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Abnormal Amplitude of Low-Frequency Fluctuations of Intrinsic Brain Activity in Alzheimer's Disease

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Abstract. We used resting-state functional magnetic resonance imaging to measure the amplitude of low-frequency fluctuations (ALFF) of intrinsic brain activity in 23 patients with moderate Alzheimer's disease (AD) and 27 age- and gender-matched healthy controls. Two different frequency bands were analyzed (slow-5:0.01–0.027 Hz; slow-4:0.027–0.073 Hz). In many brain regions, widespread ALFF differences between the two frequency bands were observed, including predominantly the posterior cingulate cortex/precuneus (PCC/PCu), hippocampus/parahippocampal gyrus (Hip/PHG), insula, thalamus, and basal ganglia. Compared to controls, AD patients showed decreased ALFF values in the bilateral PCC/PCu, inferior parietal lobe, and several temporal regions, and increased ALFF values mainly in the bilateral Hip/PHG, and middle and inferior temporal gyri. Intriguingly, the ALFF abnormalities in the left PCu, left supramarginal gyrus, and several temporal regions were greater in the slow-5 band compared to the slow-4 band. Moreover, correcting for gray matter volume loss significantly affected the functional analytical results, suggesting that gray matter loss can partially account for the functional imaging analytical results obtained in AD. Finally, we showed that regions with changes in ALFF demonstrated a significant correlation with patient cognitive performance as measured using Mini-Mental State Examination scores. The results also demonstrated a significant correlation between hippocampal volume and the ALFF in slow-5 band in the AD group. This study demonstrated widespread ALFF abnormalities of intrinsic brain activity in AD and revealed that the ALFF abnormalities in severe specific regions were frequency-dependent. Taken together, our findings provided novel insights into the pathophysiological mechanism of AD and may be helpful in the development of imaging biomarkers for disease diagnosis.

Keywords: Alzheimer's disease, amplitude of low-frequency fluctuation, intrinsic brain activity, resting-state functional magnetic resonance imaging

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia, accounting for 50% to 70% of all cases [1]. As a progressive, incurable, and neurodegenerative disorder, it is clinically characterized by a decline in memory and other cognitive functions, including attention, language, reasoning, and executive function. To

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date, the pathophysiological mechanisms underlying the disease are not completely understood, and there is still no effective treatment for AD.

Resting-state functional magnetic resonance imaging (R-fMRI) techniques can be used to characterize intrinsic brain activity, providing an efficient, feasible, and noninvasive way to investigate the biological mechanisms of AD *in vivo*. Most R-fMRI studies have focused on the relationship between different brain areas, e.g., functional connectivity techniques based on the region of interest or independent component analysis. In addition, the amplitude of low-frequency fluctuation (ALFF) has been used in several areas of neuroscience and neurological diseases as an index for measuring the amplitude of regional spontaneous neuronal activity [2–4]. Biswal et al. [5] demonstrated that low-frequency (0.01–0.10 Hz) fluctuations (LFFs) of the R-fMRI signal are physiological meaningful and may reflect spontaneous neuronal activity. Buzsaki and Draguhn [6] divided the low frequency range into four distinct 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). Slow-3 and -2 bands mainly reflect white matter signals and high-frequency physiological noises, respectively [7], and slow-4 and -5 bands reflect gray matter signals. In recent years, the ALFF technique of R-fMRI has been used to investigate the intrinsic brain activity in patients with mild cognitive impairment (MCI) and AD. Specifically, several research groups have reported that MCI patients exhibit abnormal intrinsic brain activity [8–13]. Recently, Han et al. [14] showed that aMCI patients demonstrate widespread abnormalities in intrinsic brain activity, and that these abnormalities are dependent on the type of frequency bands (slow-4 versus slow-5) of the R-fMRI data. With respect to AD, only two studies have explored ALFF changes in AD patients. Using R-fMRI, Wang et al. [15] found abnormal ALFFs in various brain regions by examining intrinsic brain activity in AD patients. In addition, Xi et al. [16] reported local abnormalities in ALFF in mild AD patients. However, it is still largely unknown whether the abnormalities of ALFF in patients with AD are associated with specific frequency bands (slow-4 versus slow-5).

In the current study, we employed ALFF as an index to investigate intrinsic brain activity in patients with AD. We hypothesized that AD patients show abnormal ALFF of intrinsic brain activity, and that these abnormalities are associated with specific frequency bands. To the best of our knowledge, our study was the first to utilize ALFF to investigate whether alterations in intrinsic brain activity amplitude are dependent on specific frequency bands in patients with AD.

MATERIALS AND METHODS

Participants

Twenty-five patients with moderate AD and twenty-nine normal control subjects participated in this study. All of the subjects were right-handed with no significant differences in age, gender, or years of education between groups. AD patients were recruited from a memory clinic at the Neurology Department, Xuanwu Hospital, Capital Medical University, Beijing, China. Normal controls were recruited from the local community using advertisements. Diagnoses of probable AD were made by experienced neurologists according to the NINDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) [17]. All healthy controls had no history of neurological or psychiatric disorders, cognitive complaints, or sensorimotor impairment, and no abnormal findings were identified using conventional brain MR imaging. Each participant was clinically evaluated using a standardized clinical evaluation protocol, which included the Mini-Mental State Examination (MMSE) [18] and Clinical Dementia Rating Scale [19]. This study was approved by the Medical Research Ethics Committee of Xuanwu Hospital, and an informed consent was obtained from each participant. The data obtained from four subjects (two AD patients and two normal controls) were excluded from further analysis due to excessive head motion (see data preprocessing). Details of the demographics and clinical characteristics of the remaining participants are presented in Table 1.

Data acquisition

All of the participants were scanned using a 3.0 T Siemens Trio scanner at Xuanwu Hospital, Capital Medical University within a single session. Headphones and foam pads were used to reduce noise and motion artifacts, respectively. The participants were instructed to keep their eyes closed, but not to fall asleep or think of anything in particular during the data acquisition. Resting-state BOLD-fMRI images were acquired axially using an echo-planar imaging sequence using the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 240 mm ×

Table 1
Demographics and clinical characteristics of the participants

	Healthy controls ($n = 27$)	Alzheimer's disease ($n = 23$)	p-value
Gender (male/female)	14/13	11/12	0.777[a]
Age (years)	48–83 (63)	46–78 (61)	0.748[b]
Education (years)	6–16 (11.7 ± 3.4)	0–16 (10.0 ± 5.0)	0.162[b]
MMSE	21–30 (27.2 ± 2.8)	0–24 (10.4 ± 6.0)	≤0.0001[b]
CDR	0	2	

Data are presented as the range of min-max (mean ± SD), age values are expressed in the Median. MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale. [a]The p-value was obtained by a two-tail Pearson chi-square test. [b]The p-value was obtained by two-sample two-tail t test.

240 mm, number of slices = 33, slice thickness = 4 mm, gap = 1 mm, voxel size = $3.8 \times 3.8 \times 4.0\,mm^3$, and matrix = 64×64. This scan lasted for 480 s. Three-dimensional T1-weighted magnetization-prepared rapid gradient echo sagittal images were collected using the following parameters: TR = 1900 ms, TE = 2.22 ms, FA = 9°, FOV = 256 mm × 256 mm, number of slices = 176, slice thickness = 1 mm, gap = 0.5 mm, voxel size = $1.0 \times 1.0 \times 1.0\,mm^3$ and matrix = 256×256.

Data preprocessing

Data preprocessing was performed using Statistical Parametric Mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm). The first five images were discarded in consideration of the magnetization equilibrium and adaptation of the participants to the circumstances. The remaining 235 images were corrected for the different acquisition times of signals between slices and the inter-volume geometrical displacement due to head movement. Two patient and two normal controls were excluded because of excessive head movement (more than 3 mm of displacement or 3° of rotation in any direction). The corrected images were further spatially normalized to the Montreal Neurological Institute space and re-sampled to a 3-mm isotropic voxel using the transformation parameters obtained from the structural images. Next, the normalized images underwent spatial smoothing with a 4 mm full width at half maximum Gaussian kernel and removal of linear trends. Finally, temporal filtering was performed so that only the slow-5 (0.01–0.027 Hz) and slow-4 (0.027–0.073 Hz) bands could be examined in subsequent analyses of the LFFs amplitude.

ALFF analysis

ALFF analysis was performed using REST software (http://restfmri.net/forum/index.php). ALFF calculations were performed as previously described [2, 3]. Briefly, the time series were first transformed to the frequency domain using a Fast Fourier Transform. The square root of the power spectrum was computed and then averaged square root was obtained across a predefined frequency interval at each voxel. This averaged square root was determined as the ALFF. To reduce the global effects of variability across the participants, the ALFF of each voxel was divided by the global mean ALFF value for each participant [3]. In the present study, we computed the ALFF at the slow-4 and -5 bands. Given the previous observations of hippocampal volume decrease in AD patients [20], we further investigated the relationship between hippocampal volume and their corresponding mean ALFF values at the two bands (slow-5 and slow-4) for the AD group. The hippocampal volume for each subject was obtained as follows. First, we defined a hippocampal mask based on the bilateral hippocampus regions at the automated anatomical labeling atlas [21]. Secondly, we applied the mask to the unified T1 image and then accumulated the volume within the mask. The mean hippocampal ALFF for each subject was obtained by averaging the ALFF values within the hippocampal mask at each band. We then computed the Pearson's correlation coefficients between the hippocampal volume and ALFF for each group with age and gender treated as covariates.

Statistical analysis

To determine the effects of group and frequency band on the ALFF, a two-way repeated-measures analysis of variance (ANOVA) was performed on a voxel-by-voxel basis with group (AD patients and normal controls) as a between-subject factor and frequency band (slow-4 and slow-5) as a repeated-measures. To explore the pattern of gray matter loss in AD patients, we performed a voxel-based two-sample t-test on the smoothed gray matter intensity maps. To further analyze the effects of gray matter atrophy on the functional results, two-way repeated-measures ANOVA

was performed using the voxel-wise gray matter volume as covariates [22]. To investigate the relationship between the ALFF and patient cognitive performance as measured using the MMSE scores in AD patients, we computed the Pearson's correlation coefficients between the ALFF and MMSE scores in a voxel-wise manner. The statistical threshold was set at $p < 0.05$ at a cluster size >1566 mm^3, where the statistical threshold was corrected for multiple comparisons to a significant level of $p < 0.05$ using Monte Carlo simulations [23]. For clusters showing significant main effects and an interaction between group and frequency band, *post-hoc* two-sample *t*-tests were further performed.

RESULTS

Demographic and clinical characteristics

There were no significant differences in gender distribution ($p = 0.777$), age ($p = 0.748$), or years of education ($p = 0.162$) between the AD and healthy control groups. However, the AD group exhibited significantly lower scores on the MMSE compared to the healthy control group ($p < 0.0001$) (Table 1).

ALFF analysis

Most of the brain showed significant differences in the ALFF between the two frequency bands (slow-4 versus slow-5) (Fig. 1). Specifically, the posterior cingulated cortex/precuneus (PCC/PCu), hippocampus/parahippocampal gyrus (Hip/PHG), insula, thalamus, basal ganglia, inferior parietal lobe (IPL), and several occipital regions showed a greater ALFF in the slow-5 band compared to the slow-4 band, whereas some regions in the frontal, temporal, and occipital regions showed a lower ALFF in the slow-5 band compared to the slow-4 band. Brain regions with a main effect of group are shown in Fig. 2. Compared to controls, the AD patients showed decreased ALFF values in the bilateral PCC/PCu, IPL, middle and superior temporal gyri, and increased ALFF values mainly in the bilateral Hip/PHG, middle and inferior temporal gyri. ALFF abnormalities in the left PCu, left supramarginal gyrus, bilateral middle and inferior temporal gyri exhibited greater group differences in the lower slow-5 band compared to in the slow-4 band (Fig. 3).

ALFF analysis with gray matter correction

We performed a voxel-based morphometry analysis to reveal the gray matter volume differences between the controls and AD patients. Consistent with previous studies, our results revealed that the AD patients showed a significant gray matter loss in many brain regions, including the frontal, temporal, parietal, and occipital regions (Fig. 4) [24–27]. After correcting for the effects of gray matter volume, we found that gray matter volume correction processing significantly reduced the significance of the group differences. For example, compared with the controls, the AD patients only showed increased ALFF values in the bilateral Hip/PHG, amygdaloidal nucleus middle and inferior temporal gyri in the slow-5 band.

Correlation analysis of the ALFF and hippocampal volume

We measured the correlation between the ALFF and hippocampal volume. The results demonstrated a significant correlation between hippocampal volume and the ALFF in slow-5 brand ($p = 0.021$) in the AD group. The correlation was significant ($p = 0.037$) even when the effects of age and gender were corrected. No significant correlation was detected between hippocampal volume and the ALFF (both slow-4 and slow-5 frequencies) in healthy controls ($p > 0.05$).

Correlation analysis of the ALFF and MMSE

Correlation maps between the ALFF and MMSE scores in the AD patients at two different frequency bands are shown in Fig. 5. There were significant negative correlations found in the right medial frontal cortex and significantly positive correlations in the right inferior frontal gyrus, right postcentral gyrus, right supplementary motor area, and left anterior cingulate in the slow-4 band (Fig. 5A). There were significant negative correlations found in the bilateral superior frontal gyrus and significant positive correlations in the right middle frontal gyrus, right inferior frontal gyrus, and right IPL regions in the slow-5 band (Fig. 5B).

DISCUSSION

The present study employed R-fMRI to systematically investigate changes in ALFF in patients with AD at two different frequency bands (slow-4 and slow-5 bands). We found significant ALFF differences at two different frequency bands (slow-4 and −5 bands), and in two different groups (AD patients and healthy controls) in several brain regions. There was a significant interaction between frequency band and group, including predominantly the PCu, supramarginal gyrus,

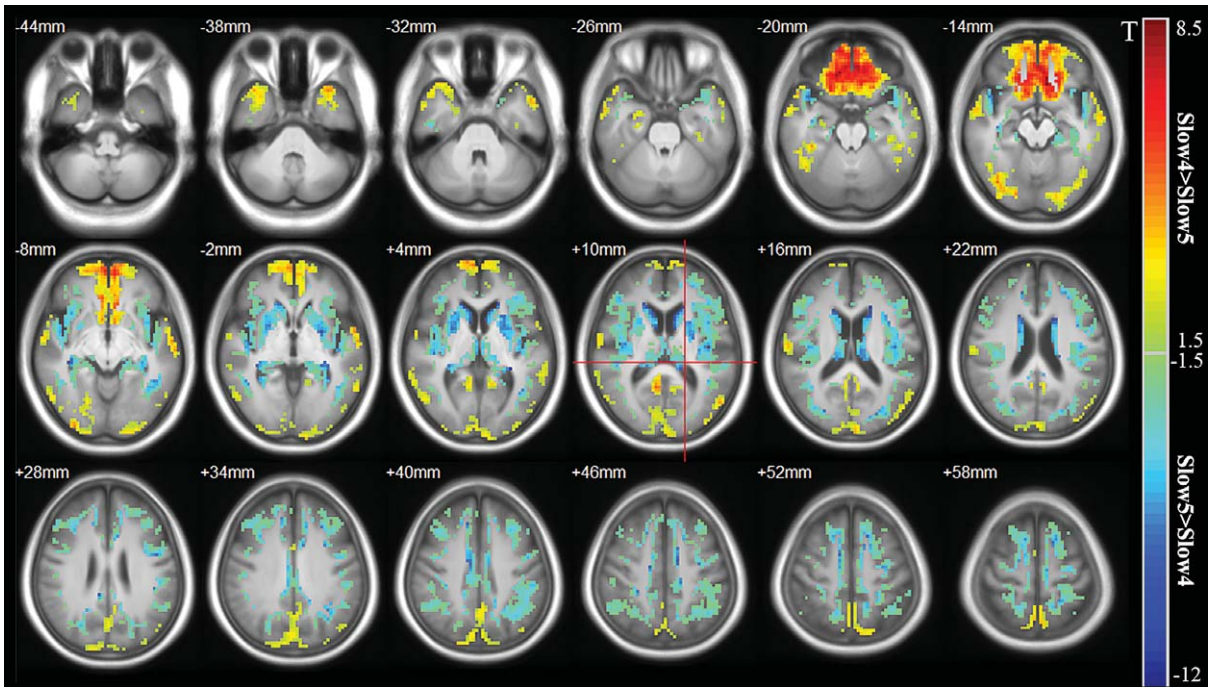

Fig. 1. The main effect for frequency band on ALFF. The warm color represents a higher ALFF in the slow-4 band compared to the slow-5 band, whereas the cool color represents a lower ALFF.

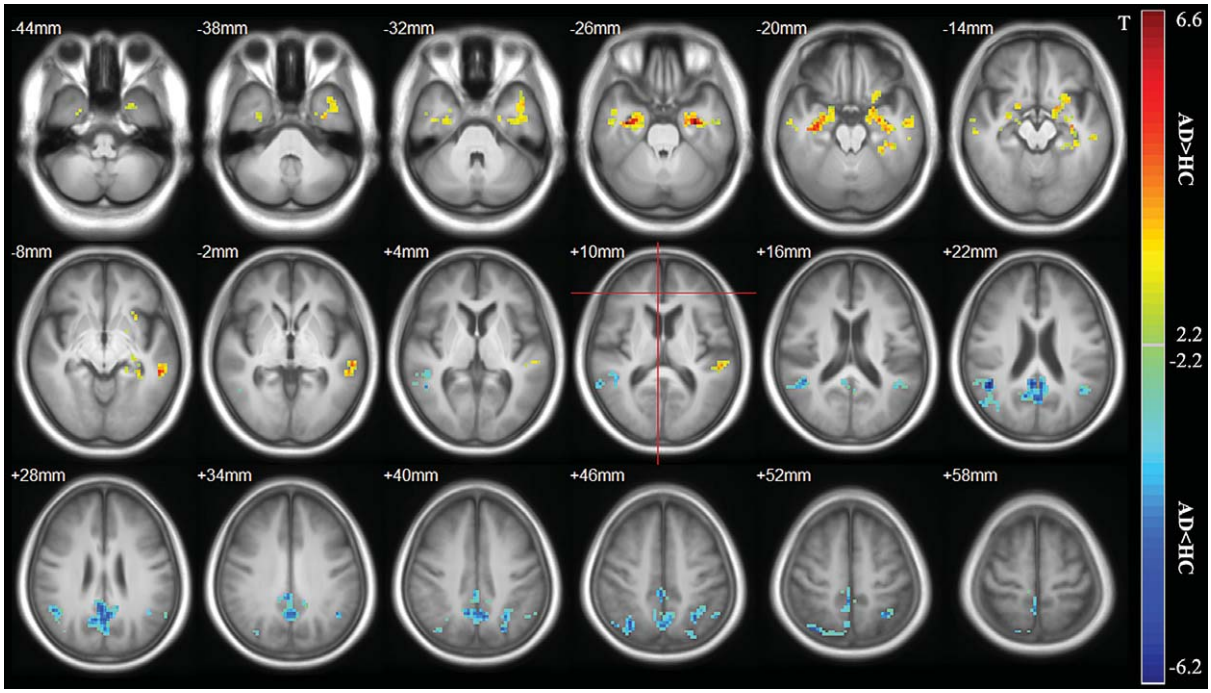

Fig. 2. The main effect of group on ALFF. The warm color represents a higher ALFF in Alzheimer's disease (AD) patients compared to control subjects (HC), whereas the cool color represents a lower ALFF.

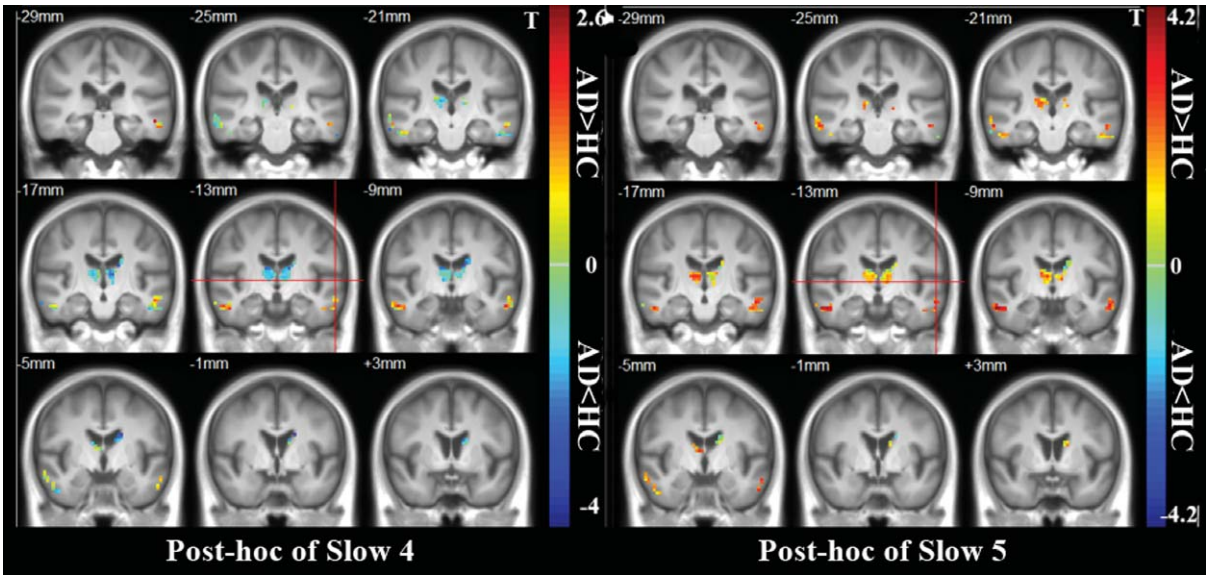

Fig. 3. The interaction between frequency band and group on ALFF. These results were obtained using a two-way repeated-measure ANOVA and *post-hoc* test. AD, Alzheimer's disease; HC, healthy control.

middle and inferior temporal gyri, where the group differences in the ALFF in the slow-5 band were greater than those in the slow-4 band. In addition, using the gray matter volume as a covariate, we found that the results of ALFF were significantly influenced after gray matter correction, implying that gray matter loss had effects on the ALFF results. Finally, we showed that regions with ALFF changes had significant correlations with the cognitive performance of patients as measured using MMSE scores. This study demonstrated widespread ALFF abnormalities of intrinsic brain activity in AD. Our findings provide novel insights into the pathophysiological mechanism of AD and may be helpful in the development of imaging biomarkers for disease diagnosis.

Differences in ALFF between frequency bands

In this study, we found significant differences in the ALFF between two different frequency bands (slow-4 versus slow-5). We found greater ALFF in several brain regions (including the PCC/PCu, Hip/PHG, insula, thalamus, basal ganglia, IPL, and several occipital regions) in the slow-5 band compared to the slow-4 band. Previous studies have suggested that lower frequency oscillations allow for an integration of neuronal networks [6, 28], which is a notion that is consistent with our results of greater brain activity in these regions in the lower slow-5 band. In addition, the thalamus, basal ganglia, and middle and inferior temporal gyri showed greater ALFF in the slow-4 band compared to the slow-5 band in the present study. Zuo et al. [7] showed that LFFs amplitudes in the slow-4 band were higher compared to those in the slow-5 band in many brain regions, such as the frontal, temporal and occipital regions, indicating that the ALFF was higher in the thalamus and basal ganglia, providing further support for our findings. The human brain is a complex dynamic system, which generates a multitude of oscillatory waves, where the origins, relationships, and specific physiological functions of different frequency bands have yet to be fully elucidated. Recently, low-frequency oscillations have gained increased attention on the basis of observations using R-fMRI approaches and electroencephalographic scalp recordings [29, 30]. Thus, future studies should identify the neurophysiological basis of specific frequency bands.

Differences in ALFF between groups

We showed that the PCC/PCu had decreased ALFF in AD. PCC is mainly involved in episodic memory and short-term memory processing [31, 32] and it is a critical node in human brain structural and functional networks [33–36]. Studies have shown that the PCC is one of the most robust brain regions in the resting state. The PCu is also an important component of the default mode network, and is closely related

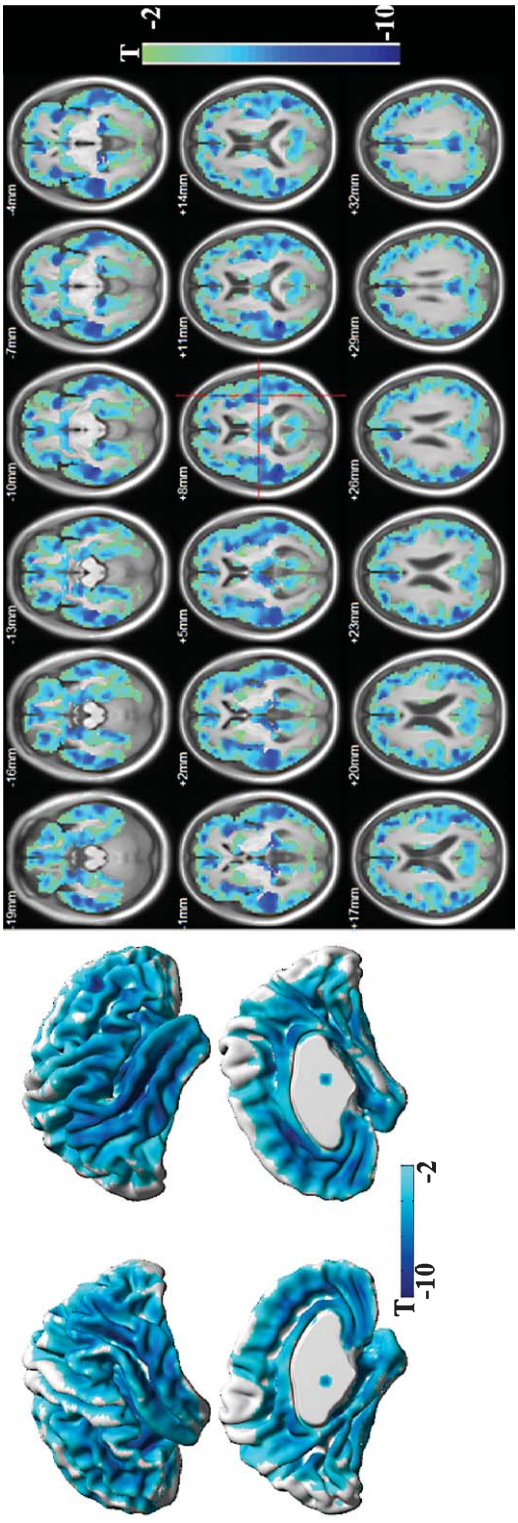

Fig. 4. t-statistical maps of gray matter volume differences between the AD patients and control subjects. These results were obtained using a two-sample *t*-test.

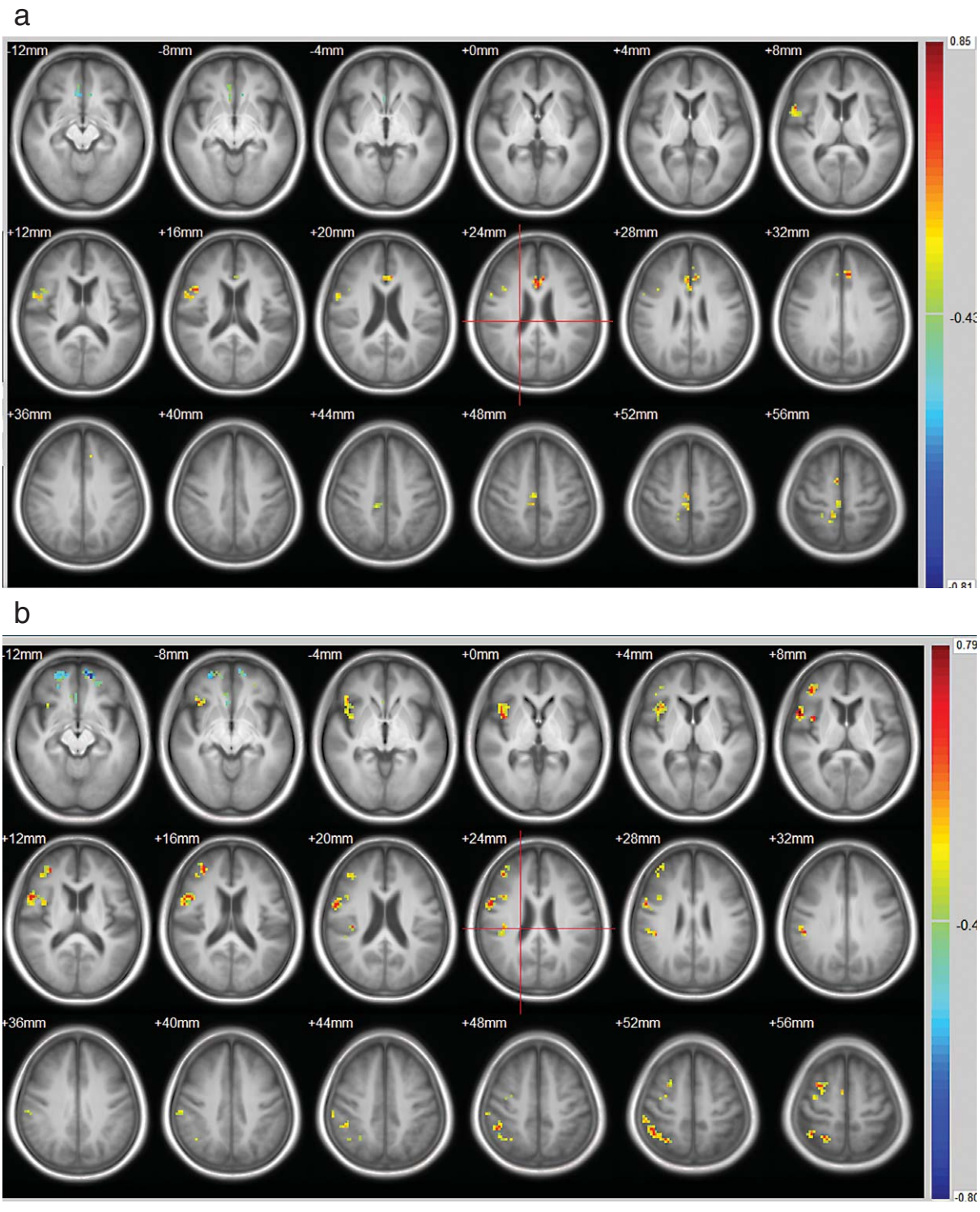

Fig. 5. A) Correlation maps of the MMSE score and ALFF for AD patients in the slow-4 band. B) Correlation maps of the MMSE score and ALFF for AD patients in the slow-5 band.

to the extraction of episode memory [37]. Using R-fMRI, several recent studies have suggested that in AD patients, the PCC/PCu exhibits reduced regional activity [38] and functional connectivity with other brain regions, such as the hippocampus [39, 40]. Our results of decreased LFFs amplitudes in AD patients indicated that the patients had an abnormality of brain spontaneous activity in these regions, which was consistent with previous R-fMRI studies [10]. Moreover, we found that AD patients had reduced ALFF activities in the IPL, which was associated with memory impairment, and abnormal activation of ALFF in this brain region might underlie the significant impairment observed in AD patients.

We found that AD patients also showed increased ALFF in the bilateral Hip/PHG. The Hip/PHG is considered to be critical to memory function. Previous studies using PET and SPECT have demonstrated that patients with AD exhibited hypoperfusion and hypometabolism in this region [41]. Furthermore, several functional neuroimaging studies have demonstrated that some brain regions, including the frontal, temporal, and parietal lobes, showed additional compensatory activation during the performance of cognitive tasks [42]. Our results showed that AD patients had increased brain activity in these regions, which reflect compensatory processes in these patients. Several previous studies have also provided further support for our findings [8, 15]. In this study, we also observed increased ALFF activities in the amygdaloidal nucleus. These regions are closely associated with human emotions, learning, memory, and other activities. The results of this study showed increased activity in this region, suggesting that an impairment in this cognitive functional in AD patients.

Frequency-dependent changes in ALFF in AD patients

Frequency-dependent changes in ALFF were observed in aMCI patients [14], and it remains largely unknown whether these abnormalities are related to specific frequency bands of LFFs in AD patients. In this study, we found that the abnormalities of intrinsic brain activity in AD patients were associated with specific frequency bands. Specifically, ALFF abnormalities in the left PCu, left supramarginal gyrus, bilateral middle and inferior temporal gyri exhibited greater group differences in the lower slow-5 band compared to the slow-4 band. Our results suggested that the slow-5 band might be more sensitive in detecting abnormalities of spontaneous brain activity in the PCu, supramarginal gyrus, and middle and inferior temporal gyri in AD patients compared to other bands. However, future studies are still required to examine whether such frequency-specific fluctuations may be used to diagnose disease and monitor AD progression.

ALFF analysis with GM correction

To explore the relationship between gray matter loss and the functional results, we examined the ALFF with gray matter corrections. We found that gray matter volume correction processing significantly reduced the significance of the group differences. AD is a progressive neurodegenerative disorder, and moderate AD patients showed widespread gray matter loss in many brain regions, where the loss of gray matter may have potential effects on functional results.

Correlation analysis between the ALFF and MMSE

We found in several brain regions, altered ALFF correlated significantly with the MMSE scores in patients with AD, which measured the overall cognitive performance over multiple domains. The medial frontal cortex and superior frontal gyrus are associated with the feedback of reward and executive function [43]. Together with the rectus, its negative correlation with the MMSE might suggest its role as a substrate of functional compensation to limit disability. The middle frontal gyrus and inferior frontal gyrus have been widely reported to be involved in mental maintenance and the response to task difficulty [44]. The IPL is associated with memory, which is the main cognitive component of the MMSE test. Thus, abnormal activation of ALFFs in these brain regions might underlie the significant impairment observed in AD patients as measured by the MMSE scores, which are consistent with a previous study in AD [15]. In addition, we found a different relationship between the MMSE scores and ALFF at different frequency bands, and this finding requires further investigation.

CONCLUSION

In the present study, we demonstrated widespread ALFF abnormalities of intrinsic brain activity in AD patients. Furthermore, the ALFF abnormalities in some brain regions were greater in the slow-5 band compared to the slow-4 band. In addition, the results demonstrated a significant correlation between hippocampal volume and the ALFF in slow-5 brand in the

AD group. We also found that the brain regions with ALFF changes demonstrated significant correlations with the MMSE scores. Taken together, these findings suggested a complex baseline brain status of both functional impairments and adaptations, and provide novel insights into the pathophysiological mechanism of AD.

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