the following parameters: TR=2 s, TE=30 ms, FA=90°, FOV= 224×224 mm², matrix=64×64, slices=36, slice thickness =3.5 mm, gap=0.7 mm, voxel size of 3.5×3.5×3.5 mm³. The scan lasted for 240 s .

Statistical analyses

Demographic data were analyzed with IBM SPSS software version 26.0. The distributions of continuous variables approximated normality, and thus parametric tests were used. Two-sample t-tests were performed to examine the differences in age and education, while the chi-square test was used to analyze differences in sex. Two-sample t-tests were also used to compare neuropsychological test scale scores, including the HIS score and ADAS-Cog score, MoCA-B score, and the Mann–Whitney U test was used to examine the differences in HAMD scores. The average FC values of brain regions with distinct FC.

Functional connectivity analyses

Resting-state fMRI data from all participants were preprocessed using the Brainnetome fMRI Toolkit (<http://brant.brainnetome.org>) based on Statistical Parametric Mapping (SPM12, <http://www.fil.ion.ucl.ac.uk/spm>) and DPARSFA software using the MATLAB2018b platform (MathWorks). Before preprocessing, the first 10 time points were discarded because of the instability of the initial signal and the participant's adaptation to the situation. All preprocessing steps included (1) slice-timing correction; (2) realignment to the first volume for head motion correction; (3) spatial normalization to a standard EPI template with reslicing to 2 mm cubic voxels; (4) discarding the effects of head motion and other possible sources of artifacts, such as linear drift, six motion parameters, and the mean time series of all voxels within the white matter and cerebrospinal fluid, to further reduce the effects of confounding factors; and (5) temporal filtering (0.01–0.08 Hz) to reduce the effect of low-frequency and high-frequency noise. A head motion of <2 mm and rotation of < 2.0° were set as thresholds for each subject to minimize head motions. Three spherical regions of interest (ROIs) (radius=6 mm) were centered at the specified coordinates within the hippocampus (-24, -38, -2), thalamus (-36, 30, -14), and amygdala (2, 6, 1) [25].

Results

General demographic and clinical data.

Demographic information was not statistically significantly different except for age ($P < 0.05$); education years and gender were not significantly different ($P > 0.05$). General clinical data, the ischemia index (Hachinski ischemic scale) and ADL score were not statistically significantly different ($P > 0.05$), whereas the Montreal depression scale, ADAS-Cog and Hamilton depression scale (HAMD) scores were statistically significantly different ($P < 0.05$). [see Table 1]

Analysis of the functional connectivity between the hippocampus and whole brain

Using the hippocampus as a region of interest (Table 2), compared with the HC group, the whole-brain functional connectivity analysis showed that functional connectivity with the left precuneus, right precuneus, parahippocampus, right inferior occipital gyrus, right inferior temporal gyrus, left inferior occipital gyrus, left talar fissure, right middle occipital gyrus, right central sulcus cover, left superior frontal gyrus, left middle occipital gyrus, left angular gyrus, cuneiform lobe, right superior frontal gyrus, left central posterior gyrus, right central posterior gyrus was increased, and functional connectivity with the left anterior cingulate was reduced in participants with aMCI (Figure 1).

Analysis of functional connectivity between the thalamus and whole brain

Using the thalamus as a region of interest (Table 3), compared with the HC group, whole-brain functional connectivity analysis showed that functional connectivity with the fusiform gyrus, left/right inferior occipital gyrus, left middle occipital gyrus, thalamus and right thalamus, left/right caudate nucleus, middle frontal gyrus, right middle frontal gyrus, right supra marginal gyrus, precentral, right central anterior gyrus, postcentral, right superior parietal, and right middle frontal gyrus was increased in patients with aMCI (Fig. 2).

Analysis of functional connectivity between the amygdala and whole brain

Using the amygdala as a region of interest (Table 4), compared with the HC group, the whole-brain functional connectivity analysis showed that functional connectivity with the right superior frontal and right precentral regions was increased, and functional connectivity with the left thalamus and supplementary motor area were reduced in patients with aMCI (Figure 3).

Discussion

Analysis of functional connectivity between the hippocampus and whole brain

In the present study, compared with the HC group, we observed reduced functional connectivity between the hippocampus and left anterior cingulate. This pattern of alterations was consistent with findings reported in previous studies [26][27][28] and suggested that the hippocampal function of patients with aMCI may also be abnormal. During the transition from MCI to AD, the functional connectivity between the hippocampus and the left cingulate gyrus is decreased, and the

cingulate gyrus changes after MCI pathological changes occur in the cortex^{[29][30]}. The posterior cingulate gyrus is very important for predicting the outcome of the transition from MCI to AD and early identification of the disease^[31]. Therefore, we speculate that the decrease in functional connectivity between the hippocampus and the left cingulate gyrus of patients with aMCI, which may interrupt or damage the entire default network function integration, and a reduction in connectivity between these two regions plausibly represents an early imaging biomarker for aMCI.

In addition, compared with the HC group, we found increased functional connectivity between the hippocampus and cuneiform lobes, parahippocampal gyrus, upper middle occipital/inferior gyrus, superior frontal gyrus, superior temporal/inferior gyrus, left talar fissure, right central sulcus lid, left angular gyrus, and central posterior gyrus. This finding was consistent with previous studies^{[32][33]}. We propose that the hippocampus and the brain regions listed above may cooperate in information exchange or storage. The increase in functional connectivity between the hippocampus and the brain regions listed above is likely due to the mutual cooperation between the hippocampus and these brain regions in the process of information exchange or storage, resulting in functional compensation in the brain region. The increase in functional connectivity is likely to compensate for the weakening of the function of a certain brain region to balance whole-brain function.

Analysis of functional connectivity between the thalamus and whole brain

Compared to HCs, subjects with aMCI showed increased functional connectivity between the thalamus and fusiform gyrus, left/right suboccipital gyrus, left middle occipital gyrus, thalamus, right thalamus, left/right caudate nucleus, middle frontal gyrus, right middle frontal gyrus, right superior marginal gyrus, anterior central gyrus, right anterior central gyrus, posterior central gyrus and superior paracentral gyrus. The thalamus is an important part of the default network mode. Cappell(2010)^{34 [34]} postulated that the default network mode of patients with aMCI has a higher mean functional connectivity and may reflect a compensatory mechanism. This mechanism assumes that the overactive region "works harder" to compensate for the decreased function of other parts of the brain. Therefore, we speculate that increased functional connectivity between the thalamus and whole brain may indicate a compensatory mechanism in the brain of patients with aMCI. Previous studies have reported decreased functional connectivity between the bilateral thalamus and frontal cortex in patients with aMCI^[35]. This brain region is involved in episodic memory retrieval, emotional processing and executive functions and plays a prominent role in integrating information from multiple cognitive fields^{[36][37]}, however, our work did not reveal decreased functional connectivity between the thalamus and other brain regions.

Analysis of functional connectivity between the amygdala and whole brain

After exploring functional connectivity between the amygdala and whole brain, compared with HCs, patients with aMCI showed increased functional connectivity with the right superior frontal and right precentral regions. Preliminary studies also showed amygdala brain function

abnormalities in patients with MCI^[23], and the amygdala is involved in regulating cognitive functions such as attention, perception, emotional memory, explicit memory and declarative memory^[38]. Functional connectivity abnormalities of the superior frontal gyrus and the central anterior gyrus are likely to affect attention-related cognitive functions^[39]. Therefore, we hypothesize that the increased functional connectivity of the amygdala may be related to the impairment of cognitive functions, such as emotion regulation and memory consolidation, in the aMCI group, which may also provide possible medical imaging indicators for the early diagnosis of aMCI and promote a better understanding of dementia progression and potentially comprehensive interventions for aMCI. More interestingly, this study also revealed decreased functional connectivity between the amygdala and the left thalamus and right supplementary motor area in patients with aMCI; the sensorimotor cortex was only involved in the later stages of AD in a previous study^[40]. We obtained similar evidence of abnormal brain function in the sensorimotor cortex of patients with aMCI, which may be a sign of AD lesions.

Conclusions

We used the hippocampus, amygdala, and thalamus as regions of interest and found abnormalities in the functional connectivity of the brain in patients with aMCI, suggesting that the function of key brain regions in the default mode network are impaired in patients with aMCI. Our findings may provide a better and more thorough understanding of aMCI and AD, as well as a potential predictor and the possibility of comprehensive intervention for patients with aMCI.

Ethics Approvals

This study was approved by the ethics committee of Wuxi mental health center, Approval No:WXMHCIR2015LL010. All methods were performed in accordance with the relevant guidelines and regulations by including a statement in the declarations. And all participants completed the informed consent form.

Declarations

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Consent for publication

Not applicable

Availability of data and materials

All relevant data and materials of the findings are anonymised and stored at the

Scientific Research Division of the Suzhou Mental Health Center. and the data are available on request from the corresponding author.

"The datasets generated and/or analysed during the current study are not publicly available due [Our data results use matlab to load spm, and then load restplus to open it. At the same time, the capacity of the original data is very large, and there are certain difficulties in uploading] but are available from the corresponding author on reasonable request."

Competing interests

The authors declare no competing non-financial/financial interests.

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Authors' contributions

Fang-wen ZHANG designed the study, collected the data and assisted with writing the article. Teng-long WANG scored the neuroimaging data and supervised data collection. Dong WANG obtained the grant for the study, and was responsible for the statistical design of the study.

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References

1. Rickle, A. , Bogdanovic, N. , Volkman, I. , Winblad, B. , Ravid, R. , & Cowburn, R. F. Akt activity in alzheimer's disease and other neurodegenerative disorders. *Neuroreport*. 2004;15(6), 955-9.
2. Petersen, R. C. and R. O. Roberts, et al. Mild Cognitive Impairment: Ten Years Later. *Archives of Neurology*. 2009;66(12): 1447-1455.
3. Zhou, S. S. and X. Gao, et al. Selective impairment of musical emotion recognition in patients with amnesic mild cognitive impairment and mild to moderate Alzheimer disease. *Chinese Medical Journal*. 2019;132(19):2308-2314.
4. Jung, Y. H. and S. Park, et al. Frontal-executive dysfunction affects dementia conversion in patients with amnesic mild cognitive impairment. *Scientific Reports*. 2020;10(1):312-319.
5. Jia, L. and M. Quan, et al. Dementia in China: epidemiology, clinical management, and research advances. *The Lancet Neurology*. 2020;19(1):81-92.
6. Hui and Zhao, et al. 2015. Atrophic Patterns of the Frontal-Subcortical Circuits in Patients with Mild Cognitive Impairment and Alzheimer's Disease. *PLOS ONE* 2020;10:e0130017.
7. Nasrouei, S. and J. A. Rattel, et al. Fear Acquisition and Extinction Deficits in Amnesic Mild Cognitive Impairment and Early Alzheimer's Disease. *Neurobiology of Aging*. 2019; 87:26-34.
8. Bai, F. and Z. Zhang, et al. Abnormal Functional Connectivity of Hippocampus During Episodic Memory Retrieval Processing Network in Amnesic Mild Cognitive Impairment. *Biol Psychiatry* 2009; 65(11): 951-958.
9. Cai, S. and T. Chong, et al. Altered functional brain networks in amnesic mild cognitive impairment: a resting-state fMRI study. *Brain Imaging & Behavior*. 2016; 11(3): 1-13.
10. Zhou, Q. H. and K. Wang, et al. Differential Regional Brain Spontaneous Activity in Subgroups of Mild Cognitive Impairment. *Frontiers in Human Neuroence*. 2020; 14:2.
11. Kim, J. and Y. H. Kim, et al. Hippocampus–precuneus functional connectivity as an early sign of Alzheimer's disease: A preliminary study using structural and functional magnetic resonance imaging data. *Brain Research*. 2013;1495:18-29.
12. Behrens, T. E. J. and H. Johansen-Berg, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience* 2003; 6(7): 750.
13. W, S. S. M. G. (2006). *Exploring the Thalamus and Its Role in Cortical Function*. Cambridge MA: MIT Press. Second Edition.
14. Paola, Macaluso, E. , Carlesimo, G. A. , Tomaiuolo, F. , Worsley, K. J. , & Fadda, L., et al. Episodic memory impairment in patients with alzheimer's disease is correlated with entorhinal cortex atrophy. a voxel-based morphometry study. *Journal of Neurology*. 2007; 254(6), 774-781.
15. Damoiseaux, J. S. , Smith, S. M. , Witter, M. P. , Sanz-Arigita, E. J. , & Rombouts, S. White matter tract integrity in aging and alzheimer's disease. *Human Brain Mapping*. 2010;30(4), 1051-1059.
16. Zhou Bo. et al. A follow-up study on thalamic functional connectivity of mild cognitive impairment: explored by resting state functional magnetic resonance imaging. *Journal of Clinical and*

Experimental Medicine. 2014;13:784-788.

17. Zald, D. H. and J. V. Pardo. Emotion, olfaction, and the human amygdala: Amygdala activation during aversive olfactory stimulation. *Proceedings of the National Academy of Sciences of the United States of America*. 1997;94(8): 4119-4124.
18. Pessoa, L. and R. Adolphs. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nature Reviews Neuroscience*. 2010;11(11): 773-782.
19. Hariri, A. R. and V. S. Mattay, et al. Neocortical modulation of the amygdala response to fearful stimuli. *Biological Psychiatry*. 2003 53(6): 494-501.
20. Price, J. L. 2010. Comparative aspects of amygdala connectivity. *Annals of the New York Academy of Sciences*. 2010;985(1): 50-58.
21. Guo, Z. , Liu, X. , Xu, S. , H, Hou., Chen, X., & Zhang, Z. , et al. Abnormal changes in functional connectivity between the amygdala and frontal regions are associated with depression in alzheimer's disease. *Neuroradiology* 60:1315-1322.
22. Chen, Bo. Abnormal cortical regions and subsystems in whole brain functional connectivity of mild cognitive impairment and alzheimer's disease: a preliminary study. *Aging - Clinical and Experimental Research*. 2020;33(2):367-381.
23. Yao, H. , Liu, Y. , Zhou, B., Zhang, Z., An, N. , & Wang, P. , et al. Decreased functional connectivity of the amygdala in alzheimer's disease revealed by resting-state fmri. *European Journal of Radiology*. 2013;82(9), 1531-1538.
24. Petersen, R. C. , and J. C. Morris. Mild Cognitive Impairment as a Clinical Entity and Treatment Target. *Arch Neurol*. 2005; 62(7), 1160.
25. Roy, A.K., et al. Functional connectivity of the human amygdala using resting state fMRI. *Neuroimage*. 2009;45(2), 614-626.
26. Vogelaere, F. and P. Santens, et al. Altered default-mode network activation in mild cognitive impairment compared with healthy aging. *Neuroradiology*. 2012;54(11): 1195-1206.
27. Zhou, Y. and J. H. Dougherty, et al. Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimers & Dementia*. 2008;4(4): 265–270.
28. Joshi, H. and S. Bharath, et al. Resting state functional connectivity abnormalities and delayed recall performance in patients with amnesic mild cognitive impairment. *Brain Imaging and Behavior*. 2018;14(2):267-277.
29. Binnewijzend, M. A. A. and M. M. Schoonheim, et al. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging* 2012; 33(9): 2018-2028.
30. Song, J. and W. Qin, et al. Aberrant Functional Organization within and between Resting-State Networks in AD. *Plos One*. 2013;8(5): e63727.
31. Rombouts, S. A. R. B. and F. Barkhof, et al. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Human Brain Mapping*. 2010;26(4): 231-

239.

32. Pasquini L, Scherr M, Tahmasian M et al. Link between hippocampus' raised local and eased global intrinsic connectivity in AD. *Alzheimers Dement*. 2015;11:475–484.
33. Wang L, Zang Y, He Y et al. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *NeuroImage* 31:469–504.
34. Cappell, R. L. A. Neurocognitive Aging and the Compensation Hypothesis. *Current Directions in Psychological Science*. 2010;17(3): 177-182.
35. Jiang, T. and X. Zhang, et al. Impaired functional connectivity of the thalamus in Alzheimer's disease and mild cognitive impairment: a resting-state fMRI study. *Current Alzheimer Research*. 2013;10(7):754-766.
36. Ramnani, N. and A. M. Owen. Anterior prefrontal cortex: insights into function from anatomy and neuroimaging." *Nature Reiview Neuroscience*. 2004; 3(5): 84-94.
37. Gilbert, S. J. and S. Spengler, et al. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *Journal of Cognitive Neuroscience*. 2006;18(6): 932-948.
38. Basso, M. , Yang, J., Warren, L., Macavoy, M. G., Varma, P., & Bronen, R. A. , et al. Volumetry of amygdala and hippocampus and memory performance in alzheimer's disease. *Psychiatry Research*. 2006; 146(3), 251-261.
39. Wang, Z., Jia, X., Liang, P. , Qi, Z., Yang, Y., & Zhou, W., et al. Changes in thalamus connectivity in mild cognitive impairment: evidence from resting state fmri. *European Journal of Radiology*. 2012; 81(2), 277-285.
40. Peipeng, Liang, Jie, Xiang, Hong, & Liang, et al. Altered amplitude of low-frequency fluctuations in early and late mild cognitive impairment and alzheimer's disease. *Current Alzheimer Research*. 2014;11(4):389–398.

Tables

Table 1
Demographic and neuropsychological data

Items	aMCI(n=33)	NC(n=33)	<i>t/c²/MWU</i>	<i>P</i> value
Age (years), mean (SD)	68.79 (4.87)	68.88 (4.92)	-0.08	0.94 [*]
Male/Female	18/15	19/14	0.06	0.80 ^{**}
Education (years), mean (SD)	9.24 (2.73)	10.9 (3.59)	-2.16	0.04 [*]
HIS score, mean (SD)	1.48 (0.67)	1.27±0.94	1.05	0.30 [*]
ADL score, mean (SD)	14.45 (1.15)	14.03 (0.17)	2.1	0.04 [*]
HAMD score, median (Q)	2 (4)	1 (4)	361	0.01 ^{***}
ADAS-Cog score, mean (SD)	11.45±1.15	7.27±2.98	1.05	0.00 [*]
MoCA-B (SD)	21.79(3.65)	23.79(3.30)	2.3	0.023 [*]
Abbreviations: aMCI: amnesic mild cognitive impairment; NC: normal control, MWU, Mann–WhitneyU-test; HIS: Hachinski score;ADL: Activities of daily living scale; HAMD: Hamilton's depression scale; ADAS-Cog: Alzheimer's disease assessment scale-cognitive subscale; MoCA-B: Montreal Cognitive Assessment -Basic Chinese Version .				
*P values obtained by independent sample t-test.				
☐P value for sex distribution obtained by Pearson's chi-square test.				
***P values obtained by rank sum test.				

Table 2 Functional connectivity between the hippocampus and whole brain

Seed	BA	Cluster size	MNI			Peak intensity	
			x	y	z		
Parahippocampal(L)	36	14	-18	-3	-36	5.3033	MCI>HC
Precuneus(L)	31	129	-24	-36	-6	7.5466	
Precuneus(R)	31	91					
Parahippocampal Gyrus		10	-30	-12	-24	4.6996	
inferior occipital gyrus (R)	19	22	42	-78	-18	4.4835	
Inferior temporal gyrus (R)	37	10	63	-60	-12	4.1414	
Inferior occipital gyrus (L)	19	32	-30	-75	-12	5.5993	
Calcarine(L)	18	38	-9	-99	18	4.8107	
Middle occipital gyrus (R)	39	246	45	-72	39	6.425	
Rolandic Operculum(R)		15	39	-9	21	4.7932	
Superior frontal gyrus (L)	10	18	-21	63	21	4.4066	
Middle occipital gyrus (L)	19	99	-27	-87	36	5.7759	
Angular(L)	39	60					
Anterior cingulate (L)	24	12	-3	0	30	-4.9089	MCI<HC
Cuneus	7	25	3	-81	36	5.5245	MCI>HC
Superior frontal gyrus (R)	6	77	-18	36	54	6.0966	
Postcentral(L)	3	12	-36	-24	45	3.7934	
Postcentral(R)	3	19	45	-36	66	4.3482	

Note: R stands for the Right, L stands for the Left

Table 3
Functional connectivity between the thalamus and whole brain

Seed	BA	Cluster Size	MNI			Peak intensity	
			x	y	z		
Fusiform(L)	19	14	-27	-81	-18	4.13	MCI>HC
Inferior occipital gyrus (R)	19	10	48	-81	-15	4.3967	
Thalamus		22	-3	-18	9	4.8668	
Caudate(L)		19	-6	-3	6	5.3823	
Middle occipital gyrus (R)	39	98	48	-72	36	5.2411	
Thalamus(R)		48	12	-21	12	6.0615	
Caudate(R)	13	21	21	18	15	5.415	
Middle occipital gyrus (L)	19	10	-30	-90	27	3.9977	
Middle frontal gyrus	10	11	36	51	33	4.6613	
Supra Marginal(R)	40	15	63	-36	45	4.9647	
Precentral	6	17	57	9	42	5.0526	
Postcentral	3	14	57	-21	54	4.2439	
Superior parietal (R)	7	35	30	-63	63	4.5419	
Middle frontal gyrus (R)	6	16	33	6	66	4.6416	
Precentral(R)	4	17	30	-30	72	4.8142	
Note: R stands for the Right;L stands for the Left							

Table 4
Functional connectivity between the amygdala and whole brain

Seed	BA	Cluster size	MNI			Peak intensity	
			X	Y	Z		
Thalamus(L)		10	-15	-12	6	-4.8743	MCI<HC
Supplementary motor area (R)	6	23	6	6	57	-4.3916	
Superior frontal (R)	8	10	27	36	54	4.842	MCI>HC
Precentral(R)	3	10	24	-24	78	4.2343	
Note: R stands for the Right;L stands for the Left							

Figures

Figure 1

Functional connectivity of hippocampal regions of interest. Patterns of significantly positive (red) and negative (blue) relationships for the total hippocampus in sagittal ($x = -24$), coronal ($y = -38$), and axial ($z = -2$) views are presented. false-discovery rate (FDR) corrected at $p < 0.001$.

Figure 2

Functional connectivity of thalamic regions of interest. Patterns of significantly positive (red) and negative (blue) relationships for the total thalamus in sagittal ($x = 8$), coronal ($y = -24$), and axial ($z = -4$) views are presented. false-discovery rate (FDR) corrected at $p < 0.001$.

Figure 3

Functional connectivity of amygdalar regions of interest. Patterns of significantly positive (red) and negative (blue) relationships for the total amygdala in sagittal ($x= 8$), coronal ($y= -24$), and axial ($z= -4$) views are presented. false-discovery rate (FDR) corrected at $p<0.001$.