NeuroImage 55 (2011) 287–295

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: A resting-state fMRI study

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ARTICLE INFO

Article history:
Received 5 August 2010
Revised 17 November 2010
Accepted 18 November 2010
Available online 28 November 2010

ABSTRACT

Here we utilized resting-state functional magnetic resonance imaging (R-fMRI) to measure the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) in 24 patients with amnestic mild cognitive impairment (aMCI) and 24 age- and sex-matched healthy controls. Two different frequency bands (slow-5: 0.01–0.027 Hz; slow-4: 0.027–0.073 Hz) were analyzed. We showed that there were widespread differences in ALFF/fALFF between the two bands in many brain regions, predominantly including the medial prefrontal cortex (MPFC), posterior cingulate cortex/precuneus (PCC/PCu), basal ganglia, and hippocampus/parahippocampal gyrus (PHG). Compared to controls, the aMCI patients had decreased ALFF/fALFF values in the PCC/PCu, MPFC, hippocampus/PHG, basal ganglia, and prefrontal regions, and increased ALFF/fALFF values mainly in several occipital and temporal regions. Specifically, we observed that the ALFF/fALFF abnormalities in the PCC/PCu, PHG, and several occipital regions were greater in the slow-5 band than in the slow-4 band. Finally, our results of functional analysis were not significantly influenced by the gray matter loss in the MCI patients, suggesting that the results reflect functional differences between groups. Together, our data suggest that aMCI patients have widespread abnormalities in intrinsic brain activity, and the abnormalities depend on the studied frequency bands of R-fMRI data.

Introduction

Mild cognitive impairment (MCI) represents the transition state between cognitive changes of the normal aging and the earlier changes associated with Alzheimer's disease (AD) (Petersen, 2003). Amnestic mild cognitive impairment (aMCI) refers to one of MCI subtypes that is characterized by primary memory deficits and has a high risk of progression to AD (Petersen et al., 2001a,b). Previous functional brain imaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) have demonstrated that aMCI patients are associated with hypoperfusion and hypometabolism in many brain regions, including the posterior cingulate cortex (PCC), precuneus (PCu), and temporal and parietal cortical regions (Anchisi et al., 2005; Chetelat et al., 2003; Hirao et al., 2005; Jagust, 2006; Johnson et al., 1998; Matsuda, 2007; Minoshima et al., 1997; Nestor et al., 2003).

Recent studies have suggested that functional brain abnormalities of aMCI can also be studied with resting-state functional MRI (R-fMRI) (Bai et al., 2009, 2008; Li et al., 2002; Qi et al., 2010; Sorg et al., 2007). As early as 1995, Biswal et al. (1995) demonstrated that the spontaneous low-frequency (typically 0.01-0.1 Hz) oscillations (LFO) of the human brain measured with R-fMRI are physiologically meaningful. Moreover, R-fMRI has the advantages of no radiation exposure (compared to PET/SPECT) and easy application (compared to conventional task-driven paradigms). Therefore, R-fMRI has been widely applied to study brain function of normal and pathological conditions (Fox and Raichle, 2007; Zhang and Raichle, 2010). Using R-fMRI, Li et al. (2002) showed for the first time, that the aMCI patients exhibited reduced intra-regional correlations of spontaneous brain activity within the hippocampus as compared to the controls. Bai et al. (2009, 2008) reported decreased intra-regional and inter-regional functional correlations (i.e., functional connectivity) in the PCC in aMCI. Two recent studies utilized R-fMRI and independent component analysis to examine spontaneous activities of multiple functional networks in aMCI and found that the patients had reduced functional connectivity between the PCC/PCu and hippocampus (Qi et al., 2010; Sorg et al., 2007). Except for these functional connectivity abnormalities, there is also evidence for local changes in resting brain function in patients with aMCI. For example, by examining the baseline T2* signal itself, Rombouts et al. (2007) showed decreased signals in the aMCI patients in the hippocampus, PCC/PCu, and basal ganglia. Despite the advances, little is known about whether the patients with aMCI show local abnormalities in the amplitudes of LFO. Previous studies have suggested that the spatial distribution of the amplitude of LFO, which is highest in the PCC/PCu and the medial prefrontal cortex, might be related to metabolic correlates of neuronal activity (Zang et al., 2007; Zhang and

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doi:10.1016/j.neuroimage.2010.11.059

Raichle, 2010). In the R-fMRI field, several research groups have explored the amplitude of LFO in healthy populations. For instance, researchers found that LFO amplitudes had significant differences between different brain tissues [e.g., gray matter (GM) and white matter (WM)] (Biswal et al., 1995), between different brain regions (e.g., visual and auditory regions) (Kiviniemi et al., 2003), and between different physiological states (e.g., eyes closed vs. eyes open) (Yan et al., 2009; Yang et al., 2007). Several groups have also showed abnormal LFO amplitudes in brain diseases such as the attention-deficit/hyperactivity disorder (Zang et al., 2007), AD (He et al., 2007), schizophrenia (Hoptman et al., 2010), and mesial temporal lobe epilepsy (Zhang et al., 2008). However, it remains largely unknown whether aMCI patients show abnormal changes in the LFO amplitudes.

The purpose of the present study was to utilize R-fMRI to examine aMCI-related changes in LFO amplitudes. Given that many previous studies have demonstrated aMCI-related changes in functional activity in the PCC (Anchisi et al., 2005; Bai et al., 2009, 2008; Chetelat et al., 2003; Del Sole et al., 2008; Hirao et al., 2005; Jagust, 2006; Matsuda, 2007; Minoshima et al., 1997; Okamura et al., 2002; Sorg et al., 2007), we hypothesized that the patients with aMCI would show abnormal LFO amplitudes in this region. However, even if abnormal LFO amplitudes were observed in aMCI, it remains largely unknown whether the abnormalities are related to specific frequency bands of LFO. To date, most R-fMRI studies have examined spontaneous LFO activities at a specific frequency band of 0.01–0.1 Hz because the frequency band was thought to be mainly linked to neuronal fluctuations (Biswal et al., 1995; Fox and Raichle, 2007; Zhang and Raichle, 2010). Nonetheless, some researchers have observed that neuronal oscillations are distributed linearly on the natural logarithmic scale and independent frequency bands are generated by distinct oscillators with specific properties and physiological functions (Buzsaki and Draguhn, 2004; Penttonen and Buzsáki, 2003). By decomposing R-fMRI LFO into four distinct frequency bands [slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz)], Zuo et al. (2010) showed that LFO amplitudes in the slow-4 band were higher than that in the slow-5 in many brain regions such as the basal ganglia, thalamus, and PCu. Additionally, Hoptman et al. (2010) showed that the patients with schizophrenia had widespread abnormalities of LFO amplitudes in the slow-4 frequency band. These studies suggest that the pattern of intrinsic brain activity is sensitive to specific frequency bands. Therefore, it would be necessary to differentiate the frequency bands to examine the LFO amplitudes in aMCI.

To address the above issues, we utilized two R-fMRI metrics to investigate changes in the amplitudes of LFO in aMCI, the amplitude of low-frequency fluctuation (ALFF) (Zang et al., 2007), and fractional ALFF (fALFF) (Zou et al., 2008). ALFF measures the total power of a given time course within a specific frequency range (e.g., 0.01 - 0.10 Hz) (Zang et al., 2007), and fALFF measures the power within a specific frequency range divided by the total power in the entire detectable frequency range (Zou et al., 2008). The two metrics have been recently applied to the R-fMRI studies of health and disease (Hoptman et al., 2010; Zhang et al., 2008). Using both ALFF and fALFF at different frequency bands (for details, see Materials and Methods), we sought to determine (i) whether the aMCI patients show abnormal LFO amplitude in the PCC and (ii) whether the abnormalities are associated with specific frequency bands.

Materials and methods

Subjects

Subjects with aMCI ($n=25$) were recruited from the memory clinic of the Neurology Department, Xuanwu Hospital, Capital Medical University, Beijing, China. At the time of the study, none of the patients were ever treated with specific medication, such as anti-acetylcholinesterase drugs. The healthy controls ($n=26$) were recruited from the local community by advertisements. All subjects were right-handed with no significant differences in age, sex and years of education between groups. All the aMCI subjects were identified according to the criteria for amnestic MCI (Petersen, 2003; Petersen et al., 2001a, 1999, 2001b), which included (a) memory complaint, preferably confirmed by an informant; (b) objective memory impairment, adjusted for age and education; (c) normal or near-normal performance on general cognitive functioning and no or minimum impairment of daily life activities; (d) the Clinical Dementia Rating (CDR) score of 0.5; and (e) not meeting the criteria for dementia according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4rd edition, revised). Patients with aMCI were diagnosed by experienced neurologists. Subjects were excluded if they met the following clinical characteristics: (a) those who have a clear history of stroke; (b) severe depression that led to mild cognitive impairment (Hamilton Depression Rating Scale score>24 points); (c) other nervous system diseases, which can cause cognitive impairment (such as brain tumors, Parkinson's disease, encephalitis, and epilepsy); (d) cognitive impairment caused by traumatic brain injury; (e) other systemic diseases, which can cause cognitive impairment, such as thyroid dysfunction, severe anemia, syphilis, and HIV; and (f) a history of psychosis or congenital mental growth retardation. All of subjects were evaluated by using a standardized clinical evaluation protocol, which included mini-mental state exam (MMSE), Clock Drawing Test (CDT), Auditory Verbal Learning Test (AVLT), Activity of Daily Living (ADL), Hachinski Ischemic Scaling (HIS), Hamilton Depression Scale (HAMD), and Clinical Dementia Rating Scale (CDR). Of note, data from one normal control was considered an outlier to exclude from further analysis because of a high HAMD score of 16 (see Table 1). Data from two subjects (one MCI and one control) were excluded from further analysis due to excessive head motion (see Methods). Table 1 presents the details of demographics and clinical characteristics of the remaining subjects.

Table 1
Demographics and clinical characteristics of the subjects.

	NC	aMCI	*P* value
Gender (male/female)	12/12	9/15	0.383[a]
Age (years)	50–79 (64.7 ± 8.9)	41–81 (65.1 ± 10.5)	0.871[b]
Education (years)	0–22 (12.5 ± 5.3)	2–20 (11.1 ± 3.8)	0.295[b]
MMSE	20–30 (29.0 ± 2.1)	18–30 (24.4 ± 2.7)	$<10^{-7}$[b]
CDT	1–3 (2.9 ± 0.3)	1–3 (2.4 ± 0.8)	0.007[b]
HIS	0 (0 ± 0)	0–2 (0.1 ± 0.4)	0.328[b]
ADL	20 (20 ± 0)	20–33 (22.1 ± 3.0)	0.003[b]
Hamilton[c]	0–7 (1.0 ± 2.0)	0–11 (4.2 ± 3.4)	$<10^{-3}$[b]
CDR	0 (0 + 0)	0.5 (0.5 ± 0)	0[b]
AVLT—immediate recall	6.3–14.7 (9.5 ± 2.3)	2.7–8.7 (5.0 ± 1.5)	$<10^{-9}$[b]
AVLT—delayed recall	7–15 (11.5 ± 2.4)	0–14 (4.8 ± 3.1)	$<10^{-9}$[b]
AVLT—recognition	7–15 (13.0 ± 1.6)	1–14 (8.3 ± 3.5)	$<10^{-6}$[b]

Data are presented as the range of min–max (mean ± SD). aMCI, amnestic mild cognitive impairment; NC, normal controls; MMSE, Mini-Mental State Examination; CDT, Clock Drawing Test; HIS, Hachinski Ischemic Scaling; ADL, Activities of Daily Living; HAMD, Hamilton Depression Scale; CDR, Clinical Dementia Rating Scale; AVLT, Auditory Verbal Learning Test.

[a] The *P* value was obtained by a two-tail Pearson chi-square test.

[b] The *P* value was obtained by a two-sample two-tail *t* test.

[c] Note that one control subject was excluded from imaging analysis because of the outlier in HAMD score (HAMD = 16) in terms of the criteria of beyond 2.5 interquartile range from lower (0)/upper (2) quartile value of the samples.

This study was approved by the medical research ethics committee and institutional review board of Xuanwu Hospital, and informed consent was obtained from each subject.

Data acquisition

All participants were scanned on a 3.0 T Siemens scanner at Xuanwu Hospital, Capital Medical University within a single session. Resting-state functional images were collected using an echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms; echo time (TE) = 40 ms; flip angle = 90°; number of slices = 28; slice thickness = 4 mm; gap = 1 mm; voxel size = 4 × 4 × 4 mm^3; and matrix = 64 × 64. Participants were asked to lie quietly in the scanner with their eyes closed during the data acquisition. This scan lasted for 478 s. For each subject, the first five volumes were discarded to allow for T1 equilibration effects and the adaptation of the subjects to the circumstances, leaving 234 images for further analysis. In addition, 3D T1 scans and diffusion images were also collected for each participant but not used in the current study.

Functional image analysis

Image preprocessing

Data preprocessing was carried out using the SPM5 package (http://www.fil.ion.ucl.ac.uk/spm). First, all functional images were corrected for intra-volume acquisition time delay between slices and inter-volume geometrical displacement due to head movement. One patient and one normal control were excluded according to the criteria that head motion was restricted to less than 2 mm of displacement or 2 degrees of rotation in any direction. Then all functional data were normalized to the Montreal Neurological Institute (MNI) space by applying the transformation parameters obtained from the structural images (see the following "structural image analysis" section for details) to those time- and motion-corrected images. Of note, a modified procedure was proposed to correct for geometrical distortions of fMRI images, which could improve normalization accuracy (Villain et al., 2010). The resultant normalized functional images underwent spatial smoothing [6-mm full width at half maximum (FWHM) Gaussian kernel] and removal of linear trends (which was done by computing the least-squares fit of a straight line to each voxel's time series and subtracting the resulting function from the time series). No temporal filtering was implemented during preprocessing so that the entire frequency band below the Nyquist frequency [which represents the bandwidth of a sampled signal and is equal to half the sampling frequency of that signal. Here it is (1/2)*(1/TR) = 0.25 Hz] (Nyquist, 1928) can be examined in subsequent analyses of LFO amplitude.

ALFF and fALFF calculation

ALFF/fALFF was calculated using REST software (www.restfmri.net). Briefly, for a given voxel, the time series was first converted to the frequency domain using a Fast Fourier Transform. The square root of the power spectrum was computed and then averaged across a predefined frequency interval. This averaged square root was termed ALFF at the given voxel (Zang et al., 2007). Fractional ALFF (fALFF) is the fraction of ALFF in a given frequency band to the ALFF over the entire frequency range detectable in the given signal (Zou et al., 2008). The two indices reflect different aspects of LFO amplitude: ALFF measures the absolute strength or intensity of LFO, whereas fALFF represents the relative contribution of LFO within a specific frequency band to the whole detectable frequency range. We divided the full frequency range (0–0.25 Hz) into five different bands: [slow-6 (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz)] (Buzsaki and Draguhn, 2004; Hoptman et al., 2010; Zuo et al., 2010), and computed ALFF/fALFF at the slow-5 and slow-4 bands. The signals of slow-6, slow-3, and slow-2 were discarded because they mainly reflect very low frequency drift, WM signals, and high-frequency physiological noises, respectively (Biswal et al., 1995; Zuo et al., 2010). Under the studied frequency ranges, ALFF/fALFF of each voxel was computed for each participant, and it was further divided by the global mean value to reduce the global effects of variability across participants (Zang et al., 2007). Of note, all the ALFF/fALFF computations were restricted in the mask where the mean GM intensity across all subjects were larger than 0.15 (for details, see the following "structural image analysis" section).

Structural image analysis

Previous studies have demonstrated that patients with aMCI had GM loss in the medial temporal lobe region and some regions of the frontal and the parietal cortices (Chetelat et al., 2002; Karas et al., 2008; Singh et al., 2006). The loss of GM in aMCI may have potential effects on the functional results. To identify the brain regions with GM loss, in the present study we first performed a voxel-based morphometry (VBM) analysis for structural images (http://www.fil.ion.ucl.ac.uk/spm). Briefly, individual structural images (3D T1-weighted anatomical images) were coregistered to the mean functional images after motion correction using a linear transformation (Collignon et al., 1995). The transformed structural images were then segmented and spatially normalized into GM, WM, and cerebrospinal fluid in the MNI space by using a unified segmentation algorithm (Ashburner and Friston, 2005). Individual GM maps were further modulated to compensate for the effect of spatial normalization using a linear and nonlinear method. The GM images underwent a spatial smoothing using 6-mm full width at half maximum (FWHM) Gaussian kernel. The resultant images were used to identify the brain regions with GM loss. Moreover, these maps were also entered into the following statistical analysis to examine the effects of GM atrophy on the functional results. In the study, we utilized the mean GM map (threshold = 0.15) to generate a group-based GM mask and used this mask for analyzing ALFF/fALFF differences between the two groups.

Statistical analysis

To determine the effects of group and frequency band on ALFF/fALFF, we performed a two-way repeated-measures analysis of variance (ANOVA) on a voxel-by-voxel basis with group (MCI patients and healthy controls) as a between-subject factor and frequency band (slow-4 and slow-5) as a repeated-measures. To determine the pattern of GM loss in the aMCI patients, we performed a voxel-based two-sample *t* test on the smoothed GM intensity maps. To further analyze the effects of GM atrophy on functional results, we performed a two-way repeated-measures ANOVA in which the GM intensity maps were entered as covariates. All the statistical maps were corrected for multiple comparisons to a significant level of $P<0.05$ by combining the individual voxel P value <0.05 with cluster size >3591 mm^3 based on using Monte Carlo simulations (Ledberg et al., 1998). For those clusters showing significant main effects and interaction between group and frequency band, post-hoc two-sample *t* tests were further performed.

Results

ALFF/fALFF analysis

ALFF

Main effects from the two-way repeated-measures ANOVA are shown in Figs. 1 and 2. Brain regions showing a significant main effect for frequency band were identified in the anterior medial prefrontal cortex (aMPFC)/anterior cingulate cortex (ACC), PCC/PCu, inferior

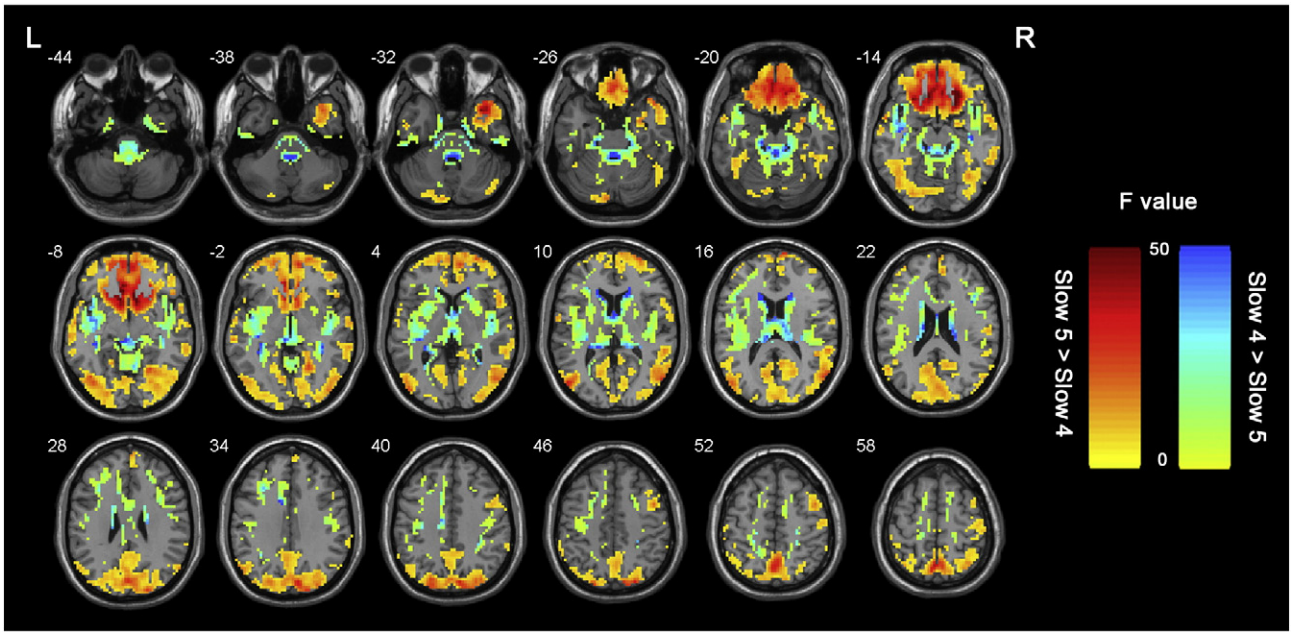

Fig. 1. The main effect for frequency band on ALFF. Most of the brain showed significant differences in ALFF between the two frequency bands (slow-4 vs. slow-5). Hot color represents greater ALFF in the slow-5 band than in the slow-4 band, whereas blue color represents lower ALFF. The results were obtained by a two-way repeated-measures ANOVA. Of note, the results are very similar with fALFF. For details, see the Methods.

parietal lobe (IPL), occipital (Fig. 1, slow-5>slow-4), basal ganglia, hippocampus/parahippocampal gyrus (PHG), insula, brain stem and lateral frontal regions (Fig. 1, slow-5<slow-4) in a bilateral fashion. Of note, the brain regions with higher ALFF values in the slow-5 band showed a large overlap with the components of default-mode networks (Greicius et al., 2003; Raichle et al., 2001). Fig. 2 shows brain regions with a main effect of group, including the PCC/PCu, orbital frontal gyrus, MPFC/ACC, the left inferior temporal gyrus, the left inferior and middle frontal gyri, the bilateral insula (Fig. 2, MCI patients<controls), the bilateral lingual gyrus/fusiform gyrus/calcarine cortex, and the right superior temporal gyrus (Fig. 2, MCI patients>controls). We observed significant interaction between frequency band and group in the PCC/PCu, the right PHG, and some regions of occipital and parietal cortices (Fig. 3). Further post-hoc t test reveals that the group differences in fALFF in the slow-5 band were greater than those in the slow-4 (Fig. 3).

fALFF

The pattern of the main effect for frequency band (Fig. S1) was very similar to that in ALFF (Fig. 1). Brain regions with a main effect of group included the PCC/PCu, the right hippocampus/PHG/basal ganglia (Fig. 4, MCI patients<controls), the bilateral lingual gyrus/calcarine cortex/

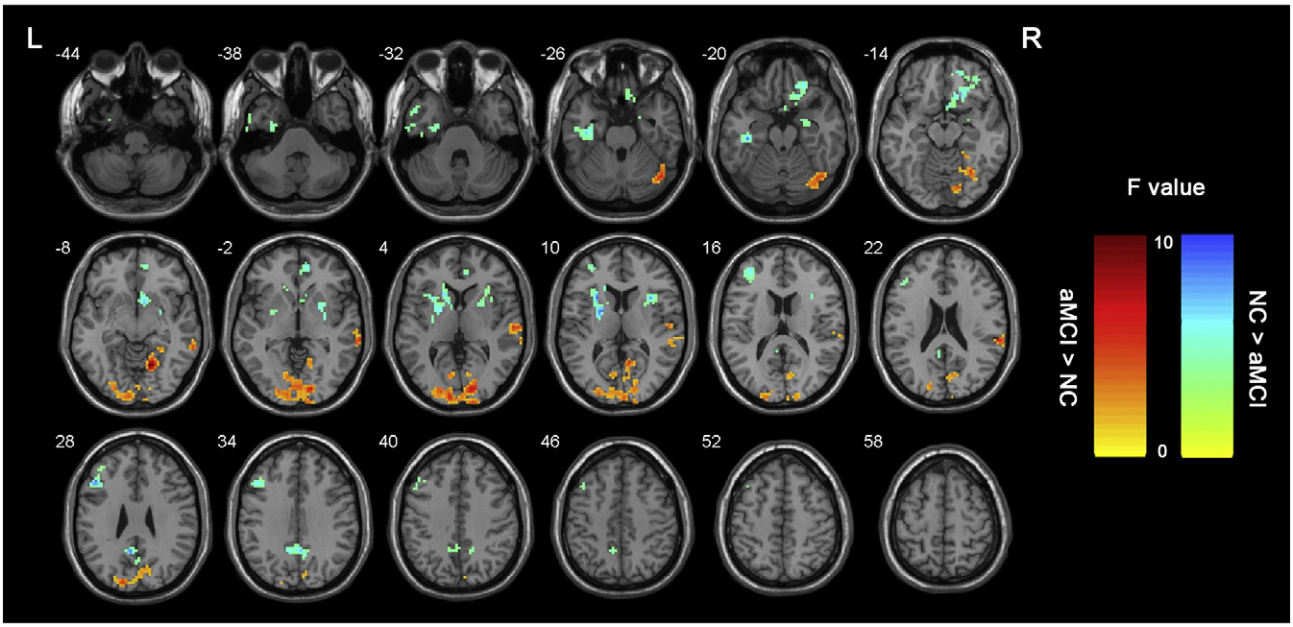

Fig. 2. The main effect for group on ALFF. Hot color represents higher ALFF in the aMCI group than in the control group, whereas blue color represents lower ALFF. The results were obtained by a two-way repeated-measures ANOVA. Of note, we showed a 3456-mm^3 cluster in the PCC/PCu that survived the height but not the extent threshold. For details, see the Methods.

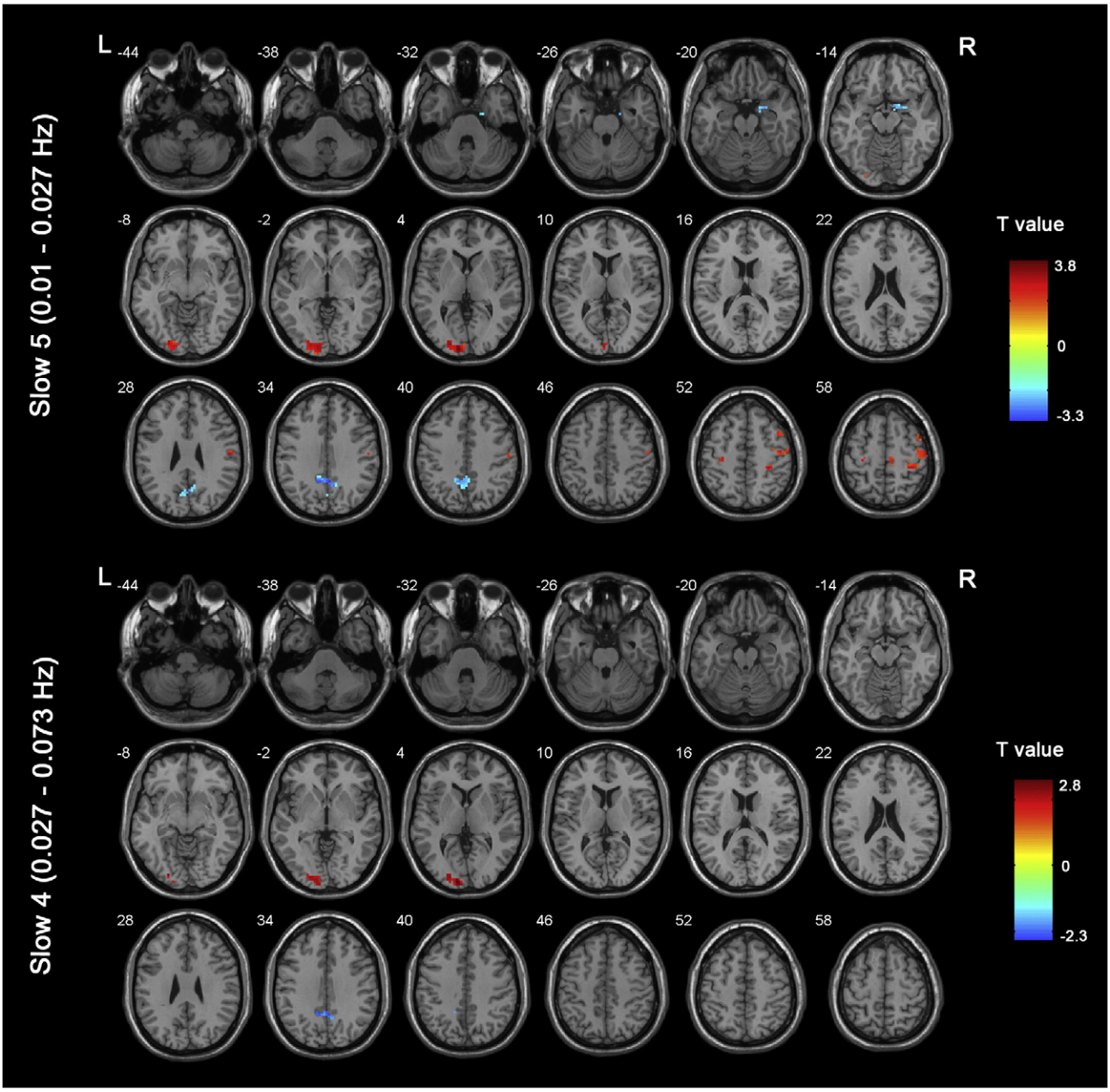

Fig. 3. The interaction between frequency band and group on ALFF. The results were obtained by a two-way repeated-measures ANOVA and a post-hoc test. Of note, there were greater ALFF decreases in PCC in patients with MCI for slow band 5 compared to slow band 4, which reflects the results of the interaction of group and frequency band. For details, see the Methods.

fusiform gyrus, and the left precentral gyrus/poscentral gyrus (Fig. 4, MCI patients>controls). We observed significant interaction between frequency band and group in the left angular gyrus and some regions of occipital and parietal cortices (Fig. 5). Further post-hoc *t* test reveals that the group differences in fALFF in the slow-5 band were greater than those in the slow-4 (Fig. 5).

VBM analysis

Compared with the controls, the aMCI patients exhibited significant GM loss in many brain regions, including the hippocampus/PHG, anterior and posterior cingulate cortices, insula, cerebellum and some regions of frontal and parietal cortices (Fig. 6). The results are consistent with previous studies in MCI (Chetelat et al., 2002; Karas et al., 2008; Singh et al., 2006).

ALFF/fALFF analysis with GM correction

After correcting for the effects of GM volume, we found that the results were similar to those without the corrections (Supplemental Figs. S2–S7). Of note, the GM correction processing partly reduced the significance of group differences. For example, the PCC/PCu shows between-group differences in a cluster size of 3456 mm^3, which were reduced to 3186 mm^3 after the GM correction.

Discussion

In the current study, we examined changes in LFO amplitude (i.e., ALFF and fALFF) in the patients with aMCI at two different frequency bands (slow-4 and slow-5 bands). We found that many brain regions showed significant differences in ALFF/fALFF between slow-4 and slow-5 bands and between the aMCI patients and controls.

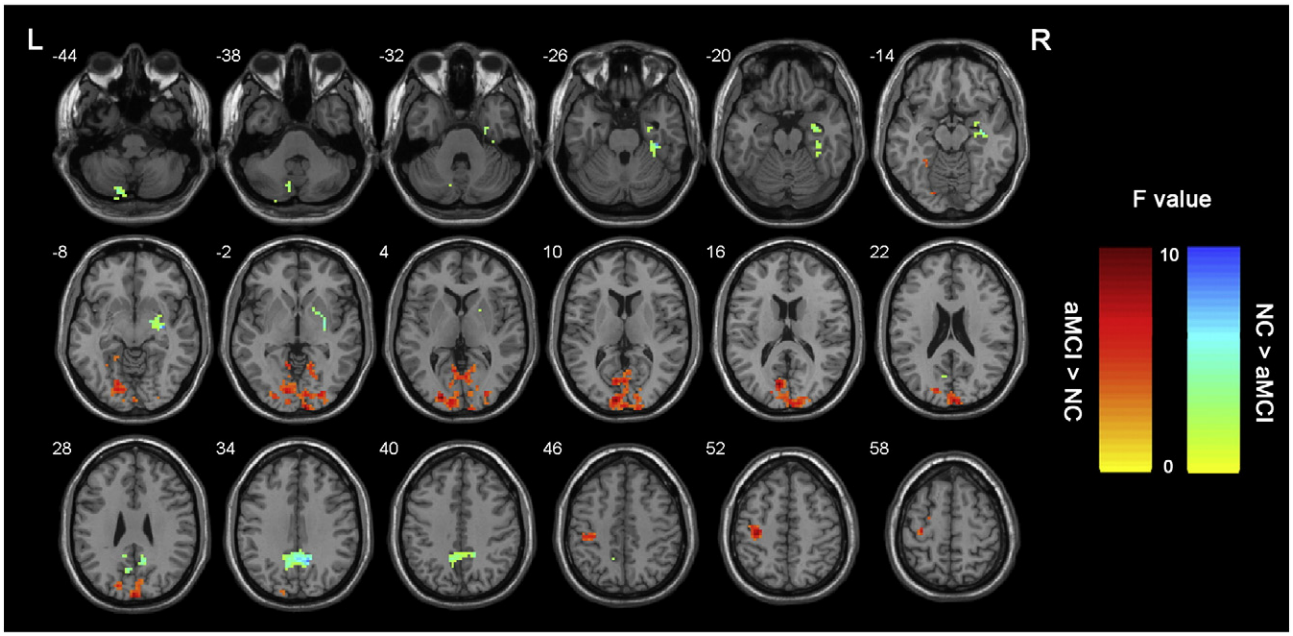

Fig. 4. The main effect for group on fALFF. Hot color represents higher fALFF in the aMCI group than in the control group, whereas blue color represents lower fALFF. The results were obtained by a two-way repeated-measures ANOVA. For details, see the Methods.

Interestingly, we found that several brain regions (the PCC/PCu, PHG and several occipital and frontal regions) showed significant interaction between frequency band and group, with greater group differences in the slow-5 band than in the slow-4 band. Our results suggest that the aMCI patients had abnormal LFO amplitude in intrinsic brain activity and that the abnormalities are associated with specific frequency bands.

Differences in ALFF/fALFF between frequency bands

In this study, we found that there were significant differences in ALFF/fALFF between two different frequency bands (slow-4 vs. slow-5). Several default-mode regions (the PCC/PCu, MPFC and IPL) showed greater ALFF/fALFF in the slow-5 band than in the slow-4 band. Many previous studies have demonstrated that these regions constitute a structurally and functionally connected neuronal network that supports the default function of the human brain (Greicius et al., 2003; Raichle et al., 2001). Previous studies have suggested that lower frequency oscillations allow for an integration of neuronal networks (Buzsaki and Draguhn, 2004; Penttonen and Buzsáki, 2003). This notion is compatible with our results of greater brain activity in the default-mode network in the lower slow-5 band. In this study, we also showed greater brain activity in several brain regions (including the basal ganglia) in the slow-4 band than in the slow-5 band. This result is consistent with a

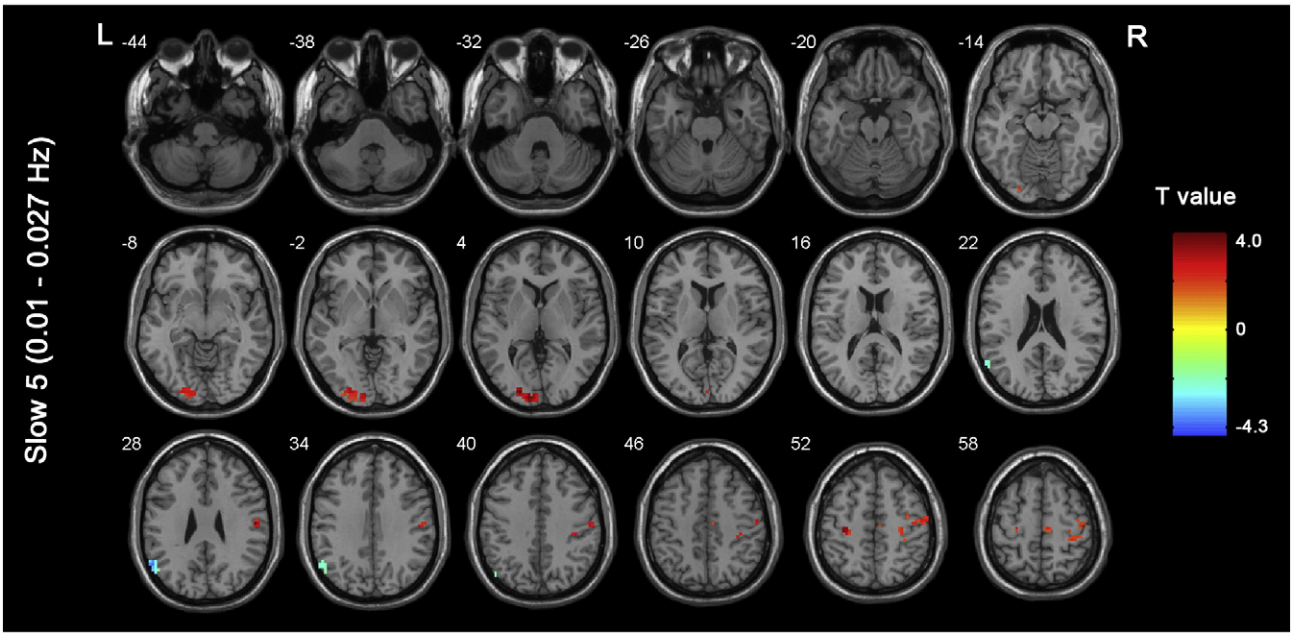

Fig. 5. The interaction between frequency band and group on fALFF. The results were obtained by a two-way repeated-measures ANOVA and a post-hoc test. Of note, we observed the differences in fALFF between the groups only in the slow-5 band. There were no significant differences in fALFF between the groups in the slow-4 band. These reflect the results of the interaction of group and frequency band. For details, see the Methods.

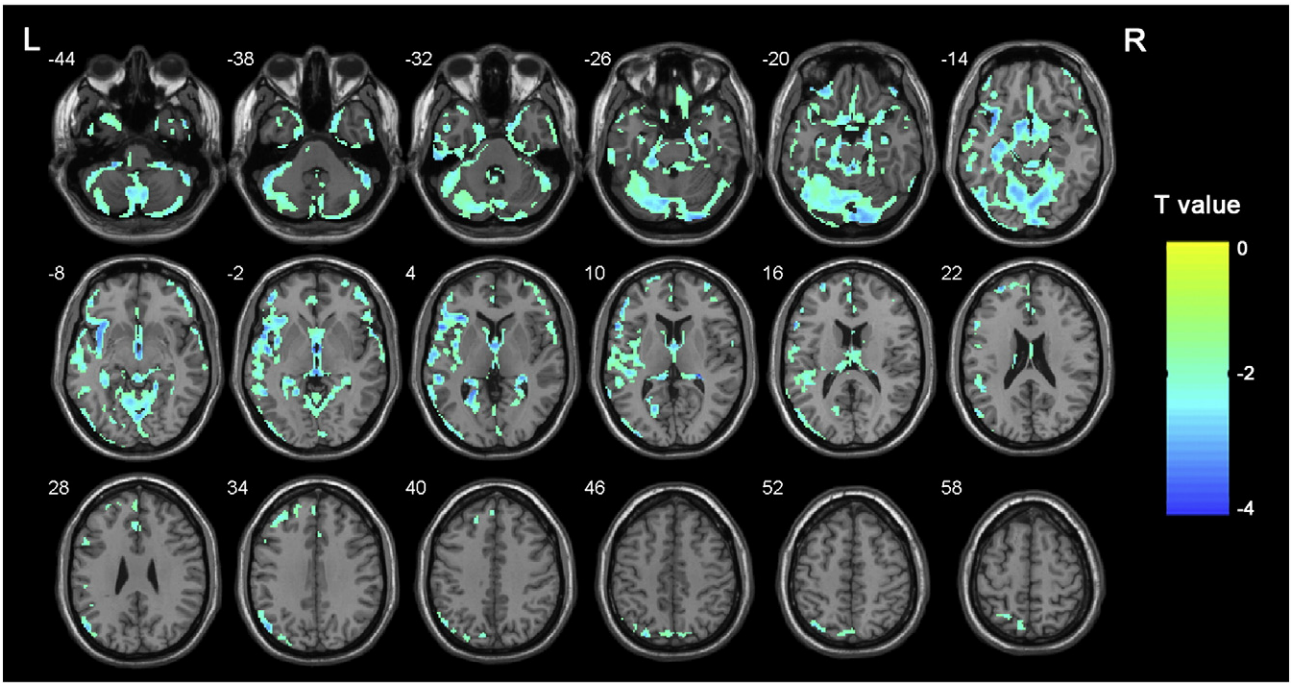

Fig. 6. *t*-statistical difference map in GM volume between the aMCI patients and controls. The results were obtained by a two-sample *t* test.

recent R-fMRI study showing the most significant ALFF/fALFF differences in the basal ganglia between the two bands (Zuo et al., 2010). It has suggested that the oscillations of the brain cover a wide range of frequencies and each of these oscillatory bands is generated by different mechanisms and has different physiological functions (Buzsaki and Draguhn, 2004; Engel et al., 2001; Penttonen and Buzsáki, 2003). Although the origins, relation, and specific physiological functions of different frequency bands have yet to be fully clarified, neighboring bands have been found to be typically associated with different brain states and compete with each other (Buzsaki and Draguhn, 2004; Engel et al., 2001; Penttonen and Buzsáki, 2003). Future work by combining EEG recordings and R-fMRI would be helpful to ascertain the neurophysiological basis of the signals located at different frequency bands.

Decreased ALFF/fALFF activity in aMCI patients

We showed that the PCC/PCu had decreased ALFF/fALFF in aMCI. Many previous studies that used PET and SPECT have demonstrated that patients with aMCI exhibited hypoperfusion and hypometabolism in this region (Anchisi et al., 2005; Chetelat et al., 2003; Del Sole et al., 2008; Hirao et al., 2005; Jagust, 2006; Matsuda, 2007; Minoshima et al., 1997; Okamura et al., 2002). Using R-fMRI, several recent studies have suggested that in the aMCI patients the PCC/PCu had reduced regional activity (Bai et al., 2008; Rombouts et al., 2005; Rombouts et al., 2007) and functional connectivity with the other regions such as the hippocampus (Qi et al., 2010; Sorg et al., 2007). Thus, our results are in agreement with previous studies. In this study, we also showed that aMCI patients had reduced ALFF/fALFF activities in the medial prefrontal cortex, which is consistent with previous R-fMRI studies (Qi et al., 2010; Sorg et al., 2007). Additionally, we found that aMCI patients had decreased ALFF/fALFF activity in several lateral prefrontal regions. Using independent component analysis (ICA), Sorg et al. (2007) showed that aMCI patients had reduced spontaneous activity in the executive function network including the lateral prefrontal regions, which provided further support for our findings. However, using ICA, Qi et al. (2010) showed that aMCI patients had increased brain activity in these regions, which has been explained as compensatory processes in these patients. The findings of abnormal prefrontal activity in aMCI are still controversial and need to be further studied. Of note, the present study showed reduced ALFF/fALFF activity in the basal ganglia, which is also comptilbe with a previous R-fMRI study (Rombouts et al., 2007).

Increased ALFF/fALFF activity in aMCI patients

In this study, we observed increased ALFF/fALFF activity in the aMCI patients, predominantly in several temporal and occipital regions. A previous R-fMRI study has suggested that aMCI patients had increased connectivity in the middle temporal region as compared to the controls (Qi et al., 2010), which is consistent with the present study. Using PET, a previous study showed a significant increase in metabolism in the inferior occipital gyrus in aMCI brains (Truchot et al., 2008). Likewise, increased occipital activities in AD were also observed during the performance of cognitive tasks (Backman et al., 2000; Prvulovic et al., 2002) and in the resting state (Dosenbach et al., 2007). Thus, our results of increased LFO amplitude in aMCI suggest that the patients had relative preservation of brain spontaneous activity in these regions.

Frequency-dependent changes in ALFF/fALFF activity in aMCI patients

It is important to note here that the abnormalities of brain spontaneous activity in the aMCI patients are associated with the choice of specific frequency bands. For instance, we showed that aMCI patients had greater decreases in LFO amplitude in the PCC/PCu and PHG in the slow-5 band (0.01–0.027 Hz) than in the slow-4 band (0.027–0.073 Hz). Recent studies have suggested that BOLD oscillations can be directly linked to the EEG signals. For example, by recording full-bands and resting-state BOLD signals simultaneously, He et al. (2008)found that there was a direct association between BOLD LFO and slow fluctuations (<0.1 Hz) observed in neuronal activity. Hoptman et al. (2010) showed that the patients with schizophrenia had widespread abnormalities of LFO amplitudes in the slow-4 frequency band. Di Martino et al. (2009) showed greater diagnostic information for children with attention-deficit hyperactivity disorder in the slow-4 band rather than other

bands. These studies suggest that the pattern of intrinsic brain activity is sensitive to specific frequency bands. In this study, we showed that PCC/PCu and PHG activity exhibited greater group differences in the lower slow-5 band than in the slow-4 band. As mentioned above, within the same neuronal networks neighboring bands are typically associated with different brain states (Buzsaki and Draguhn, 2004; Engel et al., 2001; Penttonen and Buzsáki, 2003). Thus, our results imply that the slow-5 band could be more sensitive in detecting abnormalities of spontaneous brain activity in the PCC/PCu and PHG in aMCI patients compared to the other bands. Future studies are important to examine whether such frequency specific fluctuations could be used for disease diagnosis and monitoring progression in MCI.

Conclusion

In this study, we provided evidence that aMCI patients had abnormal LFO amplitude in many brain regions, including the basal ganglia, PCC/PCu, lateral frontal regions and several occipital and temporal regions. These results were approximately compatible with previous studies of aMCI patients. Specifically, we showed that the abnormalities of brain function in aMCI patients exhibited different spatial patterns in different frequency bands. The results highlight abnormalities of LFO in aMCI and provide insights into the understanding of the pathophysiology of aMCI.

Acknowledgments

This work was supported by National Natural Science Foundation of China (grants 30970823, 81030028, 30870667 and 30830045).

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2010.11.059.

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