

Spatial Patterns of Intrinsic Brain Activity in Mild Cognitive Impairment and Alzheimer's Disease: A Resting-State Functional MRI Study

Zhiqun Wang,¹ Chaogan Yan,² Cheng Zhao,¹ Zhigang Qi,¹
Weidong Zhou,³ Jie Lu,¹ Yong He,^{2*} and Kuncheng Li^{1,4*}

¹Department of Radiology, Xuanwu Hospital of Capital Medical University, Beijing 100053, China

²State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China

³Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing 100053, China

⁴Key Laboratory for Neurodegenerative Diseases, Capital Medical University, Ministry of Education, Beijing 100053, China

Abstract: We used resting-state functional MRI to investigate spatial patterns of spontaneous brain activity in 22 healthy elderly subjects, as well as 16 mild cognitive impairment (MCI) and 16 Alzheimer's disease (AD) patients. The pattern of intrinsic brain activity was measured by examining the amplitude of low-frequency fluctuations (ALFF) of blood oxygen level dependent signal during rest. There were widespread ALFF differences among the three groups throughout the frontal, temporal, and parietal cortices. Both AD and MCI patients showed decreased activity mainly in the medial parietal lobe region and lentiform nucleus, while there was increased activity in the lateral temporal regions and superior frontal and parietal regions as compared with controls. Compared with MCI, the AD patients showed decreased activity in the medial prefrontal cortex and increased activity in the superior frontal gyrus and inferior and superior temporal gyri. Specifically, the most significant ALFF differences among the groups appeared in the posterior cingulate cortex, with a reduced pattern of activity when comparing healthy controls, MCI, and AD patients. Additionally, we also showed that the regions with ALFF changes had significant correlations with the cognitive performance of patients as measured by mini-mental state examination scores. Finally, while taking gray matter volume as covariates, the ALFF results were approximately consistent with those without gray matter correction, implying that the functional analysis could not be explained by regional atrophy. Together, our results demonstrate that there is a specific pattern of ALFF in AD and MCI,

Additional Supporting Information may be found in the online version of this article.

Zhiqun Wang and Chaogan Yan contributed equally to this work.

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*Correspondence to: Yong He, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China. E-mail: yong.he@bnu.edu.cn; or Kuncheng Li, Department of Radiology, Xuanwu Hospital of Capital Medical University, Beijing 100053, China. E-mail: likuncheng@xwh.ccmu.edu.cn

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Key words: posterior cingulate cortex; resting-state; default-mode; dementia; Alzheimer's disease; mild cognitive impairment; intrinsic brain activity

INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative disease that is clinically characterized by the decline of memory and other cognitive functions. Mild cognitive impairment (MCI), the most important disease state associated with AD, refers to some level of memory loss and cognitive declines among an elderly population that does not meet the criteria for dementia. It has been reported that about 10–15% of individuals presenting with MCI progress to develop dementia annually. Previous functional brain imaging studies with positron emission tomography and single-photon emission computerized tomography have demonstrated that AD and/or MCI subjects exhibit abnormally low resting cerebral blood flow and a decreased cerebral metabolic rate for glucose in the posterior cingulate, temporal, parietal, and prefrontal cortex [Bokde et al., 2001; de Leon et al., 2001; Herholz et al., 2002; Salmon et al., 2000]. In this study, we report altered patterns of intrinsic or spontaneous brain activity in both AD and MCI affected individuals using resting-state functional magnetic resonance imaging (fMRI).

Using resting fMRI, Biswal et al. [1995] were the first to demonstrate that spontaneous low-frequency fluctuations (LFFs; <0.08 Hz) of the blood oxygen level dependent (BOLD) signal during rest were of physiological importance. It was suggested that regional spontaneous BOLD fluctuations likely reflect spontaneous neuronal activity [Biswal et al., 1995; Fransson, 2005; Kiviniemi et al., 2000]. So far, this resting-state fMRI approach has been widely applied to the examination of various neuropsychiatric diseases such as multiple sclerosis [Lowe et al., 2002], attention deficit hyperactivity disorder [Castellanos et al., 2008; Tian et al., 2006; Zang et al., 2007], schizophrenia [Garrity et al., 2007; Hoptman et al., 2010; Liang et al., 2006], and major depression [Anand et al., 2005; Greicius et al., 2007]. For a comprehensive review of resting-state fMRI, see Fox and Raichle [2007] and Greicius [2008]. Recently, this technique has been used to investigate the intrinsic or spontaneous brain activity in subjects with AD or MCI [Bai et al., 2008; Greicius et al., 2004; He et al., 2007; Li et al., 2002; Maxim et al., 2005; Sorg et al., 2007; Wang et al., 2006, 2007; Zhang et al., 2009].

Resting-State fMRI Studies in AD

In one of the first studies of resting-state fMRI in AD patients, Li et al. [2002] reported significantly decreased functional synchrony of spontaneous LFFs in the hippocam-

pus and found they decreased remarkably in AD patients. Abnormalities of regional LFFs in AD patients were also found in other brain regions such as the medial and lateral temporal lobes [Maxim et al., 2005], as well as the medial parietal lobe, including the posterior cingulate cortex/pre-cuneus (PCC/PCu) [He et al., 2007]. Using regions of interest (ROIs) based methods, several groups have reported reduced functional integrity related to the hippocampus [Allen et al., 2007; Wang et al., 2006], prefrontal regions [Wang et al., 2007], and PCC [Zhang et al., 2009] in AD patients. Using independent component analysis (ICA), Greicius et al. [2004] showed an AD-related reduction of spontaneous brain activity within a default-mode network including the PCC and medial prefrontal cortex (MPFC).

Resting-State fMRI Studies in MCI

To the best of our knowledge, there have only been three resting-state fMRI studies examining intrinsic brain activity in MCI. Li et al. [2002] were the first to report the abnormalities of intrinsic functional activity in MCI subjects. They observed a general pattern of the LFFs in the hippocampus of healthy elderly, MCI and AD subjects (healthy elderly > MCI > AD). Recently, Bai et al. [2008] found reduced PCC LFFs in MCI patients as compared with controls. Using ICA, Sorg et al. [2007] showed eight spatially consistent resting-state brain networks, and found the default-mode areas (e.g., PCC/PCu and MPFC) had markedly reduced LFFs in MCI patients. Despite fewer studies, the findings examining subjects affected by MCI are highly consistent with those of previous AD studies [Greicius et al., 2004; He et al., 2007].

Resting-state fMRI studies have provided valuable insights into the pathophysiology of AD and MCI. However, only one study has compared the patterns of intrinsic brain activity between AD and MCI subjects [Li et al., 2002], and it focused exclusively on the hippocampus. Thus, differences in the patterns of intrinsic or spontaneous brain activity between AD and MCI across the whole cortex are still poorly understood.

Here, we investigated AD and MCI-related changes in intrinsic or spontaneous brain activity by examining the regional amplitude of low-frequency BOLD fluctuations across the whole cortex. Zang et al. [2007] proposed the use of the amplitude of low frequency fluctuations (ALFF) obtained by calculating the square root of the power spectrum in a frequency range (usually 0.01–0.08 Hz) to assess the amplitude of resting-state spontaneous brain activity. Several recent resting fMRI studies in healthy subjects

TABLE I. Characteristics of the AD, MCI patients and healthy controls

Characteristics	AD	MCI	Controls	<i>P</i> value
N (M/F)	16 (8/8)	16 (7/9)	22 (7/15)	0.51 ^a
Age, years	69.56 ± 7.65	69.38 ± 7.00	66.55 ± 7.67	0.38 ^b
Education, years	10.06 ± 3.39	10.94 ± 3.40	10.00 ± 3.93	0.70 ^b
MMSE	18.50 ± 3.24	26.50 ± 1.03	28.59 ± 0.59	<0.01 ^b

MMSE, mini-mental state examination; plus-minus values are means ± S.D.

^aThe *P* value for gender distribution in the three groups was obtained by chi-square test.

^bThe *P* values were obtained by one-way analysis of variance tests.

have shown that the ALFF was able to represent different physiological states of the brain [Hoptman et al., 2010; Lui et al., 2009; Yan et al., 2009; Yang et al., 2007]. In addition, He et al. [2007] recently used a limited ROI approach to show abnormal spontaneous LFFs in the PCC of AD patients. In this study, we sought to determine the characteristic patterns of ALFF changes in both early-stage AD and MCI compared with controls, as well as the differences in ALFF between AD and MCI. Given that MCI is in the preclinical stage of AD and many previous studies have commonly reported reduced spontaneous PCC activity in both AD and MCI [Bai et al., 2008; Greicius et al., 2004; He et al., 2007; Sorg et al., 2007; Zhang et al., 2009], we hypothesized that ALFF changes within the PCC would also follow a general pattern of $ALFF_{AD} < ALFF_{MCI} < ALFF_{Healthy\ elderly}$. In addition, we also expected to find AD- or MCI-related ALFF changes in other brain regions.

MATERIALS AND METHODS

Subjects

Sixty-one right-handed subjects (19 AD, 18 MCI patients, and 24 healthy elderly) participated in this study after giving written informed consent. The AD and MCI subjects were recruited from patients who had consulted a memory clinic for memory complaints at Xuanwu Hospital, Beijing, China. The healthy elderly controls were recruited from the local community by advertisements. This study was approved by the Medical Research Ethics Committee of Xuanwu Hospital.

All AD patients underwent a complete physical and neurological examination, standard laboratory tests, and an extensive battery of neuropsychological assessments. The diagnosis of AD fulfilled the Diagnostic and Statistical Manual of Mental Disorders 4th Edition criteria for dementia [American Psychiatric Association, 1994], and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible or probable AD [McKhann et al., 1984]. The subjects were assessed with the Clinical Dementia Rating (CDR) score [Morris, 1993] as being in the early-stages of AD (7 patients with CDR = 1 and 12 patients with CDR = 0.5).

Participants with MCI had memory impairment but did not meet the criteria for dementia. The criteria for identi-

cation and classification of subjects with MCI [Petersen et al., 1999] were the following: (a) impaired memory performance on a normalized objective verbal memory delayed-recall test; (b) recent history of symptomatic worsening in memory; (c) normal or near-normal performance on global cognitive tests, including Mini-Mental State Examination (MMSE) score >24, as well as on activities described in a daily living scale; (d) global rating of 0.5 on the CDR Scale, with a score of at least 0.5 on the memory domain; (e) absence of dementia.

The criteria for healthy elderly were as follows: (1) no neurological or psychiatric disorders such as stroke, depression, epilepsy; (2) no neurological deficiencies such as visual or hearing loss; (3) no abnormal findings such as infarction or focal lesion in conventional brain MR imaging; (4) no cognitive complaints; (5) MMSE score of 28 or higher; (6) CDR score of 0.

Data from seven subjects (three AD patients, two MCI patients, and two healthy elderly) were excluded due to excessive motion (see data preprocessing). Clinical and demographic data for the remaining 54 participants are shown in Table I. There were no significant differences among the three groups in gender, age, and years of education, but the MMSE scores were significantly different ($P < 0.01$) among groups.

Data Acquisition

MRI data acquisition was performed on a SIEMENS Trio 3-Tesla scanner (Siemens, Erlangen, Germany). Foam padding and headphones were used to limit head motion and reduce scanner noise. The subjects were instructed to hold still, keep their eyes closed but not fall asleep and think of anything in particular. Functional images were collected axially by using an echo-planar imaging (EPI) sequence with the following settings: repetition time (TR)/echo time (TE)/flip angle (FA)/field of view (FOV) = 2,000 ms/40 ms/90°/24 cm, resolution = 64 × 64 matrix, slices = 28, thickness = 4 mm, voxel size = 3.75 × 3.75 × 4 mm³, gap = 1 mm, bandwidth = 2,232 Hz/pixel. The scan lasted for 478 s. All the subjects had not fallen asleep according to a simple questionnaire after the scan. Three dimensional T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sagittal images were collected by using the following parameters: TR/TE/inversion time (TI)/FA = 1,900 ms/2.2

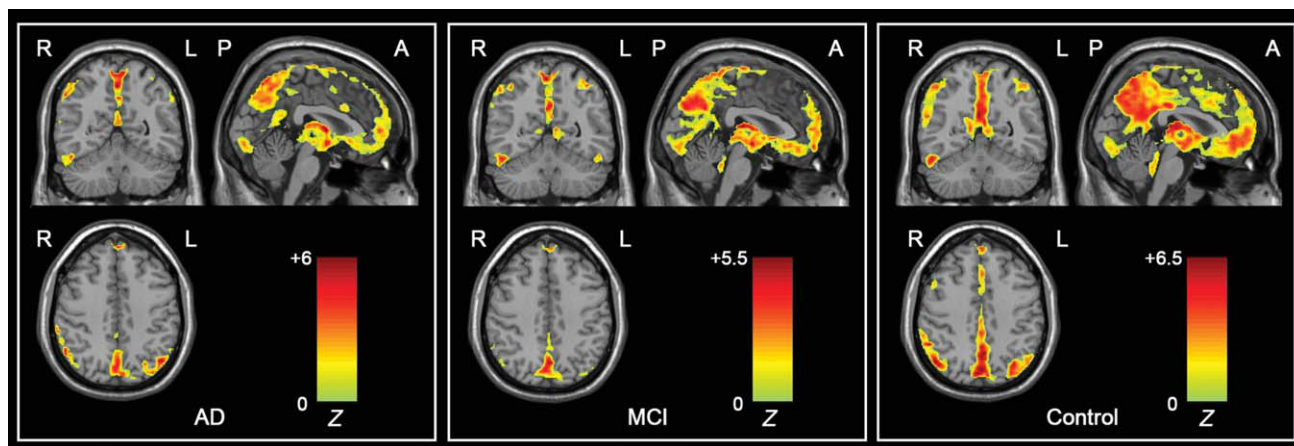


Figure 1.

Within-group ALFF maps within the AD, MCI, and healthy elderly control groups. Visual inspection indicated that the PCC and adjacent PCu had the highest ALFF values within each group and had different strengths among the three groups. The statistical threshold was set at $Z > 3.09$ ($P < 0.001$) and cluster size $> 189 \text{ mm}^3$, which corresponded to a corrected $P < 0.001$. R, right; L, left; P, posterior; A, anterior. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ms/900 ms/9°, resolution = 256×256 matrix, slices = 176, thickness = 1.0 mm, voxel size = $1 \times 1 \times 1 \text{ mm}^3$.

Data Preprocessing

Unless otherwise stated, all preprocessing were carried out using Statistical Parametric Mapping (SPM5, <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for Resting-State fMRI (DPARSF) [Yan and Zang, 2010]. The first 10 volumes of the functional images were discarded due to signal equilibrium and to allow the participants' adaptation to the scanning noise. All slices of the remaining 229 volumes were corrected for different acquisition times of signals by shifting the signal measured in each slice relative to the acquisition of the slice acquired in the middle time of each TR. Then the time-series of images of each subject were motion-corrected using a least squares approach and a six-parameter (rigid body) linear transformation [Friston et al., 1995]. Seven subjects' data (2 AD patients with CDR = 1, one AD patient with CDR = 0.5, two MCI patients and two healthy elders) were excluded from further analysis because of excessive movement ($>2 \text{ mm}$ or 2°). The individual structural image (T1-weighted MPRAGE images) was coregistered to the mean functional image after motion correction using a linear transformation [Collignon et al., 1995]. The transformed structural images were then segmented into gray matter (GM), white matter, and cerebrospinal fluid by using a unified segmentation algorithm [Ashburner and Friston, 2005]. The motion corrected functional volumes were spatially normalized to the Montreal Neurological Institute (MNI) space and resampled to 3 mm isotropic voxels using the normalization parameters estimated during unified segmentation. After this, the functional images were

spatially smoothed with a 4 mm full width at half maximum Gaussian kernel. Finally, using the Resting-State fMRI Data Analysis Toolkit (REST, <http://rest.restfmri.net>), linear trend subtraction and temporal filtering (0.01–0.08 Hz) were performed on the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise [Biswal et al., 1995; Lowe et al., 1998].

ALFF Analyses

We applied REST to calculate the ALFF, which has been described in previous studies [Yang et al., 2007; Zang et al., 2007]. Briefly, the time courses were first converted to the frequency domain using a Fast Fourier Transform. The square root of the power spectrum was computed and then averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. To reduce the global effects of variability across participants, as done in many PET studies [Raichle et al., 2001], the ALFF of each voxel was divided by the global mean ALFF value for each subject, resulting in a relative ALFF. The global mean ALFF value was calculated for each participant within a group GM mask obtained by selecting a threshold of 0.2 on the mean GM map of all 54 subjects. The relative ALFF value in a given voxel reflects the degree of its raw ALFF value relative to the average ALFF value of the whole brain.

Statistical Analyses

Within-group ALFF analysis

To explore the within-group ALFF patterns, one-sample *t*-tests (within the group GM mask) were performed on the individual ALFF maps in a voxel-wise way for each

group. The within-group statistical threshold was set at $Z > 3.09$ ($P < 0.001$) and cluster size $>189 \text{ mm}^3$, which corresponded to a corrected $P < 0.001$. This correction was confined within the group GM mask (size: $1,575,720 \text{ mm}^3$) and was determined by Monte Carlo simulations [Ledberg et al., 1998] using the AFNI AlphaSim program (<http://afni.nih.gov/afni/docpdf/AlphaSim.pdf>).

Between-group ALFF analysis

To determine the ALFF differences among the three groups, a one-way analysis of variance (ANOVA) was performed at each voxel (within the group GM mask). To examine the between-group ALFF differences, two sample t -tests were further performed between every pair of the three groups on individual ALFF maps. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $>1,404 \text{ mm}^3$ (search volume: $1,575,720 \text{ mm}^3$), which corresponded to a corrected $P < 0.05$. Likewise, the corrections were conducted using Monte Carlo simulations in AFNI.

Correlation analysis of ALFF and MMSE

To investigate the relationship between the ALFF and cognitive performance in the patients, we computed the Pearson's correlation coefficients between the ALFF and MMSE scores in the combined AD and MCI groups in a voxel-wise way. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $>1,404 \text{ mm}^3$ (search volume: $1,575,720 \text{ mm}^3$), which corresponded to a corrected $P < 0.05$.

ALFF Analysis With GM Volume as Covariates

Recent studies of fMRI have suggested that functional results could potentially be influenced by structural differences among groups [He et al., 2007; Oakes et al., 2007]. To explore the possible effect, in this study, we performed a voxel-based morphometry (VBM) analysis for structural images. Briefly, GM intensity maps in the MNI space were obtained by the unified segmentation algorithm [Ashburner and Friston, 2005] as described in the previous Data Preprocessing section. As pointed out by Ashburner and Friston [2005], unified segmentation could solve the circularity problem of registration and tissue classification in optimized VBM [Good et al., 2001]. After spatially smoothed with a 10 mm full width at half maximum Gaussian kernel, one-way ANOVA was performed on the smoothed GM intensity maps across the three groups. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $>1,404 \text{ mm}^3$ (search volume: $1,575,720 \text{ mm}^3$), which corresponded to a corrected $P < 0.05$. Furthermore, we reanalyzed the relative ALFF results (i.e., ANCOVA, two-sample t -tests and correlation analysis) by taking voxel-wise gray matter volume as covariates [Oakes et al., 2007], which was done by using REST-Statistical Analysis (written by Chaogan Yan, www.restfmri.net). The statistical threshold was also set at $|Z| > 1.96$ ($P < 0.05$) and

cluster size $>1,404 \text{ mm}^3$ (search volume: $1,575,720 \text{ mm}^3$), which corresponded to a corrected $P < 0.05$.

RESULTS

Within-Group ALFF Maps

Figure 1 shows the ALFF maps of healthy elderly, AD, and MCI groups. Visual inspection indicated that the PCC and adjacent PCu had the highest ALFF values in all groups but exhibited different strengths ($\text{ALFF}_{\text{AD}} < \text{ALFF}_{\text{MCI}} < \text{ALFF}_{\text{Healthy elderly}}$). Additionally, we also noted that several other brain regions such as the MPFC and inferior parietal lobe (IPL) also exhibited high ALFF values. The ALFF patterns were highly similar to those of the human default-mode network demonstrated in previous studies [Greicius et al., 2003; Raichle et al., 2001]. Additionally, we also observed high ALFF in several other brain regions such as the occipital areas, pre and postcentral gyri. Here these within-group maps were merely for visualizing ALFF.

Group Differences in ALFF

Figure 2A shows the one-way ANOVA analysis of the ALFF values among the three groups. Significant group differences in ALFF were observed in frontal regions, including the MPFC/orbitofrontal gyrus (OFG), supplemental motor area (SMA), superior frontal gyrus (SFG), and middle frontal gyrus (MFG), in addition to temporal regions such as the inferior temporal gyrus (ITG), superior temporal gyrus (STG), fusiform gyrus (FG), parahippocampus (PHG), and hippocampus (Hip), as well as parietal regions such as the PCC/PCu, IPL, paracentral lobule (PCL), and postcentral gyrus (PoCG). There was little difference in the occipital lobes among the groups except for a small cluster of inferior occipital gyrus (IOG). Additionally, differences were also found in several subcortical regions such as the lentiform nucleus (LN) and anterior lobe of the cerebellum (ALC). Of note, the most significant differences appeared in the PCC/PCu. See Table II for a detailed list of the regions.

Figure 3A shows ALFF differences between AD patients and healthy elderly. The most significant ALFF decreases in the AD patients were found in the PCC/PCu, while decreases were also seen in the left OFG, left LN, and right ALC. Significant ALFF increases in AD were observed in the bilateral PHG/Hip, bilateral SMA, bilateral SFG, left FG, left ITG/STG and left PoCG. See Table III for the list of these regions.

Figure 4A shows ALFF differences between the MCI patients and healthy elderly. Interestingly, the changing ALFF patterns in MCI (Fig. 4A and Table IV) were very similar to those in AD patients as described above (Fig. 3A and Table III). That is, significant decreases in ALFF were mainly located at the bilateral PCC/PCu, bilateral SFG, left MFG, left LN, and left IPL. In addition, increases in ALFF were in the bilateral SMA, bilateral PCL, bilateral SFG, left PoCG, left FG, right IOG, and right ITG.

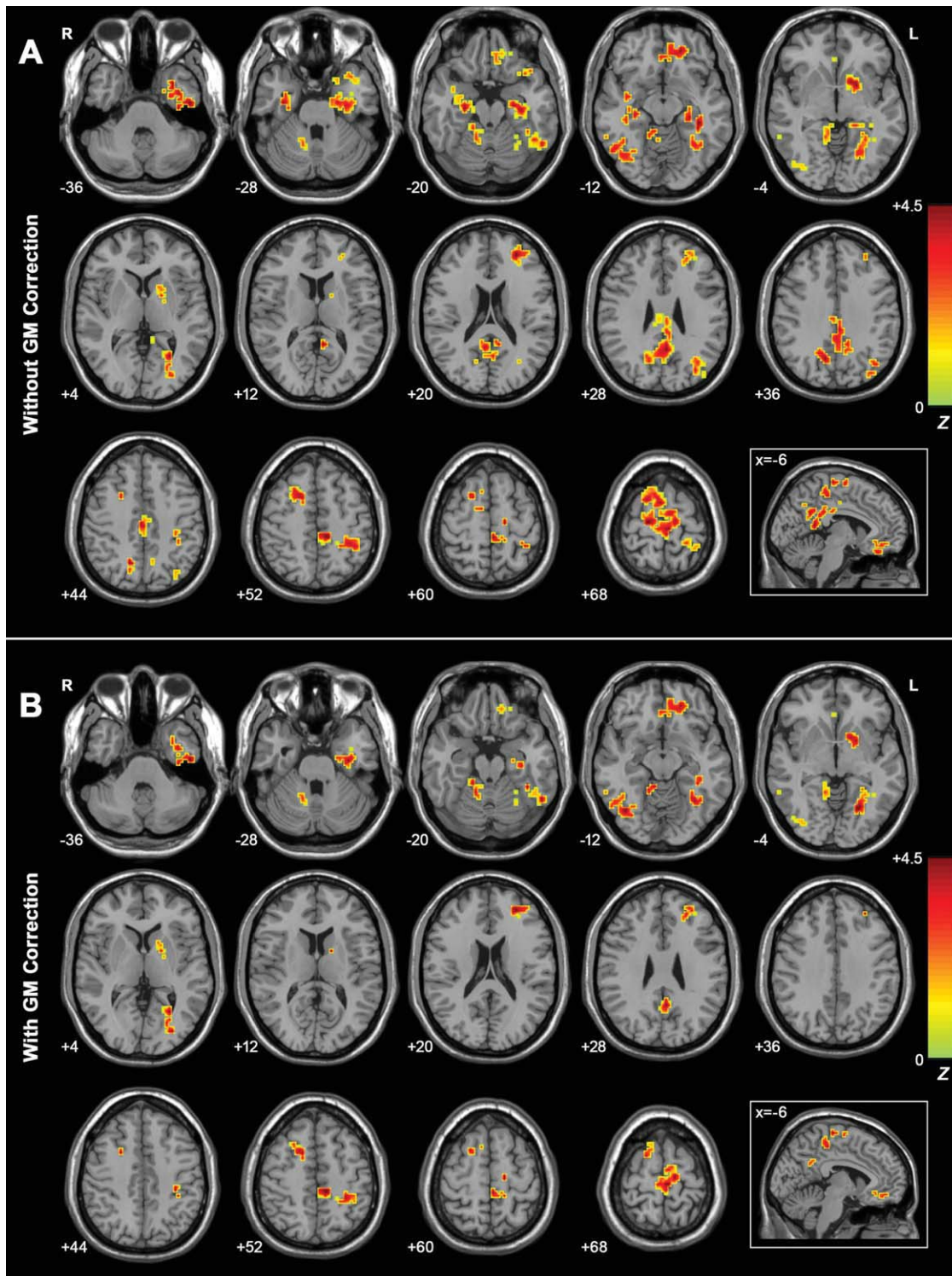


Figure 2.

A: Z-statistical maps among the AD, MCI, and healthy elderly (without GM correction). There were significant ALFF differences among the three groups in the bilateral PCC/PCu, bilateral PHG, bilateral Hip, bilateral ITG, bilateral SFG, bilateral SMA, left IPL, left LN, left FG, left STG, left PCL, left MFG, left MPFC, left OFG, left PoCG, right ALC, and right IOG. For the details of the regions, see Table II. **B:** Z-statistical maps among the AD, MCI and healthy elderly (with GM correction). There were significant ALFF differences among the three groups in the bilateral SFG, bilateral SMA, bilateral ITG, left PHG, left Hip, left STG, left FG, left PCL, left LN,

left PoCG, left MFG, left MPFC, left OFG, right ALC, and right IOG. Additionally, we also found that there was a cluster in the PCC/PCu that survived the height but not the extent threshold. For the details of the regions, see Table II. The statistical threshold was set as $|Z| > 1.96$ ($P < 0.05$) and cluster size $> 1,404 \text{ mm}^3$, which corresponded to a corrected $P < 0.05$. Of note, we showed the ANCOVA results within a mask showing significant group differences in the ANOVA analysis (Fig. 2A). R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Regions showing ALFF differences among the AD, MCI patients, and healthy controls (without and with GM correction)

Brain regions	BA	Vol (mm ³)	MNI coordinates (mm)			Maximum Z
			x	y	z	
Without GM correction						
PCC/PCu	23/31/7	8,883	12	-63	33	7.92
Left PHG/Hip/STG	35/28/22	7,398	-33	-21	-24	7.54
Left LN	N/A	1,701	-21	6	-6	6.88
Left FG/ITG	37/36/20	4,104	-27	-60	6	6.86
Right PHG/Hip	35/36	2,538	36	-12	-27	6.75
Left IPL	40	1,620	-33	-75	30	6.54
Left PCL	5	4,779	-9	-30	54	6.24
Left MFG/MPFC/OFG	10/11	2,133	-18	42	-12	5.87
Left SFG/MFG	10/11	1,890	-27	45	18	5.80
SFG/SMA	5/6	3,591	3	3	69	5.65
Right ALC	N/A	1,890	6	-36	-6	5.52
Left PoCG	40	1,944	-39	-42	51	5.51
Right IOG/ITG	19/37	2,160	39	-69	-9	4.99
With GM correction						
Left PHG/Hip/STG	35/28/22	2,484	-33	-21	-24	7.51
Left FG/ITG	37/36/20	3,537	-27	-60	6	6.83
Left PCL	5	3,267	-9	-30	54	6.41
Right IOG/ITG	19/37	1,998	39	-66	-12	6.34
Left LN	N/A	1,296	-21	6	-6	6.12
Left PoCG	40	864	-33	-27	42	6.03
Right ALC	N/A	1,620	9	-42	-12	6.01
Left MFG/MPFC/OFG	10/11	1,566	-18	42	-12	5.97
PCC/PCu ^a	23/31/7	837	-3	-51	30	5.78
SFG/SMA	5/6	1,593	15	9	51	5.57
Left SFG/MFG	10/11	1,512	-27	39	15	5.18

x, y, z, coordinates of primary peak locations in the MNI space; *Z*, statistical value of peak voxel showing ALFF differences among the three groups. ALC, anterior lobe of cerebellum; BA, Brodmann's area; FG, fusiform gyrus; Hip, hippocampus; IOG, inferior occipital gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LN, lentiform nucleus; MFG, middle frontal gyrus; MPFC, medial prefrontal cortex; N/A, not applicable; OFG, orbitofrontal gyrus; PCC/PCu, posterior cingulate cortex/precuneus; PCL, paracentral lobule; PHG, parahippocampal gyrus; PoCG, postcentral gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus. $P < 0.05$, corrected for multiple comparisons.

^aThe PCC survived the height but not the extent threshold.

However, we also noted that there were some discrepancies in the changing ALFF patterns in MCI. For instance, The ALFF values showed significant differences in the bilateral PHG/Hip and left OFG between the AD patients and healthy elderly, but were unchanged between the MCI patients and healthy elderly.

Figure 5A shows a direct comparison of the ALFF values between the AD and MCI patients. Compared with the MCI patients, the AD patients showed significantly decreased ALFF in the left MPFC/OFG and increased ALFF in the right SFG, left ITG, and left STG. (Fig. 5A, Table V).

PCC ALFF Analyses

As shown above, the PCC is the region with the most significant ALFF differences among the three groups,

which raises a possibility that the ALFF values for the PCC might serve as markers to differentiate the AD/MCI patients from healthy controls. To explore the possibility, we first calculated the mean ALFF value of each subject within a PCC mask (Fig. 6A), where the mask was composed of the bilateral posterior cingulate gyri in the automated anatomical labeling (AAL) template [Tzourio-Mazoyer et al., 2002]. Subsequently, the group differences were measured using ANOVA. As expected, the ALFF values of PCC for all groups had a pattern of $ALFF_{AD} < ALFF_{MCI} < ALFF_{healthy\ elderly}$ (Fig. 6B,C) ($F = 3.18$, $P = 0.05$), but significant differences only existed between the AD patients and healthy elderly ($t = -3.87$, $P = 0.0004$). Furthermore, we plotted receiver operating characteristic curves (ROC) to explore whether the PCC ALFF values could differentiate the patients from the healthy controls. Figure 6D shows the sensitivity and specificity of the

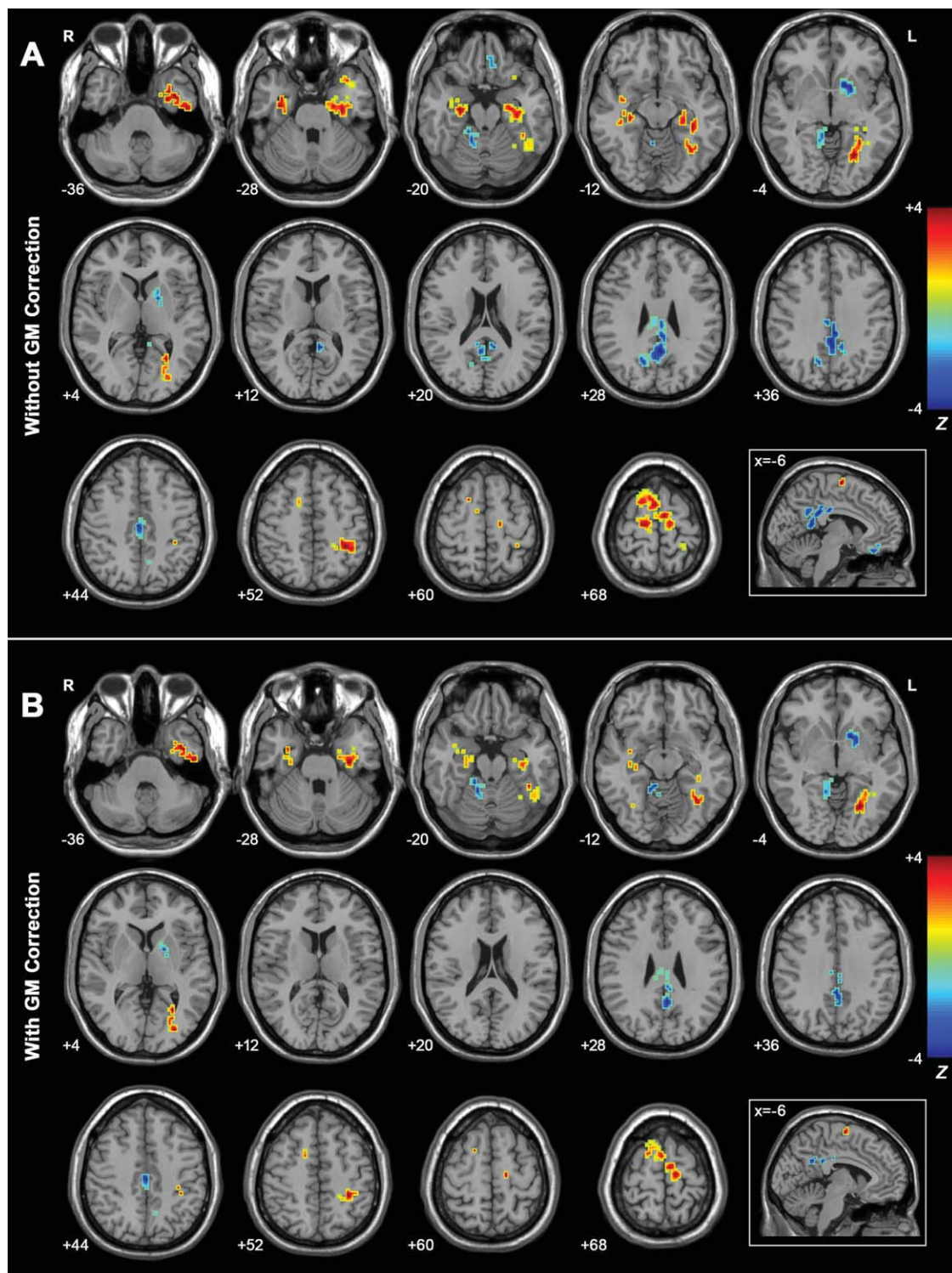


Figure 3.

A: Z-statistical difference maps between the AD patients and healthy elderly (without GM correction). The AD patients showed significantly decreased ALFF in the bilateral PCC/PCu, left LN, left OFG, and right ALC, and increased ALFF in the bilateral PHG, bilateral Hip, bilateral SFG, bilateral SMA, left FG, left PoCG, left ITG, and left STG. For the details of the regions, see Table III. **B:** Z-statistical difference maps between the AD patients and healthy elderly (with GM correction). The AD patients showed significantly decreased ALFF in the bilateral PCC/PCu, left LN, and right ALC,

and increased ALFF in the bilateral PHG, bilateral Hip, bilateral SFG, bilateral SMA, left FG, left PoCG, left ITG, and left STG. For the details of the regions, see Table III. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $> 1,404 \text{ mm}^3$, which corresponded to a corrected $P < 0.05$. Of note, we showed the two-sample t-tests results within a mask showing significant group differences in the ANOVA analysis (Fig. 2A). R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE III. Regions showing ALFF differences between the AD patients and healthy controls (without and with GM correction)

Brain regions	BA	Vol (mm ³)	MNI coordinates (mm)			Maximum Z
			x	y	z	
Without GM correction						
PCC/PCu	23/7/29	6,939	-3	-36	30	-4.24
Left LN	N/A	1,593	-21	6	-6	-3.65
Right ALC	N/A	459	15	-48	-21	-3.52
Left OFG	11	351	-6	33	-21	-2.77
Left PHG/Hip	35/36/28	3,078	-30	-18	-24	4.34
Right SFG/SMA	6	2,079	3	3	69	4.01
Left FG	37	3,321	-27	-57	0	3.95
Left SFG/SMA	6	1,053	-6	-9	66	3.81
Right PHG/Hip	35/28	1,728	30	-18	-27	3.79
Left PoCG	40	1,107	-30	-33	48	3.55
Left ITG/STG	20/22	2,835	-39	-3	-42	3.40
With GM correction						
PCC/PCu	23/7/29	1,161	-3	-51	30	-3.54
Left LN	N/A	1,161	-18	3	6	-3.43
Right ALC	N/A	1,296	15	-48	-18	-3.60
Left PHG/Hip	35/36/28	1,134	-30	-18	-24	4.20
Left FG	37	3,240	-33	-57	-15	4.09
Left PoCG	40	621	-30	-33	48	3.82
SFG/SMA	6	1,053	3	3	69	3.51
Left ITG/STG	20/22	1,350	-39	-3	-39	3.48
Right PHG/Hip	35/28	783	33	-3	-27	3.15

x, y, z, coordinates of primary peak locations in the MNI space; *Z* statistical value of peak voxel showing ALFF differences between the AD subjects and healthy elders (negative values: AD < NC; positive values: AD > NC). ALC, anterior lobe of cerebellum; BA, Brodmann's area; FG, fusiform gyrus; Hip, hippocampus; ITG, inferior temporal gyrus; LN, lentiform nucleus; N/A, not applicable; OFG, orbitofrontal gyrus; PCC/PCu, posterior cingulate cortex/precuneus; PHG, parahippocampal gyrus; PoCG, postcentral gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus. *P* < 0.05, corrected for multiple comparisons.

ALFF of PCC for the AD and control subjects. The cut-off point of the ALFF value for sensitivity and specificity evaluations was 1.02. Using this cut-off value, the ALFF of the PCC correctly classified 16 of 22 controls and 13 of 16 AD subjects, yielding a sensitivity of 81% and specificity of 73%. The area under the curve for the ROC was 0.82 (95% confidence intervals from 0.67 to 0.96), thereby indicating that the PCC ALFF values could be used as markers for the diagnosis of early AD. However, further ROC analysis revealed that the PCC ALFF values were not able to differentiate the MCI subjects from the AD or healthy subjects (data not shown).

Correlations Between the ALFF and MMSE

Figure 7A shows the correlation maps between the ALFF and MMSE scores in the combined AD and MCI groups. There were significant negative correlations found in the bilateral PHG, left ITG, and right SFG and significant positive correlations in the Left MPFC/OFG and left PCL (Fig. 7A, Table VI). Additionally, we also found that there were two clusters in the left PCC and right PCu that

survived the height but not the extent threshold (Fig. 7A, Table VI).

ALFF Analysis With GM Volume as Covariates

We performed a VBM analysis to reveal the GM volume differences among the three groups. The results showed most significant differences in the frontal, temporal, and parietal regions (see Fig. 8). While taking regional GM volume as covariates, we found that the results of ALFF (Figs. 2B, 3B, 4B, 5B, 7B and 7C. For details, see Table II–VI) were approximately consistent with those without GM correction. However, we also noted that some results were partly influenced after GM correction. For example, there was a 8,883-mm³ cluster in the PCC/PCu showing significantly group differences in ALFF (Fig. 2A) but the cluster decreased to 837 mm³ after the GM correction (Fig. 2B).

DISCUSSION

The current study investigated the AD- and MCI-related changes in the intrinsic or spontaneous brain activity by

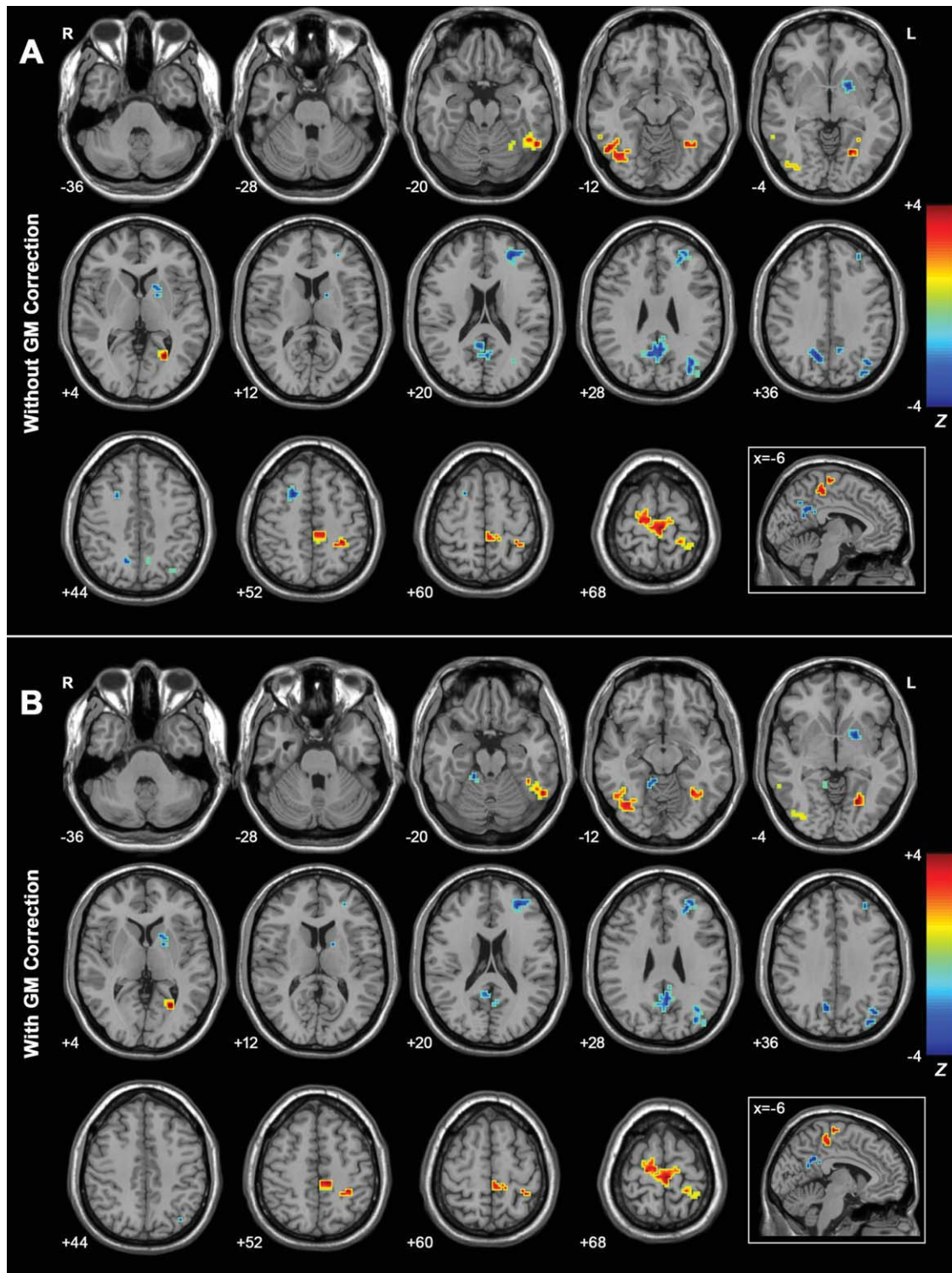


Figure 4.

A: Z-statistical difference maps between the MCI patients and healthy elderly (without GM correction). The MCI patients showed significantly decreased ALFF in the bilateral PCC/PCu, bilateral SFG, left IPL, left MFG, and left LN, and increased ALFF in the bilateral SMA, bilateral PCL, left PoCG, left FG, right IOG, and right ITG. For the details of the regions, see Table IV. **B:** Z-statistical difference maps between the MCI patients and healthy elderly (with GM correction). The MCI patients showed significantly decreased ALFF in the bilateral PCC/PCu, left MFG, left SFG, left IPL, left LN,

right ALC and increased ALFF in the bilateral SMA, bilateral PCL, left FG, left PoCG, right IOG, and right ITG. For the details of the regions, see Table IV. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $> 1,404 \text{ mm}^3$, which corresponded to a corrected $P < 0.05$. Of note, we showed the two-sample t -tests results within a mask showing significant group differences in the ANOVA analysis (Fig. 2A). R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE IV. Regions showing ALFF differences between the MCI patients and healthy controls (without and with GM correction)

Brain regions	BA	Vol (mm ³)	MNI coordinates (mm)			Maximum Z
			x	y	z	
Without GM correction						
Left IPL	39/40	1,485	-36	-75	30	-4.24
Left MFG/SFG	10/6	1,782	-27	39	15	-3.76
PCC/PCu	31/23/7	4,023	12	-60	33	-3.76
Right SFG	6	756	21	12	51	-3.36
Left LN	N/A	891	-18	6	-3	-3.09
PCL/SFG/SMA	5/6	3,537	-3	-30	66	3.58
Left PoCG	40	1,107	-30	-39	51	3.52
Left FG	37	1,458	-54	-54	-18	3.44
Right IOG/ITG	19/37	2,133	51	-60	-12	3.10
With GM correction						
Left MFG/SFG	10	1,620	-27	39	15	-3.78
Left IPL	39/40	1,161	-36	-75	30	-3.70
Right ALC	30	540	9	-42	-12	-3.36
PCC/PCu	31/23/7	1,755	12	-60	33	-3.14
Left LN	N/A	864	-18	6	-3	-3.04
Left FG	37	1,215	-30	-54	-12	4.08
PCL/SFG/SMA	5/6	3,456	-9	-30	54	3.82
Right IOG/ITG	19/37	1,971	39	-69	-9	3.76
Left PoCG	40	1,026	-30	-39	51	3.51

x, y, z, coordinates of primary peak locations in the MNI space; *Z*, statistical value of peak voxel showing ALFF differences between the MCI subjects and healthy elders (negative values: MCI < NC; positive values: MCI > NC). ALC, anterior lobe of cerebellum; BA, Brodmann's area; FG, fusiform gyrus; IOG, inferior occipital gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LN, lentiform nucleus; MFG, middle frontal gyrus; N/A, not applicable; PCC/PCu, posterior cingulate cortex/pre-cuneus; PCL, paracentral Lobule; PoCG, postcentral gyrus; SFG, superior frontal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area. $P < 0.05$, corrected for multiple comparisons.

measuring the ALFF values of resting-state fMRI signals. We found that there were widespread differences in ALFF values among the AD, MCI patients, and healthy elderly throughout the various brain regions of the frontal, temporal, and parietal lobes, as well as subcortical areas. Of these, decreased ALFF values were observed in both AD and MCI patients in the medial parietal regions (PCC and PCu) and subcortical regions (LN). In contrast, increased ALFF values were mainly observed in the lateral temporal cortex (ITG and FG), lateral parietal cortex (PoCG) and superior frontal cortex (SFG/SMA). Moreover, several brain regions also showed significant ALFF differences between the AD and MCI patients, which were mainly in the MPFC/OFG, SFG and ITG. Specifically, the most significant ALFF difference among the three groups appeared in the PCC, which followed a general pattern of $ALFF_{AD} < ALFF_{MCI} < ALFF_{healthy\ elderly}$. Further analysis revealed that the ALFF value for the PCC can be applied to differentiate AD patients from healthy controls with a high sensitivity and specificity. We also found that many brain regions with group ALFF differences showed significant correlations with the performance of cognitive function measured with MMSE. Finally, we showed that our results of ALFF still remain significant after statistically control-

ling for the regional atrophy. Our results suggest that the ALFF measurement of intrinsic or spontaneous brain activity could be useful to characterize the physiology of AD and MCI.

The Nature of ALFF

Recent resting fMRI studies have suggested that the ALFF of BOLD signals are physiologically meaningful. However, the exact biological mechanisms behind ALFF remain unclear to date. Nonetheless, several researchers have indicated that the ALFF likely reflects regional spontaneous neuronal activity. For instance, Biswal et al. [1995] found that the root mean square of the LFF in the white matter was reduced by about 60% relative to the gray matter. By simultaneously monitoring the local field potential and task-induced BOLD signal in anesthetized monkeys, Logothetis et al. [2001] found that the task-induced BOLD signal closely related to the local field potential. Shmuel and Leopold [2008] found significant correlations between the LFF and gamma band activity with simultaneous electrophysiological recordings in monkeys. Lu et al. [2007] found that the LFF was greatly associated with the delta band of electrophysiological recordings in rats. Goldman

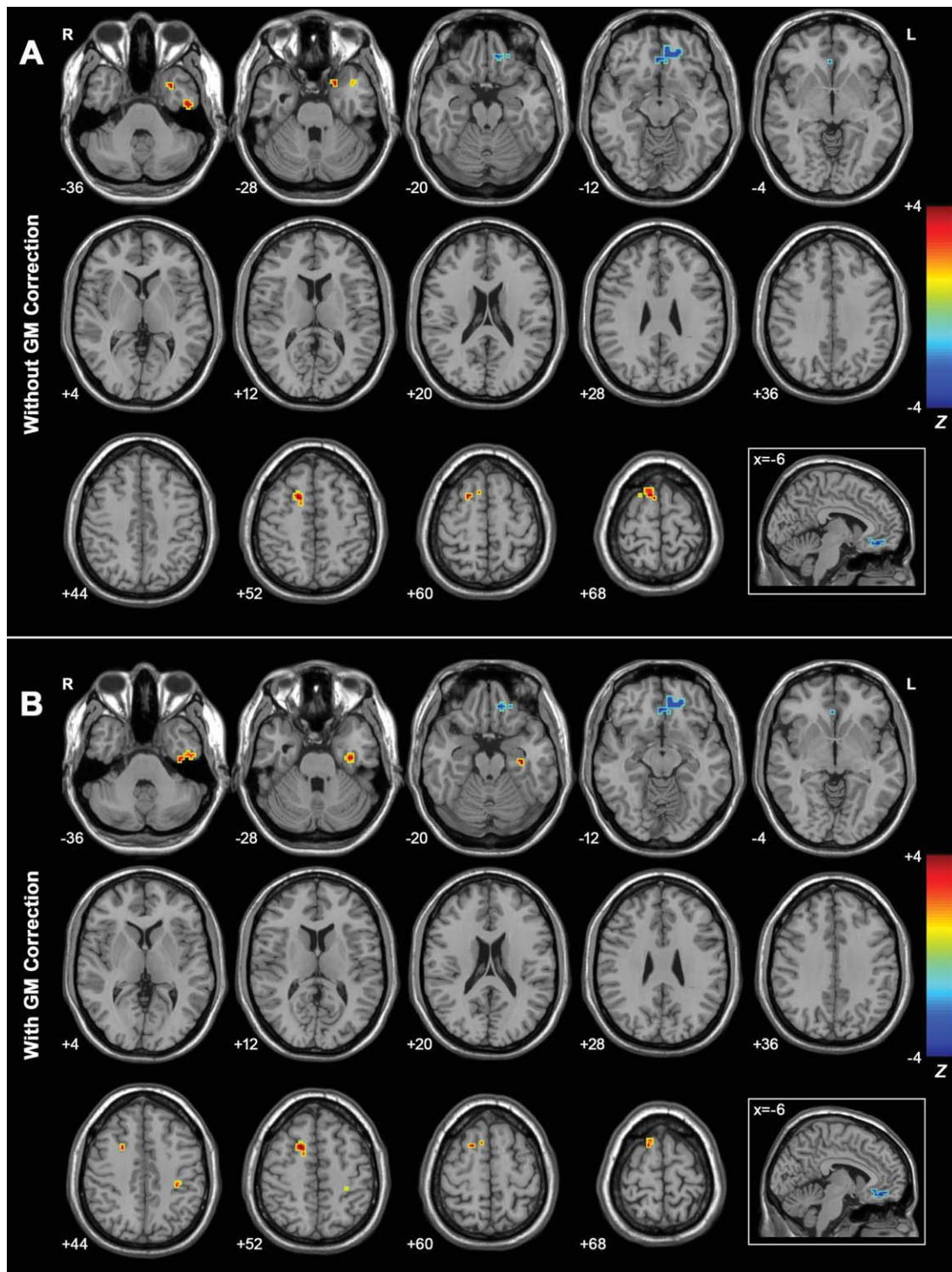


Figure 5.

A: Z-statistical difference maps between the AD and MCI patients (without GM correction). The AD patients showed significantly decreased ALFF in the left MPFC/OFG and increased ALFF in the right SFG, left ITG, and left STG. For the details of the regions, see Table V. **B:** Z-statistical difference maps between the AD and MCI patients (with GM correction). The AD patients showed significantly decreased ALFF in the left MPFC/OFG and increased ALFF in the right SFG and left ITG. For the

details of the regions, see Table V. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $> 1,404 \text{ mm}^3$, which corresponded to a corrected $P < 0.05$. Of note, we showed the two-sample t -tests results within a mask showing significant group differences in the ANOVA analysis (Fig. 2A). R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE V. Regions showing ALFF differences between the AD and MCI patients (without and with GM correction)

Brain regions	BA	Vol (mm ³)	MNI coordinates (mm)			Maximum Z
			x	y	z	
Without GM correction						
Left MPFC/OFG	11	1,404	-9	39	-18	-2.37
Right SFG	6	837	18	9	54	2.39
Right SFG	6	459	12	18	66	2.04
Left ITG	20	378	-51	-12	-39	1.83
Left STG	38	783	-39	12	-33	1.82
With GM correction						
Left MPFC/OFG	11	1,458	-9	39	-18	-2.42
Left ITG	20	1,026	-36	-15	-42	2.39
Right SFG	6	891	18	9	54	2.23
Right SFG	6	270	12	18	66	1.75

x , y , z , coordinates of primary peak locations in the MNI space; Z , statistical value of peak voxel showing ALFF differences between the AD and MCI subjects (negative values: AD < MCI; positive values: AD > MCI). BA, Brodmann's area; ITG, inferior temporal gyrus; MPFC, medial prefrontal cortex; OFG, orbit frontal gyrus; SFG, superior frontal gyrus; STG, superior temporal gyrus. $P < 0.05$, corrected for multiple comparisons.

et al. [2002] and Moosmann et al. [2003] also found the LFF in the visual cortex was closely associated with alpha band power in humans. These converging lines of evidence suggest that regional BOLD LFF signals may reflect spontaneous neural activity. By measuring the amplitude of the spontaneous activities (ALFF), several researchers have shown altered baseline brain activity in children with attention deficit hyperactivity disorder [Zang et al., 2007] and trauma survivors shortly after traumatic events [Lui et al., 2009]. Two recent resting fMRI studies also utilized ALFF to investigate the brain's spontaneous activity under eyes-open and eyes-closed conditions, and found that the activities within the visual cortex and default-mode regions were significantly different between the two conditions [Yan et al., 2009; Yang et al., 2007]. These recent studies indicate that the ALFF is physiologically meaningful for measuring intrinsic or spontaneous neuronal activity of the brain.

Decreased ALFF in AD and MCI

We found that both the AD and MCI patients showed decreased ALFF in several brain regions including the PCC, PCu, and LN compared with the healthy controls (Figs. 3A and 4A). Of these regions, the PCC showed the most significant ALFF differences among the three groups. Recent studies have suggested that the PCC is mainly involved in episodic memory processing [Buckner et al., 2008; Gusnard et al., 2001] and it is a critical node in human brain structural and functional networks [Buckner et al., 2009; Gong et al., 2009; Greicius et al., 2003; Hag-

mann et al., 2008]. Many neuroimaging studies have also consistently demonstrated that this region had structural and functional abnormalities in both AD and MCI patients, such as cortical thinning [Dickerson et al., 2009; He et al., 2008; Lerch et al., 2005; Singh et al., 2006], metabolic pathologies [de Leon et al., 2001; Salmon et al., 2000; Volkow et al., 2002], and disruptions in spontaneous or intrinsic brain activity [Bai et al., 2008; Buckner et al., 2009; Greicius et al., 2004; He et al., 2007; Sorg et al., 2007; Wang et al., 2006; Zhang et al., 2009]. Thus, our finding of decreased ALFF in AD and MCI subjects was in accordance with these previous studies. Furthermore, we observed that the ALFF activity for the PCC exhibited a general pattern of $ALFF_{AD} < ALFF_{MCI} < ALFF_{healthy\ elderly}$, which was also compatible with the notion that MCI is a transition stage between healthy elderly and AD. In this study, we noticed that there were positive correlations between the ALFF of the PCC and MMSE scores, thereby indicating that the changes in ALFF for this region were associated with cognitive performance in these patients. Specifically, while taking the ALFF values of the PCC as an index, we were able to differentiate AD patients from healthy elderly controls (with a high specificity of 73% and a high sensitivity of 81%), implying the PCC can serve as an imaging biomarker for the early diagnosis of AD.

Besides the PCC region, we also found decreased ALFF activity in the PCu of the AD and MCI patients. The PCC and adjacent PCu (i.e., medial parietal lobe regions) were often observed to show parallel structural and functional abnormalities in previous brain imaging studies of AD and MCI subjects [Buckner et al., 2005, 2009; Dickerson et al., 2009; He et al., 2008; Lustig et al., 2003; Salmon et al., 2000; Volkow et al., 2002]. Thus, our results provide further support for abnormal PCu activity in AD and MCI patients. Additionally, the LN was also found to have decreased ALFF activity in the AD and MCI patients. Although the region has been less investigated in resting fMRI studies, their structural and functional abnormalities have been demonstrated in several previous AD/MCI studies [Baron et al., 2001; Bokde et al., 2006].

Increased ALFF in AD and MCI

We also found that both AD and MCI patients showed increased ALFF in the FG, SFG, SMA, and PoCG (Figs. 3A and 4A). The FG is mainly involved in the processing of memory [Kohler et al., 1998] and facial stimuli [Allison et al., 1994; Haxby et al., 1996, 2001; Kanwisher et al., 1997]. Functional imaging studies have indicated that this region usually shows increased activity in AD/MCI patients during cognitive tasks and the resting state. For example, Prvulovic et al. [2002] observed that AD patients had increased functional activation in the FG during visuospatial processing. Bokde et al. [2006] found that MCI patients showed widespread changes in functional connectivity of FG during performance of a face-matching task. Recently, He et al. [2007] demonstrated that the FG

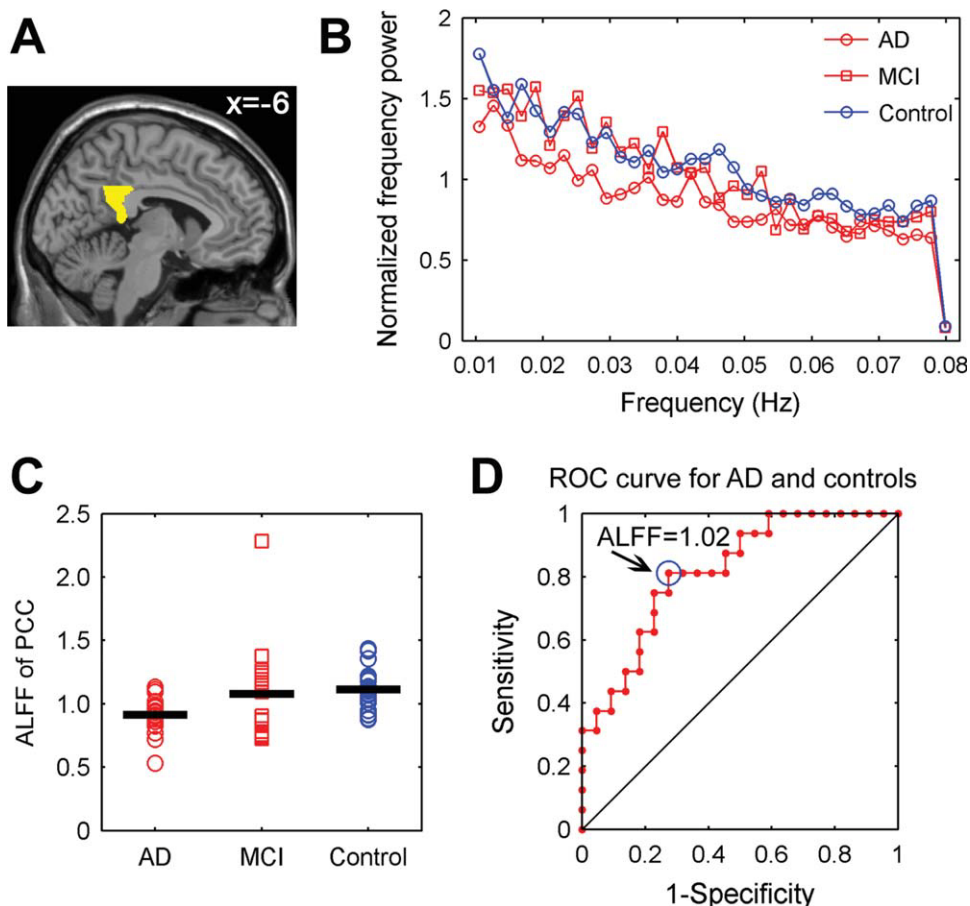


Figure 6.

The ALFF of PCC. **A:** The PCC mask extracted from the AAL template. **B:** Averaged normalized frequency power of the PCC in the AD, MCI, and healthy elderly groups. Visual examination indicated that the AD patients exhibited the lowest frequency power of PCC compared with the MCI patients and healthy controls. **C:** A scatter plot showing individual PCC ALFF in the AD, MCI, and healthy elderly groups. The group means were different among the three groups and showed a trend of $ALFF_{AD} < ALFF_{MCI} < ALFF_{healthy\ elderly}$. There were significant differences between the AD patients and healthy elderly ($t = -3.87, P = 0.0004$) but not between the AD and MCI patients ($t = -1.57, P = 0.13$), and between the MCI patients and healthy elderly ($t = -0.37, P = 0.71$). Of note, there was an outlier in the data of MCI patients according to the Dixon's test ($r = 0.66, P < 0.005$). While excluding the data of this patient, there

were still significant differences between the AD patients and healthy elderly ($t = -3.87, P = 0.0004$) but not between the AD and MCI patients ($t = -1.21, P = 0.24$), and between the MCI patients and healthy elderly ($t = -1.78, P = 0.08$). **D:** A receiver operating characteristic (ROC) curve for AD and healthy controls. The circle indicates a cutoff point of 1.02. Using this cut-off value, 13 of 16 AD subjects and 16 of 22 elderly subjects were correctly classified, yielding a sensitivity of 81% and a specificity of 73%. The area under the curve for the ROC was 0.82 (95% confidence intervals 0.67 to 0.96). Notably, the PCC ALFF index was not able to well discriminate the MCI subjects from either AD subjects or healthy controls (data not shown). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

had increased functional homogeneity of intrinsic brain activity in AD patients using resting fMRI. Thus, our results demonstrating increased ALFF in AD and MCI patients were compatible with these previous studies. Likewise, the findings of AD- and MCI-related ALFF increases in the frontal regions (SFG and SMA) were also in accordance with previous studies. For example, several groups have reported increased prefrontal activity during some cogni-

tive tasks in AD patients compared with healthy elders [Backman et al., 1999; Becker et al., 1996; Gould et al., 2006; Grady et al., 2003; Saykin et al., 1999]. AD-related increases in the functional connectivity of prefrontal regions have also been reported in several studies [Horwitz et al., 1995; Wang et al., 2006]. In a recent fMRI study, Yetkin et al. [2006] found that both AD and MCI patients had more functional activation in the SFG and FG during

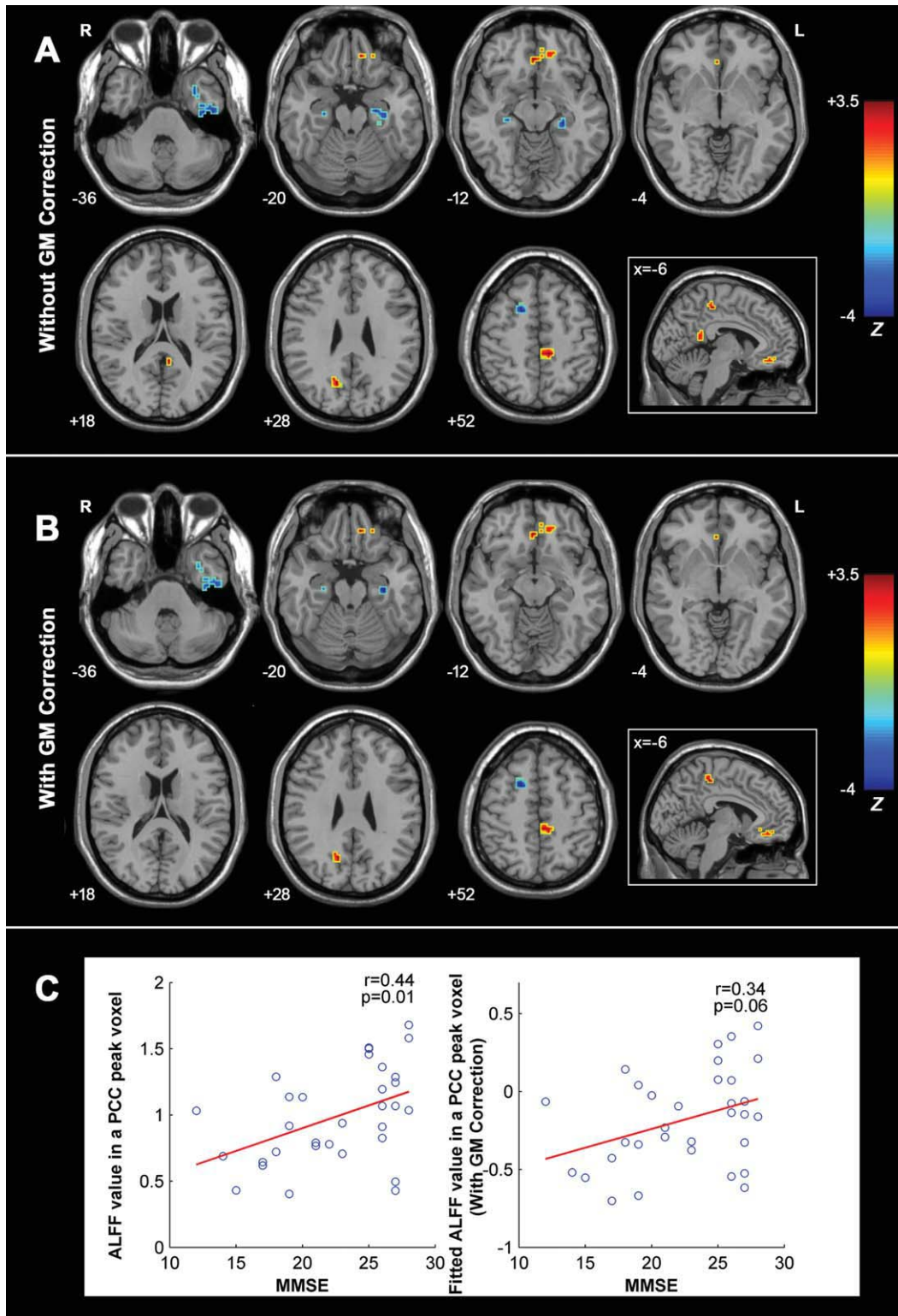


Figure 7.

A: Correlation maps of MMSE score and ALFF for the AD and MCI patients ($n = 32$) (without GM correction). Significant negative correlations were found in the bilateral PHG, left ITG, and right SFG, and positive correlations in the left MPFC/OFG and left PCL. Additionally, we also found that there were two clusters in the left PCC and right PCu that survived the height but not extent threshold. For the details of the regions, see Table VI. **B:** Correlation maps of MMSE score and ALFF for the AD and MCI patients ($n = 32$) (with GM correction). Significant negative correlations were found in the bilateral PHG, left ITG and right SFG, and positive correlations in the left MPFC and left

PCL. We also observed that there was a cluster in the right PCu that survived the height but not extent threshold. For the details of the regions, see Table VI. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $> 1,404 \text{ mm}^3$, which corresponded to a corrected $P < 0.05$. Of note, we showed the correlation results within a mask showing significant group differences in the ANOVA analysis. R, right; L, left. **C:** The scatter plots between ALFF of PCC and MMSE scores with and without GM correction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE VI. Regions showing significant correlations between ALFF and MMSE for the AD and MCI patients (without and with GM correction)

Brain regions	BA	Vol (mm ³)	MNI coordinates (mm)			Maximum Z
			x	y	z	
Without GM correction						
Left PHG/ITG	20	1,917	-36	-15	-42	-4.84
Right PHG	20	270	36	-12	-27	-4.19
Right SFG	8	1,161	21	12	57	-3.26
Left PCL	5	702	-12	-33	51	3.48
Left MPFC/OFG	11	918	-9	39	-18	3.19
Right PCu ^a	31	351	15	-66	24	2.58
Left PCC ^a	29	189	-6	-48	15	2.52
With GM correction						
Left PHG/ITG	20	1,134	-36	-15	-42	-4.76
Left PHG/ITG	20/19	351	-33	-21	-24	-3.35
Right PHG	20	135	27	-15	-24	-3.21
Right SFG	8	1,026	21	12	57	-3.14
Left MPFC/OFG	11	702	-9	39	-18	3.21
Left PCL	5	540	-6	-33	51	3.07
Right PCu ^b	31	297	15	-66	24	2.54

x, y, z, coordinates of primary peak locations in the MNI space; *Z*, statistical value of peak voxel showing significant correlations between ALFF and MMSE score in the AD and MCI subjects. Negative *Z* values indicate negative correlations between ALFF and MMSE scores, vice versa. BA, Brodmann's area; ITG, inferior temporal gyrus; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PCL, paracentral lobule; PCu, precuneus; PHG, parahippocampal gyrus; SFG, superior frontal gyrus. $P < 0.05$, corrected for multiple comparisons.

^aTwo clusters in the PCC (243 mm³) and PCu (459 mm³) survived the height but not the extent threshold.

^bThe cluster in the PCu (378 mm³) survived the height but not the extent threshold.

a working memory task as compared with controls, which was consistent with our results. The increased functional activity or functional connectivity has been proposed as a compensatory reallocation or recruitment of cognitive resources in AD/MCI patients [Bokde et al., 2006; Grady et al., 2003; He et al., 2007; Prvulovic et al., 2002]. Our findings demonstrating the negative correlations between the ALFF values of the SFG and MMSE scores provide further support for this compensatory hypothesis.

ALFF Differences Between the AD and MCI Groups

ALFF differences were also found between the AD and MCI patients (Fig. 5A). Compared with the MCI patients, the AD patients showed decreased ALFF mainly in the MPFC/OFG. The regions are considered important components of human default-mode networks [Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001] and have

been shown to exhibit AD- and MCI-related structural and functional abnormalities. Our finding of decreased ALFF in AD patients reflects a continuous breakdown of spontaneous brain activity during disease progression. In this study, we also observed that AD patients showed increased ALFF in several frontal and temporal regions (e.g., SFG, ITG, and STG) as compared with the MCI patients. These increases could be interpreted as compensatory reallocation or recruitment of cognitive resource (see the above section). It is worthy to note that a previous resting fMRI study showed increased functional connectivity between the right lateral prefrontal cortex and left hippocampus in AD patients [Wang et al., 2006]. The increased frontal activation/connectivity has been proposed as compensatory mechanisms in patients with AD. It should be noted that the analytic approach (ALFF) used in this study is very different from those applied in the previous studies. Based on these considerations, we speculate that the increases of ALFF in the AD patients could be biologically meaningful (e.g., reflect a compensatory recruitment), but it needs to be further confirmed in future studies.

ALFF Analysis with GM Correction

This study examined the ALFF changes in AD and MCI by using resting fMRI and whether the functional results could be influenced by regional GM atrophy. As we have known, AD and MCI are associated with widespread GM loss in many brain regions involving the frontal, temporal, and parietal regions [Baron et al., 2001; Buckner et al., 2005; Dickerson et al., 2009; He et al., 2008; Lerch et al., 2005]. The GM atrophy may lead to artificial reduction in measured functional signals. While comparing functional differences among the AD, MCI patients, and controls, this issue could potentially be crucial due to individual or group differences in the degree of regional atrophy. Several recent fMRI studies have attempted to clarify the relationship between regional GM atrophy and BOLD signals during the performance of tasks [Johnson et al., 2000; Oakes et al., 2007; Prvulovic et al., 2002] and the resting-state [He et al., 2007]. Most of them found that the functional results still retained statistically significant but reduced significance after GM correction. In this study, after controlling for the regional atrophy, we found that the results of ALFF were partly influenced, but the patterns were approximately consistent with those without GM correction. It implies that our results of ALFF could reflect the changes in intrinsic brain functional activities in the patients.

Further Considerations

Notably, several issues need to be further addressed. First, in this investigation all participants were instructed to close their eyes during the resting-state scans. This

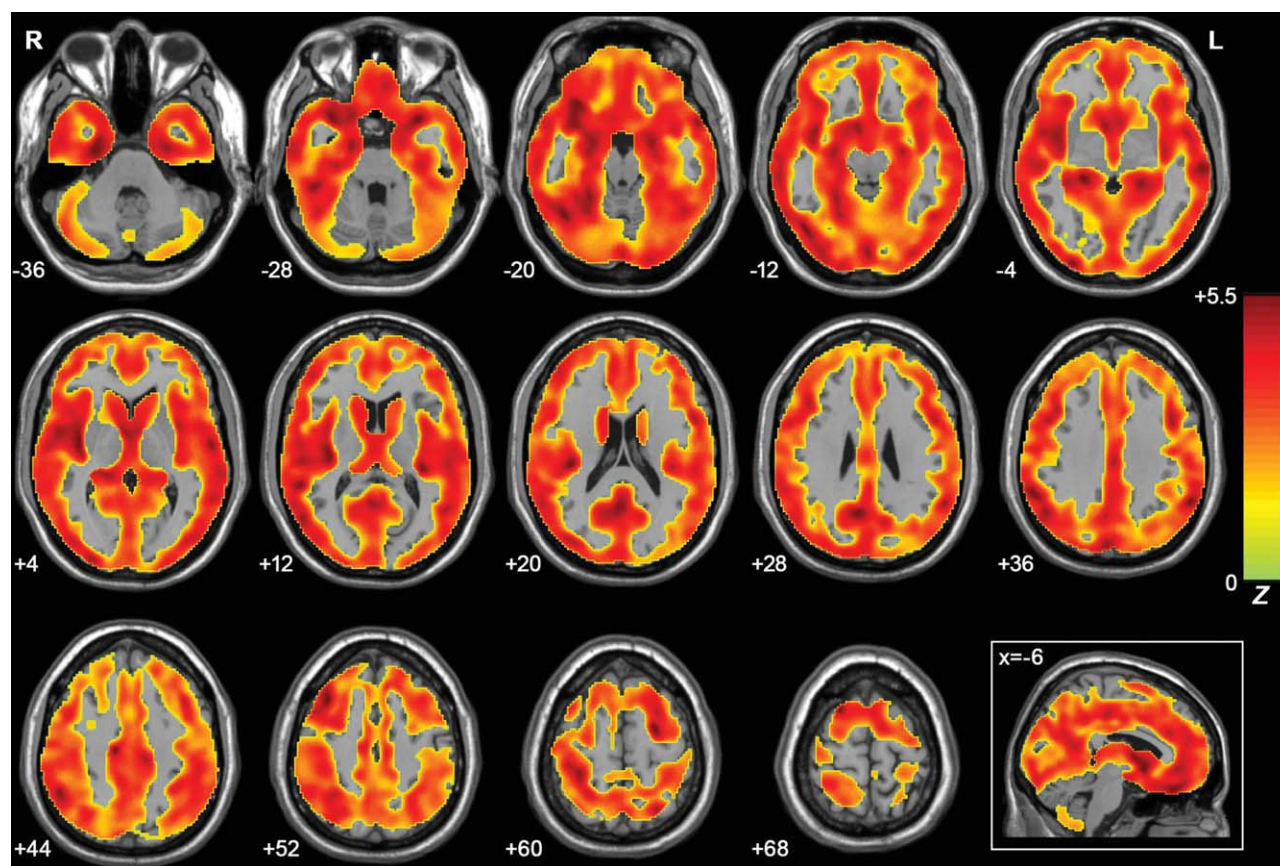


Figure 8.

Z-statistical maps of GM volume differences among the AD, MCI, and healthy elderly using a voxel-based-morphometry method. There were significant differences in the bilateral frontal, temporal, parietal, occipital lobe, and cerebellum. The statistical threshold was set at $|Z| > 1.96$ ($P < 0.05$) and cluster size $> 1,404 \text{ mm}^3$ (search volume: $1,575,720 \text{ mm}^3$), which corresponded to a corrected $P < 0.05$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

protocol has been used in many previous resting fMRI studies [Fox et al., 2005; Greicius et al., 2003; He et al., 2007; Zang et al., 2007]. However, there are also several researchers who have instructed their subjects to open their eyes during scans [Fox et al., 2005; Fransson, 2005]. Interestingly, two recent studies have reported that there were significant differences in the spontaneous brain activity between the eyes-closed and eyes-open conditions, and suggested that researchers should be cautious to choose between different resting conditions [Yan et al., 2009; Yang et al., 2007]. In future AD and MCI studies, it would be interesting to compare the results obtained under different resting-state conditions, and examine which condition could be more sensitive for detecting AD/MCI-associated changes in intrinsic brain activity. Second, the head motion of the participants may affect our results. Among the six translations and rotations parameters in x , y , or z directions, the mean z translation and roll rotation show signifi-

cant differences among the AD, MCI patients, and normal controls (Table VII). We also reanalyzed the data by taking the head-motion parameters as covariates, and found that the results remained nearly unchanged. It implies that our results of ALFF were not significantly influenced by the head motion. Third, this study compared relative ALFF changes in AD and MCI (see Methods). While analyzing raw ALFF values, we also revealed abnormal activities in many brain regions in AD and MCI (Supporting Information Fig. 1), which was approximately consistent with the relative ALFF results. Fourth, long-term physiological shifts and instrumental instability may contribute to a systematic increase or decrease in the signal with time [Lowe and Russell, 1999; Turner et al., 1997]. To reduce the effect, in this study, the linear trend was removed. In addition, the fMRI data is bandpass (0.01–0.08Hz) filtered to reduce the effects of very low frequency and high frequency physiological noise such as respiratory and aliased cardiac

TABLE VII. Head motion characteristics of the AD, MCI patients, and healthy controls

Head motion Characteristics	AD	MCI	Controls	<i>P</i> value
X translation (mm)	0.19 ± 0.16	0.14 ± 0.12	0.11 ± 0.10	0.20
Y translation (mm)	0.14 ± 0.08	0.17 ± 0.15	0.15 ± 0.12	0.78
Z translation (mm)	0.16 ± 0.08	0.27 ± 0.18	0.16 ± 0.10	0.02
Pitch (degree)	0.23 ± 0.22	0.32 ± 0.26	0.20 ± 0.21	0.26
Roll (degree)	0.24 ± 0.17	0.27 ± 0.22	0.12 ± 0.08	0.009
Yaw (degree)	0.24 ± 0.21	0.20 ± 0.14	0.13 ± 0.10	0.08

The *P* value was obtained by one-way analysis of variance test on head motion characteristics (mean absolute translation or rotation for each participant). Within the six translation and rotation parameters in *x*, *y*, or *z* directions, only the *Z* translation and roll rotation show significant (*P* < 0.05) differences among the AD, MCI, and control groups.

signals. It needs to be note that, according to the Nyquist-Shannon sampling theorem, the cardiac signals (usually 1.3Hz) can not be removed completely in the long TR (e.g., TR = 2 s) acquisition. However, it would be difficult to cover the whole brain if using a short TR (e.g., TR = 200 ms). Fifth, this study only examined the ALFF changes in AD and MCI patients. It would be interesting to ascertain whether the findings shown here are only specific to AD/MCI or might also be observed in other types of dementia such as vascular dementia, Lewy body dementia, and frontotemporal dementia. Further studies conducted on several different dementia groups would be helpful to clarify this issue. Finally, this study was cross-sectional. It has been suggested that about 50% of individuals with MCI develop AD. It would be important to explore changes in intrinsic brain activity between those who do and do not progress to AD, and to investigate longitudinal changes in MCI/AD subjects.

CONCLUSION

In this study, we found that AD and MCI patients showed abnormal ALFF in various brain regions of the frontal, temporal, and parietal lobes by examining intrinsic or spontaneous brain activity during rest. We demonstrated that the PCC showed the most significant group differences in ALFF, and the ALFF values in this region exhibited a general pattern of $ALFF_{AD} < ALFF_{MCI} < ALFF_{healthy\ elderly}$. Moreover, by using the ALFF for the PCC as an index, AD patients can be differentiated from healthy elderly with high sensitivity and specificity. Thus, this study offers insights into understanding the disease progression of the brain's intrinsic activities from healthy elderly to those with AD. In addition, our findings have implications for the understanding of the pathophysiology of dementia. Further work needs to be conducted to examine the developing progression of changes in intrinsic or

spontaneous brain activity by longitudinal studies of patients with AD and MCI.

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