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Structural and Functional Brain Changes in the Default Mode Network in Subtypes of Amnestic Mild Cognitive Impairment

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Abstract

Background: Various amnestic mild cognitive impairment (aMCI) subtypes have been identified as single domain (SD) or multiple domain (MD), with differential probabilities of progression to Alzheimer disease (AD). Detecting the differences in the alterations in gray matter (GM) and intrinsic brain activity between the subtypes of aMCI help to understand their pathophysiological mechanisms and was conducive to construct such potential biomarkers to monitor the progression of aMCI. **Methods:** In all, 22 normal controls (NCs), 18 patients with SD-aMCI, and 17 patients with MD-aMCI participated in the study. The amplitude of low-frequency fluctuations (ALFFs) during rest represented intrinsic brain activity. Voxel-based morphometry analysis was used to measure the GM volume. **Results**: The MD-aMCI showed reduced GM in hippocampus (Hip), parahippocampal gyrus (PHG), and other regions than SD-aMCI. The SD-aMCI had reduced GM only in Hip and PHG than in NC. The MD-aMCI showed decreased ALFF in posterior cingulate cortex (PCC) and precuneus and increased ALFF in anterior cingulate cortex (ACC), PHG, and Hip compared with both SD-aMCI and NC. However, no ALFF difference was found between SD-aMCI and NC. Neuropsychological measures were correlated with ALFF in PCC and ACC only in the MD-aMCI. **Conclusions:** Patients with MD-aMCI displayed more severe GM atrophy and ALFF changes than patients with SD-aMCI. The results suggested that aMCI is heterogeneous and that MD-aMCI may be a prodromal stage which is more close to AD.

Keywords

resting-state functional MRI, spontaneous brain activity, mild cognitive impairment, gray matter volume

Introduction

Amnestic mild cognitive impairment (aMCI) is a term used to describe individuals who display relative memory impairment compared with their contemporaries and do not fulfill the criteria of dementia.[1] Previous studies have demonstrated that approximately 80% of patients with aMCI will progress to clinically diagnosable Alzheimer disease (AD) within 6 years, with an annual conversion rate of 10% to 15%.[2] To further describe the clinical characteristics and investigate the pathological mechanisms, aMCI has been divided into 2 subtypes: single-domain aMCI (SD-aMCI), which is characterized by isolated memory impairment and multiple-domain aMCI (MD-aMCI), which is characterized by memory impairment and impairment in at least one more cognitive domain, such as executive function, attention, and language abilities.[3]

Neuroimaging techniques such as volumetric and functional magnetic resonance imaging (MRI) have been widely used to investigate the structural and functional changes in patients with various aMCI subtypes.[4-7] Based on volumetric MRI, for example, patients with SD-aMCI were observed to have cortical thinning in the left medial temporal lobe and patients with MD-aMCI were observed to have more diffused cortical thinning in the left medial temporal lobe, precuneus (PCu), and several other brain regions.[4] Shu et al, using diffusion tensor imaging, reported that the global topological organization of white matter networks was significantly disrupted in patients with MD-aMCI but not in patients with SD-aMCI.[7] In another single photon emission computed tomography study, hypometabolism in the medial temporal lobe and fronto–parieto–

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temporal areas was observed in both the SD-aMCI and the MD-aMCI groups, with the MD-aMCI group presenting additional deficit in the left posterior cingulate gyrus.[5] Findings from these studies support the idea that deficit patterns in patients with MD-aMCI are similar to those in patients with AD and MD-aMCI may represent a more advanced prodromal stage of AD.[6,7]

Previous neuroimaging studies suggest that the deficits in brain regions by subtype aMCI are mainly located in the default mode network (DMN). The core DMN regions include the ventral medial prefrontal cortex, posterior cingulate/retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, dorsal medial prefrontal cortex, and hippocampal formation.[8] These regions are also vulnerable to amyloid-β depositions.[9] Alzheimer disease is characterized by the pathological accumulation of amyloid-β.[10] The amyloid accumulation in these vulnerable brain areas is followed by synaptic dysfunction and neuronal loss, ultimately resulting in cognitive dysfunction.[10,11] Many studies have reported that the DMN regions display significantly reduced amplitude of low-frequency fluctuations (ALFFs) in patients with MCI.[12,13] Patients with MCI having lower DMN connectivity are more likely to progress to a diagnosis of AD.[14] The key regions (hubs) in the DMN serve to integrate diverse informational sources and aid in the minimization of metabolism costs by providing a limited number of long-distance connections that integrate local networks.[15] Therefore, the intrinsic activity in DMN regions is very important to representing progress from MCI to AD.

Little is known regarding the alteration in intrinsic brain activity within the DMN regions in patients with aMCI subtype from a regional perspective. Recent studies have suggested that the ALFFs, calculated as the square root of the power spectrum in a low frequency range, can be used to assess the spontaneous brain activity during resting-state using functional MRI (fMRI) techniques.[16,17] In other studies, the ALFF was physiologically meaningful and able to represent different states of the brain.[18,19] Using this method, Wang et al demonstrated that patients with MCI had decreased activity in the medial parietal lobe and increased activity in the lateral temporal regions and superior frontal regions,[20] which are mainly located within the DMN.

To our knowledge, ALFF-measured DMN activity differences among aMCI subtypes have not been reported in the literature. Such differences, if identified, could be used as an early indication of a higher risk of AD, given that patients with SD-aMCI and MD-aMCI occasionally reveal similar degrees of memory loss and are difficult to distinguish between using any single neuropsychological test. The feasibility of such use of ALFF as an early detection of risk to AD is consistent with the belief that regional spontaneous neuronal activity reflects mild cortex functional alteration.[16,20] In addition, we are interested in examining the possible structural aberration in the brains of patients with these aMCI subtypes alone or their effects on functional ALFF measurements. We finally also aim to investigate the relationship between the functional activities and the clinical and cognitive measures. A strong association of the observed ALFF with the neuropsychological measures would confirm the validity of using ALFF as a possible imaging biomarker to differentiate the aMCI subtypes and relate them to the degree of risk of AD.

Materials and Methods

Patients

In this study, 59 right-handed elderly patients participated all of who were from the Beijing Aging Brain Rejuvenation Initiative, which is an ongoing longitudinal study investigating the aging and cognitive impairment of urban elderly people in Beijing, China. All of the patients filled in an Activities of Daily Living (ADL) scale[21] and received a battery of neuropsychological tests that included the Chinese version of the Mini-Mental State Examination (MMSE),[22] the Auditory Verbal Learning Test (AVLT),[23] the Rey-Osterrieth Complex Figure (ROCF),[24] the Symbol Digit Modalities Test,[25] the Trail Making Test (TMT),[26] the Clock-Drawing Test,[27] the Category Verbal Fluency Test, the Boston Naming Test,[28] and the Stroop Color and Word Test.[29]

The diagnostic criteria for MCI included subjective memory complaints, cognitive impairment in memory (scoring more than 1.5 standard deviation below the age- and education-adjusted norms on the AVLT and the ROCF), relatively preserved general cognitive function, and intact ADL (scoring 0 on the ADL scale), as stated in Petersen et al.[1] The patients who had isolated episodic memory impairment were considered to be SD-aMCI whereas patients were considered to be MD-aMCI if memory together with one or more additional cognitive domains was affected as evaluated using neuropsychological tests (1.5 standard deviations below age and education norms). The criteria for the normal controls (NCs) were no cognitive complaints, normal cognitive ability, and normal activities of daily life.

Two patients were removed from the study due to excessive head motion during the acquisition of their MRI data. The patients were divided into 3 groups: SD-aMCI ($n = 17$), MD-aMCI ($n = 18$), and NCs ($n = 22$). None of the patients reported a history of head trauma, psychiatric or neurological disorders, or alcohol or drug abuse. All patients voluntarily joined this study with informed consents. The use of patients for this study has been approved by institutional review board at the Imaging Center for Brain Research at Beijing Normal University.

Data Acquisition

Magnetic resonance imaging data acquisition was performed using a Siemens Trio 3.0 Tesla scanner (Trio; Siemens, Erlangen, Germany) in the Imaging Center for Brain Research at Beijing Normal University. Foam padding and headphones were used to reduce head motion and scanner noise. The patients were instructed to keep still with their eyes closed, not to fall asleep, and not to think about anything in particular. The functional images were acquired using an echo-planar imaging sequence: 33 axial slices, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, slice thickness = 3.5 mm, flip angle = 90°, field of view (FOV) = 200 mm × 200 mm, and acquisition matrix = 64 × 64. The scan lasted for 480s. The T1-weighted structural images were

Table 1. Demographic Information for Each Group.[a]

	NC (n = 22)	SD-aMCI (n = 18)	MD-aMCI (n = 17)	*F* Value (χ^2)	*P* Value
Age, years	62.6 ± 5.8	65.6 ± 6.4	67.0 ± 7.9	2.39	.111
Education, years	11.3 ± 2.7	12.5 ± 2.8	11.1 ± 3.3	1.23	.299
Gender (M/F)	11/11	6/12	9/8	1.22	.544[b]

Abbreviations: NC, normal control; SD-aMCI, single-domain amnestic mild cognitive impairment; MD-aMCI, multiple-domain amnestic mild cognitive impairment; M, male; F, female.

[a] All patients (NC, SD-aMCI, and MD-aMCI) were matched across the groups for age, gender, and education. Values are mean ± standard deviation. The comparisons of demographics among the 3 groups (SD-aMCI, MD-aMCI, and NC) were performed using separate 1-way analysis of variance (ANOVA). Post hoc pair-wise comparisons were then performed using *t* tests. $P < .05$ was considered significant.

[b] The *P* value for gender distribution in the 3 groups was obtained using a chi-square test.

acquired using 3-dimensional (3D) magnetization prepared rapid gradient echo sequences: 176 sagittal slices, TR = 1900 ms, TE = 3.44 ms, slice thickness = 1 mm, flip angle = 9°, FOV = 256 mm × 256 mm, and gap = 9.

Structural Image Analysis

All of the patients' individual structural images (3D T1-weighted anatomical images) were coregistered to the mean functional images after motion correction using a linear transformation.[30] The transformed 3D T1-weighted images were then segmented and spatially normalized into gray matter (GM), white matter, and cerebrospinal fluid in standard Montreal Neurological Institute (MNI) space using a unified segmentation algorithm.[31] Modulation was further applied to the GM images to compensate for the effect of spatial normalization using linear and nonlinear methods. All of the resultant images were resampled with 3-mm isotropic voxels and smoothed with a 6-mm full width and half maximum (FWHM) Gaussian kernel. In the study, we utilized the mean GM map (threshold = 0.2) of all of the patients to obtain a group-based brain mask and used it for subsequent analysis.

Functional Image Analysis

All image preprocessing and analyses were conducted using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI.[32] The first 5 volumes of the functional images were discarded for each patient to allow for signal equilibrium and the patients' adaptation to the situation. The remaining functional images were corrected intravolume for time delay between the slices and the realigned intervolume for head motion. Next, all of the images were spatially normalized to the template in MNI space by applying the transformation parameters that were obtained from the structural images (see above-mentioned Structural Image Analysis section for details) to those time- and motion-corrected images. The resultant normalized functional images were spatially smoothed with a 6-mm FWHM Gaussian kernel and the linear trends removed. Finally, all of the images were temporally filtered (0.01-0.1 HZ) to eliminate high-frequency noise and low-frequency drift.

For each voxel in the brain, its blood oxygenation level-dependent time series was first transformed to the frequency domain using a fast Fourier transform. The square root of the power spectrum, the ALFF for this voxel,[16] was computed and then averaged across the 0.01 to 0.1 HZ frequency interval. To account for whole brain variation, the ALFF value was then divided by the global mean ALFF value for each patient.

Statistical Analyses

The statistical analyses were performed using REST software (www.restfmri.net). In particular, an analysis of covariance (ANCOVA) with group as the factor and age, gender, and formal education years as covariants was conducted to identify the ALFF differences among the SD-aMCI, MD-aMCI, and NC groups. Post hoc 2-sample *t*-tests were also performed. To determine the pattern of GM loss in the patients, we also performed ANCOVA on the GM volume maps. To further analyze the effects of GM atrophy on functional results, we performed ANCOVA in which the GM volume maps were entered as covariates. All the statistical maps were corrected for multiple comparisons at a significance level of $P < .05$ by combining the individual voxel P value $< .05$ with cluster size > 3240 mm^3 using Monte Carlo simulations.[46] For those clusters displaying significant differences between the groups, post hoc 2-sample *t*-tests were further performed. The results were visualized using the BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

We finally investigated the relationship between the ALFF and the cognitive performance in the 3 groups separately while controlling for age and sex as confounding variables. The correlations were computed on a voxel-by-voxel basis and only within the regions that displayed significant ALFF differences among the 3 groups.

Results

Clinical and Neuropsychological Data

The demographic information and neuropsychological characterizations for each group are shown in Tables 1 and 2. No significant differences in age, gender, and education were observed among the 3 groups. Significant differences (analysis of variance [ANOVA]) were observed between the 3 groups in

Table 2. Neuropsychological Characterizations for Each Group.[a]

	NC (n = 22)	SD-aMCI (n = 18)	MD-aMCI (n = 17)	*F*-value (χ^2)	*P*-value
General mental status					
MMSE	28.5 ± 1.1	26.6 ± 2.0	25.6 ± 1.27	18.77	<.001[b,c]
AVLT-delay recall	6.6 ± 2.1	1.9 ± 1.3	1.7 ± 1.5	53.38	<.001[b,c]
Memory function					
AVLT-T	33.7 ± 6.9	17.8 ± 4.1	16.2 ± 6.2	54.48	<.001[b,c]
ROCF-delay recall	16.0 ± 8.4	8.9 ± 7.2	4.2 ± 4.5	13.77	<.001[b,c]
ROCF-copy	33.7 ± 5.2	32.2 ± 3.7	29.2 ± 6.7	3.58	.035[c]
Spatial processing					
CDT	24.7 ± 6.2	23.5 ± 3.5	21.8 ± 4.9	1.58	.215
CVFT	47.1 ± 8.1	39.7 ± 5.9	34.2 ± 6.5	16.70	<.001[b,c,d]
Language					
BNT	25.6 ± 2.9	23.5 ± 2.9	19.7 ± 4.2	14.77	<.001[c,d]
SDMT	39.7 ± 9.4	34.7 ± 9.3	20.5 ± 9.2	20.96	<.001[c,d]
Attention					
TMT-A times	48.5 ± 11.4	56.3 ± 19.5	91.5 ± 36.9	16.77	<.001[c,d]
SCWT-SIE	29.7 ± 8.8	39.5 ± 26.5	49.1 ± 25.0	4.15	.021[c]
Executive function					
TMT-B times	136.9 ± 40.1	201.6 ± 81.9	286.1 ± 66.8	26.29	<.001[b,c,d]

Abbreviations: NC, normal control; SD-aMCI, single domain of amnestic mild cognitive impairment; MD-aMCI, multiple domain of amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; AVLT, Auditory Verbal Learning Test; AVLT-T, AVLT-total; ROCF, Rey-Osterrieth Complex Figure; CDT, Clock-Drawing Test; CVFT, Category Verbal Fluency Test; BNT, Boston Naming Test; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test; SCWT-SIE, Stroop interference effect of Stroop Color and Word Test.

[a] Values are mean ± standard deviation. The comparisons of neuropsychological scores among the 3 groups (SD-aMCI, MD-aMCI, and NC) were performed using separate 1-way analysis of variance (ANOVA). Post hoc pair-wise comparisons were then performed using *t* tests. $P < .05$ was considered significant.

[b] Post hoc paired comparisons showed significant group differences between NC and SD-aMCI, after least-significant difference (LSD) correction.

[c] Post hoc paired comparisons showed significant group differences between NC and MD-aMCI, after LSD correction.

[d] Post hoc paired comparisons showed significant group differences between SD-aMCI and MD-aMCI, after LSD correction.

all the cognitive domains, including MMSE, memory, spatial processing, language, attention, and executive function. Furthermore, post hoc comparisons indicated that the NC group performed better than the patients with SD-aMCI in the MMSE and the test of memory. The patients with MD-aMCI performed worse than the NC group in all the cognitive domains, especially in memory and executive function. In particular, patients with SD-aMCI displayed better performance in language, attention, and executive function domains than in patients with MD-aMCI.

Gray Matter Structural Morphology in Patients With SD-aMCI and MD-aMCI

There were significant differences in regional GM volumes among the patients with MD-aMCI and SD-aMCI, and the NC group. These included the posterior cingulate cortex (PCC)/PCu, hippocampus (Hip), parahippocampal gyrus (PHG), anterior cingulate cortex (ACC), and orbitofrontal gyrus (OFG). In addition, GM differences were also observed in the angular gyrus (AG), fusiform gyrus (FG), and middle occipital gyrus (Figure 1). Post hoc, pairwise comparisons of GM volume are shown in Figure 2 and Table 3. The GM volume alteration in patients with SD-aMCI was mainly observed

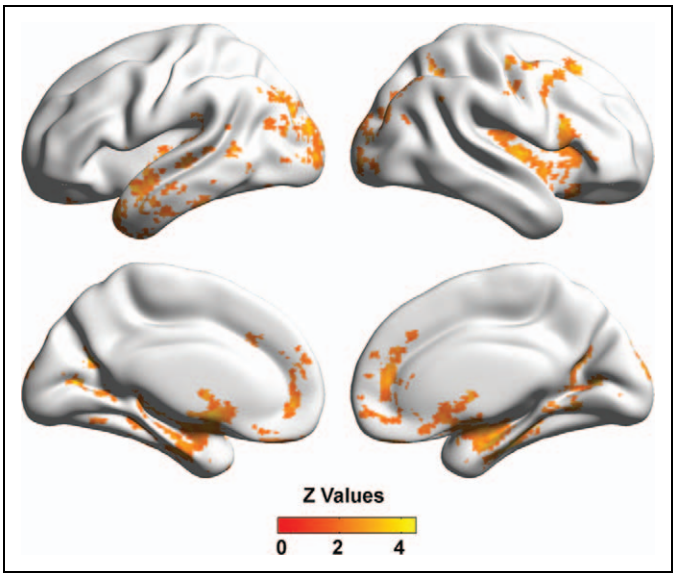

Figure 1. Z-statistical difference maps in gray matter volume among the patients with MD-aMCI, patients with SD-aMCI, and the normal controls. The statistical threshold was set at $P < .05$ and cluster size >1080 mm^3, which corresponds to a corrected $P < .05$. MD-aMCI indicates multiple-domain amnestic mild cognitive impairment; SD-aMCI, single-domain amnestic mild cognitive impairment.

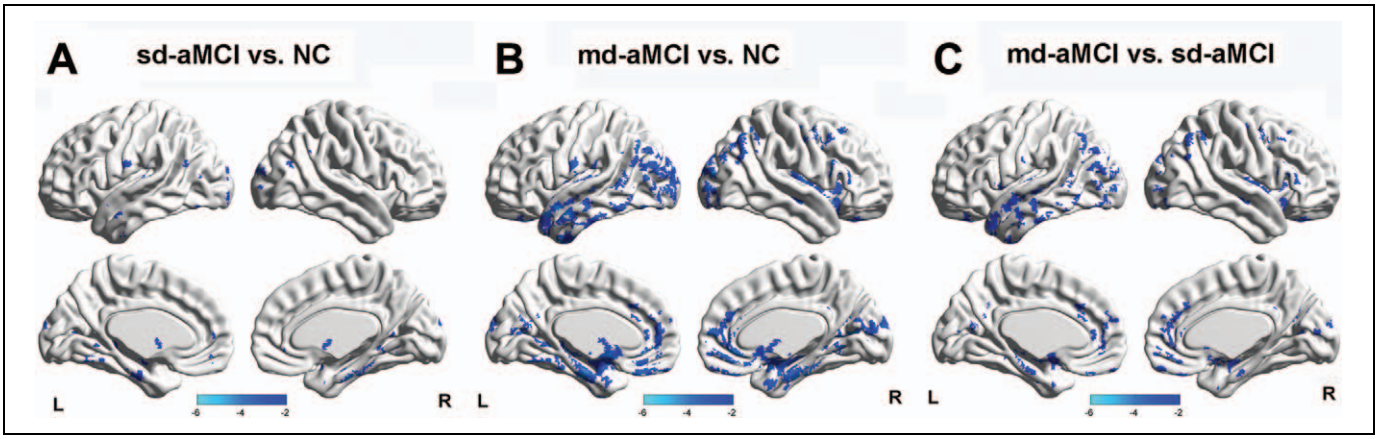

Figure 2. Voxel-wise GM volumes were compared between aMCI subtypes and the normal control group. A, Gray matter volumes difference between the patients with SD-aMCI and the healthy elderly control individuals. B, Gray matter volumes difference between the patients with MD-aMCI and the healthy elderly control individuals. C, Gray matter volumes difference between the patients with MD-aMCI and SD-aMCI. The 2 sample *t* tests were performed within a mask that indicated significant group differences in the ANOVA analysis. The statistical threshold was set at $P < .05$ and a cluster size of >708 mm^3, which corresponds to a corrected $P < .05$. GM indicates gray matter; aMCI, amnestic mild cognitive impairment; SD-aMCI, single-domain aMCI; MD-aMCI, multiple-domain aMCI; ANOVA, analysis of variance.

Table 3. Brain Areas With Significant GM Atrophy Between the Patients With MD-aMCI and SD-aMCI.[a,b]

		MNI Coordinates, mm			
Brain Regions	Volumn(mm^3)	x	y	z	T
MD-aMCI < SD-aMCI					
Left MTG	3746	−57	−51	18	4.15
Left Angular		−48	−69	42	4.01
Right SPG	433	27	−54	48	4.14
Right MOG		36	−81	21	4.1
Right IPL		57	−51	48	3.95
Right PreCG	146	36	−6	48	4.28
Right IFGtriang	143	48	18	21	3.64
Right calcarine	145	15	−60	18	2.95
Right lingual		15	−57	−6	2.07

Abbreviations: T, statistical value of peak voxel; MOG, middle occipital gyrus; MTG, middle temporal gyrus; SPG, superior parietal gyrus; IPL, inferior parietal lobe; PreCG, precentral; IFGtriang, inferior frontal (pars triangularis); GM, gray matter; MD-aMCI, multiple-domain amnestic mild cognitive impairment; SD-aMCI, single-domain amnestic mild cognitive impairment; MNI, Montreal Neurological Institute.
[a] The x, y, z coordinates of the primary peak locations in the MNI space.
[b] $P < .05$ corrected for multiple comparisons.

in the Hip and PHG. In contrast, in patients with MD-aMCI, the brain atrophy was diffused throughout the entire brain and included the frontal, parietal, occipital, and temporal gyri as well as the limbic system. Furthermore, compared to the patients with SD-aMCI, the MD-aMCI group displayed significant atrophy in the PCu, PHG, Hip, OFG, AG, FG, and the occipital lobes. Thus, the GM volume atrophy was more diffused and severe in patients with MD-aMCI.

Altered ALFF in Patients With SD-aMCI, Patients With MD-aMCI, and NC

The results of the ANCOVA of the ALFF are displayed in Figure 3. Significant group differences in the ALFF were detected in the PCC/PCu, OFG, ACC, and several regions in the temporal lobe, including the inferior temporal gyrus (ITG), middle temporal gyrus, and FG as well as the Hip. The results of the post hoc comparisons are shown in Figure 4 and Table 4. Significant ALFF decreases in the SD-aMCI group were observed in the right middle frontal gyrus (MFG) and precentral gyrus (PrCG) compared with the NC. In contrast, the most significant ALFF decreases in the MD-aMCI group were observed in the PCC/PCu and PrCG than those in the NC. Moreover, significant increases in the ALFF were observed in the bilateral ACC and the OFG as well as in the Hip, PHG, and FG in the MD-aMCI group. Interestingly, the patients with MD-aMCI displayed decreased ALFF in the PCC/PCu but increased ALFF in the bilateral ACC, PHG, Hip, and FG compared with the patients with SD-aMCI.

The correlations between the ALFF and behavior measures are shown in Figure 5. The TMT attention (TMT-A) time was significantly negatively correlated with the ALFF of the PCu/PCC in the patients with MD-aMCI, and the Stroop

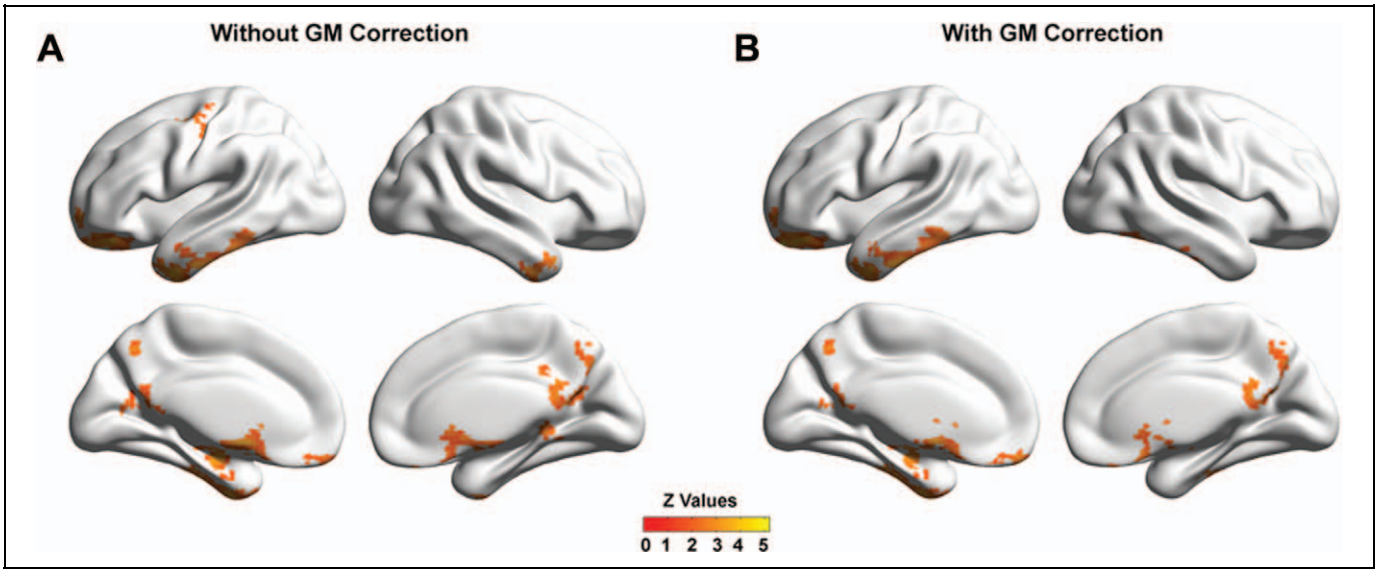

Figure 3. Z-statistical difference maps of the ALFF among patients with MD-aMCI, patients with SD-aMCI, and normal controls. The results were from an ANCOVA analysis. A, without GM correction. Significant differences were observed among the 3 groups in the PCC/PCu, OFG, anterior cingulate cortex (ACC), and several regions in the temporal lobe, including the inferior temporal gyrus (ITG), middle temporal gyrus (MTG), and fusiform gyri (FG), as well as the Hip. B, with GM correction. Significant differences were similar to those without the GM correction. The statistical threshold was set at $P < .05$ and a cluster size of >1080 mm^3, which corresponds to a corrected $P < .05$. ALFF indicates amplitude of low-frequency fluctuation; MD-aMCI, multiple-domain amnestic mild cognitive impairment; SD-aMCI, singe-domain amnestic mild cognitive impairment; GM, gray matter; PCC, posterior cingulate cortex; PCu, precuneus; OFG, orbitofrontal gyrus.

interference time was significantly negatively correlated with the ALFF of the ACC. For the NC and the SD-aMCI group, there is no correlation between cognitive performance measures and ALFF in any brain region.

Given the overlap between the structural and the functional differences, we implemented the above-mentioned analysis with the GM volume as a covariate (Figures 3 and 4). We observed that most of the results were similar to those without the GM correction. In particular, we observed no significant differences between the SD-aMCI and the NC groups when we used the GM correction.

Discussion

To our knowledge, this is the first study combining resting state fMRI with structural measures to detect differences between 2 aMCI subtypes. Compared to patients with SD-aMCI, patients with MD-aMCI displayed more obvious functional changes and more severe brain atrophy. These findings indicate that degeneration extensively exists in the GM structure and intrinsic brain activity in patients with MD-aMCI, which is more similar to what is observed in AD.[33] These results are consistent with the view that aMCI presents heterogeneity in the clinical progression and that ALFF may be a possible imaging-based biomarker that can discriminate the subtype of aMCI.

Structural Alteration in the Subtypes of aMCI

Our research revealed heterogeneity of GM atrophy in aMCI subtypes. Compared to patients with SD-aMCI, the MD-aMCI group displayed significant atrophy in the PCu, PHG, Hip, OFG, AG, FG, and the occipital lobes. Our results demonstrated that the brain regions showing significant atrophy in patients with MD-aMCI were much more widely distributed, and the atrophy was more severe than that observed in the SD-aMCI group. Compared with the controls, patients with SD-aMCI only displayed a significant GM volume decrease in the Hip and parahippocampus. The changes in GM volume were agreed with the previous studies.[4,34] Our results show that SD-aMCI and MD-aMCI are characterized by a common pattern of GM atrophy within the medial temporal cortex. Furthermore, the results exhibited a general pattern of GM $Volume_{MD\text{-}aMCI}$ < GM $Volume_{SD\text{-}aMCI}$ < GM $Volume_{NC}$. The atrophy patterns showed a linear change(Figure 6, left), which is consistent with presumably more advanced disease in the MD-aMCI group[35] and may help to predict the prognosis of the disease.

Amplitude of Low-Frequency Fluctuations Alteration in MD-aMCI

We observed that patients with MD-aMCI displayed decreased ALFF values within the posterior DMN regions, especially in the PCC and PCu, consistent with previous studies.[20] Other research has indicated that the PCu is involved in episodic memory[36] and visuospatial processing.[37] The PCu also plays a pivotal role in the DMN[38] and central executive networks.[39] Moreover, this region is vulnerable to cortical atrophy,[40] early amyloid deposition,[41] and hypometabolism[42] in patients with MCI and AD. The PCC has structural and functional similarities with the PCu and has also been shown to be altered in patients with MCI and AD.[43] Therefore, the

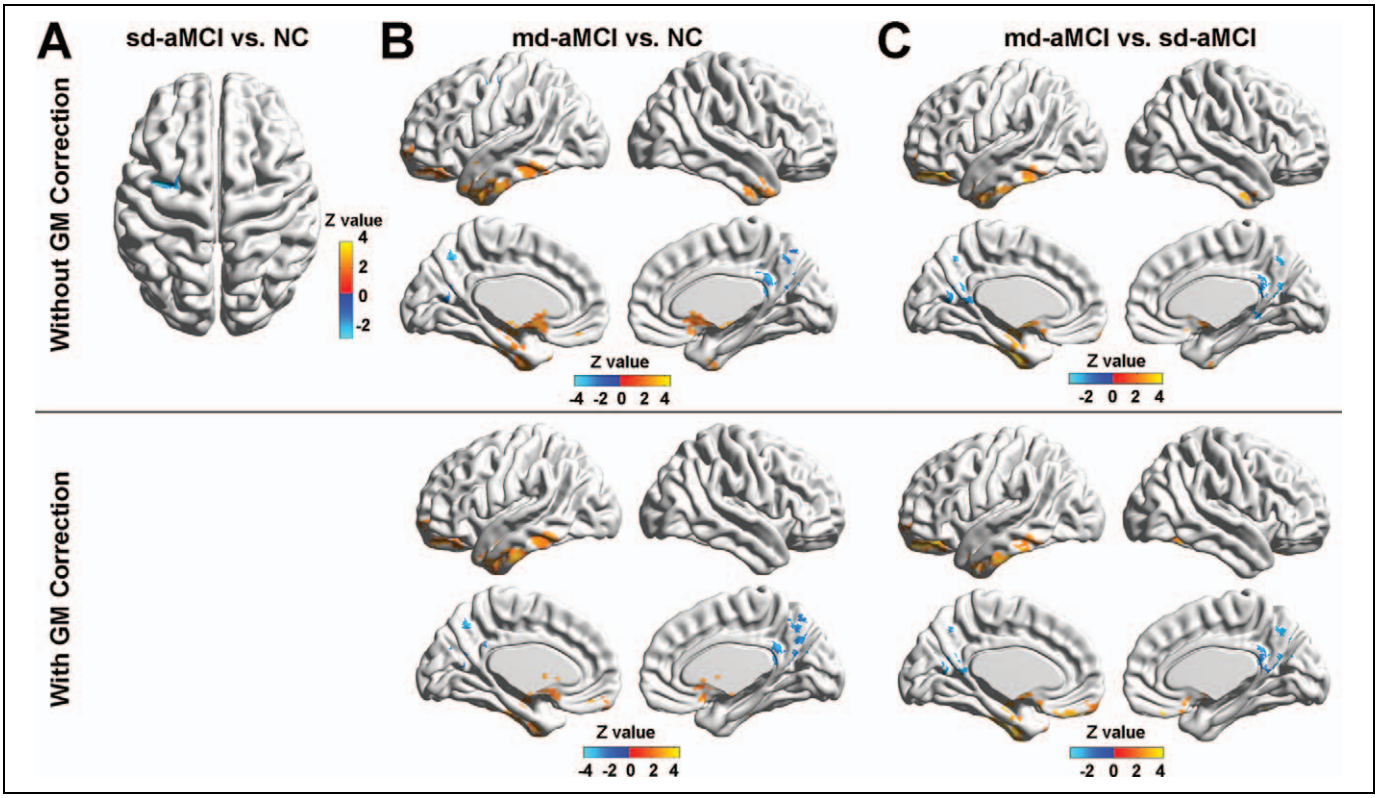

Figure 4. Z-statistical difference maps of the ALFF between the groups. Upper maps, without GM correction; lower maps, with GM correction. A, Z-statistical difference maps between the patients with SD-aMCI and the healthy elderly control individuals. Without GM correction, the SD-aMCI displayed significantly decreased ALFF in the right MFG and PrCG. No significant differences in ALFF appeared between the SD-aMCI and the normal controls after correction. B, Z-statistical difference maps between the patients with MD-aMCI and the healthy elderly control individuals. C, Z-statistical difference maps between the patients with MD-aMCI and SD-aMCI. The 2 sample *t* tests were performed within a mask that indicated significant group differences in the ANOVA analysis. For the without GM correction comparisons, the statistical threshold was set at $P < .05$ and a cluster size of >234 mm^3, which corresponded to a corrected $P < .05$. For the GM correction comparisons, the statistical threshold was set at $P < .05$ and a cluster size of >153 mm^3, which corresponded to a corrected $P < 0.05$. ALFF indicates amplitude of low-frequency fluctuation; GM, gray matter; MD-aMCI, multiple-domain amnestic mild cognitive impairment; SD-aMCI, singe-domain amnestic mild cognitive impairment; MFG, middle frontal gyrus; PrCG, precentral gyrus; ANOVA, analysis of variance.

Table 4. Brain Areas With Significant ALFF Differences Between the Patients With MD-aMCI and SD-aMCI.[a,b]

		MNI Coordinates, mm			
Brain Regions	Volumn(mm^3)	x	y	z	T
MD-aMCI<SD-aMCI					
PCu/calcarine left cuneus	61	−9	−60	12	3.35
Pcu	13	9	−66	42	3.63
MD-aMCI > SD-aMCI					
Left ITG/MTG/FG/PHG/TP	180	42	−24	−24	4.47
Right ITG/FG/PHG	15	39	−21	−24	4.01
Left OFG/GR	95	−15	51	−18	3.99
ACC/olfactory left caudate/GR	50	−12	24	−3	4.01
Right FG	6	36	−51	−18	3.63

Abbreviations: T, statistical value of peak voxel; PHG, parahippocampal gyrus; FG, fusiform gyrus; PCu, Precuneus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; ACC, anterior cingulate cortex; GR, gyrus rectus; OFG, orbitofrontal gyrus; TP, temporal pole; MNI, Montreal Neurological Institute; MD-aMCI, multiple-domain amnestic mild cognitive impairment; SD-aMCI, single-domain amnestic mild cognitive impairment; ALFF, amplitude of low-frequency fluctuation.
[a] The x, y, z coordinates of the primary peak locations in the MNI space.
[b] $P < .05$, corrected for multiple comparisons.

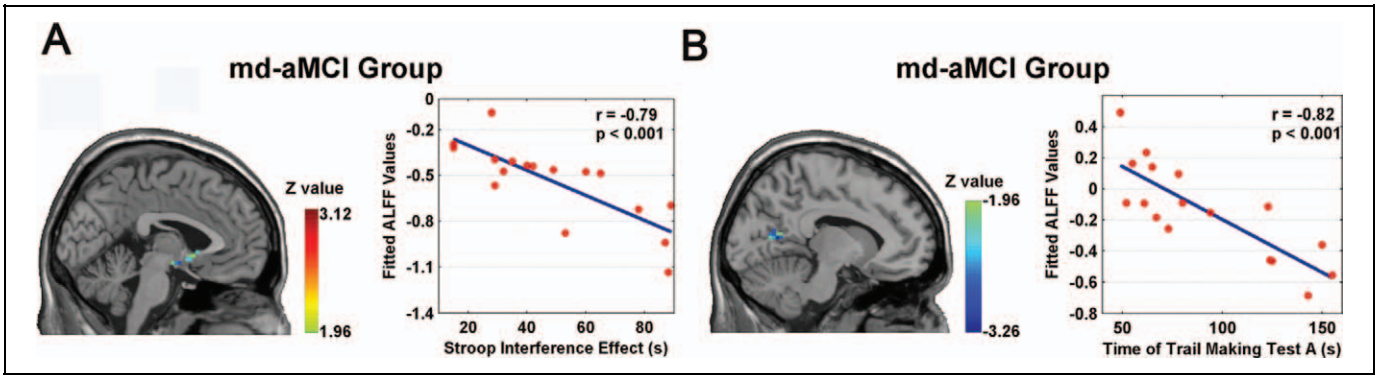

Figure 5. A, Correlation map of the ALFF with the Stroop interference effects for the MD-aMCI group. Significant negative correlations were observed in the ACC in the MD-aMCI group. B, Correlation map of the ALFF with the time of Trail Making Test A for the MD-aMCI group. Significant negative correlations were observed in the PCu/PCC in the MD-aMCI group. The statistical threshold was set at $P < .05$ and a cluster size of >708 mm^3, which corresponded to a corrected $P < .05$. ALFF indicates amplitude of low-frequency fluctuation; ACC, anterior cingulate cortex; PCu, precuneus; PCC, posterior cingulate cortex; MD-aMCI, multiple-domain amnestic mild cognitive impairment.

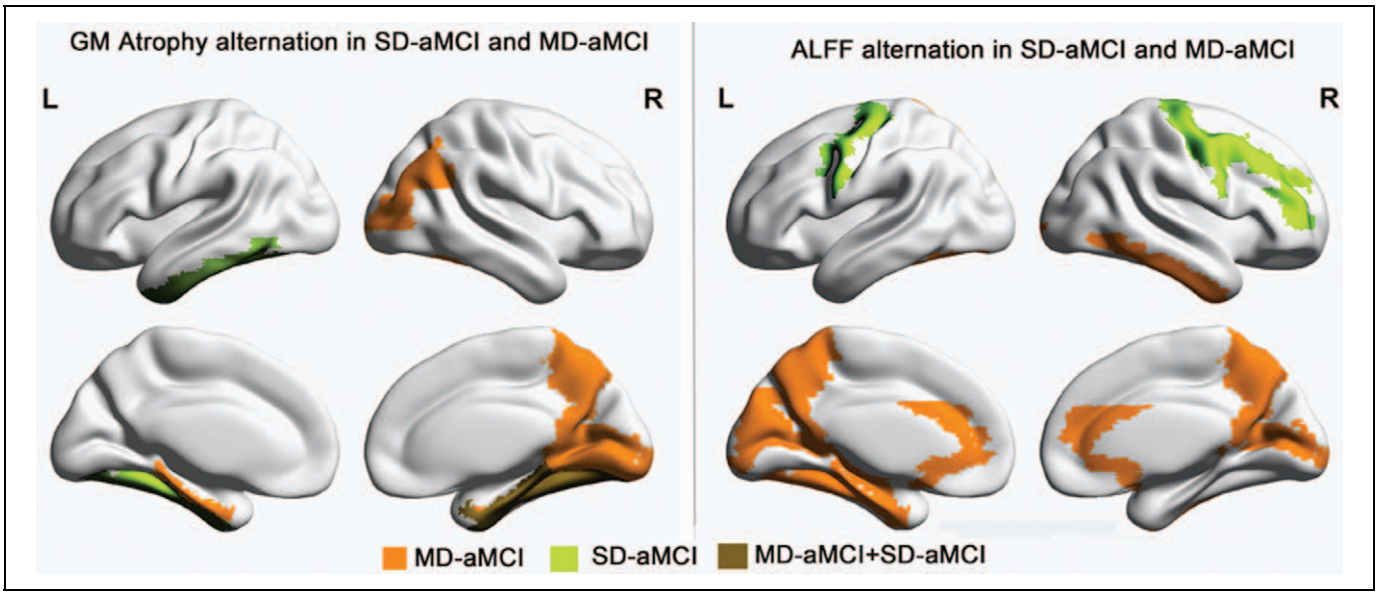

Figure 6. The schematic map of the structural and functional alterations as assessed in the aMCI subtypes. Left, Gray matter atrophy in patients with MD-aMCI (orange), in patients with SD-aMCI (green), and the overlapping regions of GM atrophy in patients with MD-aMCI and SD-aMCI (brown). Right, ALFF alteration in patients with MD-aMCI (orange) and in patients with SD-aMCI (green). aMCI indicates amnestic mild cognitive impairment; MD-aMCI, multiple-domain aMCI; SD-aMCI, single-domain aMCI; ALFF, amplitude of low-frequency fluctuation.

trend toward alterations in the PCC and PCu was consistent with our expectations. The regions are considered to be important components of human DMNs[8,44] and have been shown to exhibit AD-related structural and functional abnormalities. In patients with MD-aMCI, the deficits of brain spontaneous neuronal activity in regions of AD-related pathological change may reflect that MD-aMCI is a transition stage that may be more close to AD.

We also observed increased ALFF values of the anterior DMN, including OFG and ACC, in patients with MD-aMCI. The abnormal pattern in the anterior DMN could be interpreted as a compensatory mechanism. The increased functional activity has been proposed to be a compensatory reallocation or recruitment of cognitive resources in patients.[43,45] Yetkin et al observed that both patients with MCI and patients with AD displayed more activation than the controls in the frontal and temporal lobes.[46] In addition, He et al reported that the FG had increased functional homogeneity of spontaneous brain activity in patients with AD during the resting state.[43]

In the current study, we also examined whether the functional results could be influenced by regional GM atrophy. As noted earlier, we also observed GM atrophy in the patients with aMCI subtype and GM atrophy may lead to artificial reduction in the measured functional signals.[20] When

comparing functional differences, this issue could potentially be crucial due to the individual or group differences in the degree of regional atrophy. However, the differences in the ALFF between the MD-aMCI and NC groups remained the same after GM correction, suggesting that the changes in spontaneous brain activity in the patients with MD-aMCI were independent of brain atrophy.

Amplitude of Low-Frequency Fluctuations Alteration in SD-aMCI

We observed that ALFF maps of the individuals with SD-aMCI were very similar to those of NC participants, except in the PrCG and the MFG. However, after the GM correction, there is no significant difference between the SD-aMCI and the NC groups. These results indicate that the ALFF alterations in the brains of patients with SD-aMCI were mainly located in the central and lateral cerebral cortices (without GM correction). In contrast, the ALFF alteration in patients with MD-aMCI was mainly located in the posterior cortex (Figure 6, right).

Amplitude of Low-Frequency Fluctuations Differences Between Subtypes of aMCI

In addition, we observed that the differences in the ALFF maps of the SD-aMCI versus the MD-aMCI groups were similar to those observed when comparing the NC and MD-aMCI groups. Because of the MD-aMCI pattern of brain atrophy and spontaneous brain activity were similar to that observed in patients with mild AD,[20] we concluded that the MD-aMCI is closer to mild AD than is SD-aMCI, along the continuum from normal aging to AD. We found that ALFF-changed patterns appeared a nonlinear state. The possible reason is that there is a compensatory mechanism in patients with MCI. Many functional neuroimaging studies found that MCI showed hyperactivation in some brain regions in order to maintain intact cognitive performance[20,46,47] which is typically defined as compensation.[48]

The Relationship Between ALFF and Cognitive Performance

We observed significant negative correlations between the performance of executive function (Stroop interference effect) and the ALFF of ACC and caudate nucleus in patients with MD-aMCI, and the correlations between the performance of attention (TMT-A) times and the ALFF of the PCC/PCu were also significant. These strong correlations may imply that the ALFF values are associated with impaired functioning and have promising potential value as biomarkers for the discrimination of aMCI-related pathological change as the early stages of AD.

Structural and Functional Alterations in the DMN

Combining the voxel-based morphometry and ALFF results, we observed that in patients with MD-aMCI, the structural and functional alterations were mainly located in the Hip, PHG, PCC, and PCu. These regions are considered to be important components of human DMNs[8] and have been shown to exhibit AD-related structural and functional abnormalities in previous studies.[12,49] The DMN is particularly vulnerable to fibrillar amyloid deposition and atrophy in patients with AD and MCI.[9,50] In addition, PCC, PCu, and Hip, as the important hub regions, serve to integrate and transform diverse informational sources.[44] The deficit patterns in brains of patients with MD-aMCI reflect the more severe and diffuse cognition functional impairments.

Several limitations should be addressed in future studies. First, this study only examined local brain activity changes in patients with SD-aMCI and MD-aMCI. Exploring changes in the correlations between different brain areas should also be interesting. Moreover, this study was cross-sectional but to clearly establish a progression between the subtypes of aMCI, a longitudinal study would be essential.

In conclusion, our study indicated the heterogeneity of aMCI. Patients with MD-aMCI had more ALFF changes and more severe brain atrophy, which are similar to AD. Interestingly, the functional and structural altered regions are mainly within the DMN, which is affected by the pathology of AD. Therefore, the findings of this study support the idea that ALFF can serve as a potential image biomarker to evaluate the aMCI-related pathological change and to provide the reference for clinical diagnosis. Meanwhile, MD-aMCI may represent a more advanced prodromal stage of AD and such a state shouldn't be taken lightly in disease prevention.

Authors' Note

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Declaration of Conflicting Interests

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References

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194.
2. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58(12):1985-1992.

3. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J Intern Med*. 2004;256(3):240-246.
4. Seo SW, Im K, Lee JM, et al. Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. *Neuroimage*. 2007;36(2):289-297.
5. Caffarra P, Ghetti C, Concari L, Venneri A. Differential patterns of hypoperfusion in subtypes of mild cognitive impairment. *Open Neuroimag J*. 2008;2:20-28.
6. Deiber MP, Ibáñez V, Herrmann F, et al. Face short-term memory-related electroencephalographic patterns can differentiate multi- versus single-domain amnestic mild cognitive impairment. *J Alzheimers Dis*. 2011;26(1):157-169.
7. Shu N, Liang Y, Li H, et al. Disrupted topological organization in white matter structural networks in amnestic mild cognitive impairment: relationship to subtype. *Radiology*. 2012;265(2): 518-527.
8. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1-38.
9. Buckner RL, Snyder AZ, Shannon BJ, et al. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci*. 2005;25(34):7709-7717.
10. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128.
11. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-356.
12. Sorg C, Riedl V, Mühlau M, et al. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2007;104(47):18760-18765.
13. Hafkemeijer A, van der Grond J, Rombouts SA. Imaging the default mode network in aging and dementia. *Biochim Biophys Acta*. 2012;1822(3):431-441.
14. Petrella JR, Sheldon FC, Prince SE, Calhoun VD, Doraiswamy PM. Default mode network connectivity in stable vs progressive mild cognitive impairment. *Neurology*. 2011;76(6):511-517.
15. Bassett DS, Bullmore E. Small-world brain networks. *Neuroscientist*. 2006;12(6):512-523.
16. Zang YF, He Y, Zhu CZ, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev*. 2007;29(2):83-91.
17. Shmuel A, Leopold DA. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. *Hum Brain Mapp*. 2008;29(7):751-761.
18. Hoptman MJ, Zuo XN, Butler PD, et al. Amplitude of low-frequency oscillations in schizophrenia: a resting state fMRI study. *Schizophr Res*. 2010;117(1):13-20.
19. Yan C, Liu D, He Y, et al. Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. *PLoS One*. 2009;4(5):e5743.
20. Wang Z, Yan C, Zhao C, et al. Spatial patterns of intrinsic brain activity in mild cognitive impairment and alzheimer's disease: a resting-state functional MRI study. *Hum Brain Mapp*. 2011; 32(10):1720-1740.
21. Zhang M, Elena Y, He Y. Activities of daily living scale. *Neuroimage*. 1995;7(suppl 3):289-297.
22. Zhang M. Guideline of psychiatrical scales. *Changsha: Hum Sci Technol Press*. 1993.
23. Schmidt M. *Rey Auditory Verbal Learning Test. A Handbook*. Los Angeles: Western Psychological Services; 1996.
24. Rey A. L-examen psychologique dans les cas d'encephalopathie traumatique. *Arch Psychologie*. 1941. 1941(28):286-340.
25. Sheridan LK, Fitzgerald HE, Adams KM, et al. Normative symbol digit modalities test performance in a community-based sample. *Arch Clin Neuropsychol*. 2006;21(1):23-28.
26. Reitan R. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8(3): 271-276.
27. Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain Cogn*. 1992;18(1):70-87.
28. Edith Kaplan, Harold Goodglass, Sandra Weintraub. *Boston Naming Test*. Philadelphia: Lea & Fibier; 1983.
29. Golden C. *Stroop Color and Word Test*. Chiacago: Stoelting Company; 1978.
30. Collignon A, Maes F, Delaere D, Vandermeulen D, Suetens P, Marchal G. *Automated Multi-Modality Image Registration Based on Information Theory*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1995:263-274.
31. Ashburner J, Friston KJ. Unified Segmentation. *Neuroimage*. 2005;26(3):839-851.
32. Chao-Gan Y, Yu-Feng Z. DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Front Syst Neurosci*. 2010;4:13.
33. Busatto GF, Garrido GE, Almeida OP, et al. A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. *Neurobiol Aging*. 2003;24(2):221-231.
34. Whitwell JL, Petersen RC, Negash S, et al. Patterns of atrophy differ among specific subtypes of mild cognitive impairment. *Arch Neurol*. 2007;64(8):1130-1138.
35. Bell-McGinty S, Lopez OL, Meltzer CC, et al. Differential cortical atrophy in subgroups of mild cognitive impairment. *Arch Neurol*. 2005;62(9):1393-1397.
36. Fletcher PC, Frith CD, Baker SC, Shallice T, Frackowiak RS, Dolan RJ. The mind's eye–precuneus activation in memory-related imagery. *Neuroimage*. 1995;2(3):195-200.
37. Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van Essen DC, Corbetta M. Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *J Neurosci*. 2003;23(11):4689-4699.
38. Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. *Neuroimage*. 2008; 42(3):1178-1184.
39. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A*. 2008; 105(34):12569-12574.

40. Tondelli M, Wilcock GK, Nichelli P, De Jager CA, Jenkinson M, Zamboni G. Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. *Neurobiol Aging*. 2012; 33(4):825.e25-2e36.
41. Tosun D, Schuff N, Mathis CA, et al. Spatial patterns of brain amyloid-beta burden and atrophy rate associations in mild cognitive impairment. *Brain*. 2011;134(pt 4):1077-1088.
42. Wu X, Chen K, Yao L, et al. Assessing the reliability to detect cerebral hypometabolism in probable Alzheimer's disease and amnestic mild cognitive impairment. *J Neurosci Methods*. 2010; 192(2):277-285.
43. He Y, Wang L, Zang Y, et al. Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study. *Neuroimage*. 2007;35(2): 488-500.
44. Buckner RL, Sepulcre J, Talukdar T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci*. 2009; 29(6):1860-1873.
45. Bokde AL, Lopez-Bayo P, Meindl T, et al. Functional connectivity of the fusiform gyrus during a face-matching task in subjects with mild cognitive impairment. *Brain*. 2006;129(pt 5):1113-1124.
46. Yetkin FZ, Rosenberg RN, Weiner MF, Purdy PD, Cullum CM. FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. *Eur Radiol*. 2006;16(1): 193-206.
47. Dickerson BC, Salat DH, Greve DN, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology*. 2005;65(3):404-411.
48. Dickerson BC, Sperling RA. Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies. *Neuropsychologia*. 2008;46(6):1624-1635.
49. Wang K, Liang M, Wang L, et al. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. *Hum Brain Mapp*. 2007;28(10):967-978.
50. Van Dijk KR, Sperling RA. Defaulting on the default network: increased risk for dementia. *Neurology*. 2011;76(6):498-500.