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AMPLITUDE OF LOW FREQUENCY FLUCTUATION AT DIFFERENT FREQUENCY BANDS IN EARLY AMNESTIC MILD COGNITIVE IMPAIRMENT: RESULTS FROM ADNI

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We used resting-state functional magnetic resonance imaging (fMRI) to determine whether there are any abnormalities in different frequency bands between amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) and between 10 early amnestic mild cognitive impairment (EMCI) patients and eight normal controls participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI). We showed widespread difference in ALFF/fALFF between two frequency bands (slow-4: 0.027−0.073 Hz, slow-5: 0.01−0.027 Hz) in many brain areas including posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), suprasellar cistern (SC) and ambient cistern (AC). Compared to the normal controls, the EMCI patients showed increased ALFF values in PCu, cerebellum, occipital lobe and cerebellum posterior lobe in frequency band slow-4. While in frequency band slow-5, the EMCI patients showed decreased ALFF values in temporal lobe, left cerebrum and middle temporal gyrus5. Moreover, the EMCI patients showed increased fALFF values in frontal lobe and inferior frontal gyrus in band slow-5. While in frequency band slow-4, the EMCI patients showed decreased fALFF values in limbic lobe, cingulate gyrus and corpus callosum. These results demonstrated that EMCI patients had widespread abnormalities of amplitude of LFF in different frequency bands.

Keywords: Resting-state fMRI; amplitude of low-frequency fluctuation (ALFF); early amnestic mild cognitive impairment.

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia. It is a progressive neurodegenerative disorder characterized by the presence of amyloid-β plaques neurofibrillary tangles together with a loss of neurons. Mild cognitive impairment (MCI) is the most important at-risk state for developing AD. It refers to the transitional state between the cognitive changes of normal aging and very early dementia.[1] As a possible

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prodromal stage, about 10% to 15% of MCI patients progress to AD per year. According to Alzheimer's disease Cooperative study Clinical Trial on MCI, the amnestic mild cognitive impairment (aMCI) patients progressed to AD at a rate of 16% annually.[2] The early amnestic mild cognitive impairment (EMCI) is the early state of aMCI. The EMCI patients did not show significant memory impairment or other cognitive dysfunctions on neuropsychological examinations and did not fulfill the diagnostic criterions of aMCI. Compared to normal controls, the EMCI patients showed great difference between intelligence and memory scores or examinations. A recent study compared the differences among EMCI, aMCI and normal controls using 18F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) examination and found that EMCI had significant meaning for diagnosing the early-stage aMCI.[3]

Functional neuroimaging techniques, which mainly include positron emission tomography (PET), single photon emission computed tomography (SPECT), MR spectroscopic imaging and functional MRI (fMRI), have increasingly been utilized in the study of neurodegenerative disorder. Previous functional neuroimaging studies using PET or SPECT have demonstrated that hypoperfusion and hypometabolism are emerged in many brain areas of MCI patients.[4–11] Recently, resting-state fMRI has attracted increasing attention and been widely used in AD and MCI. Compared to PET/SPECT or fMRI that used task-driven paradigms, resting-state fMRI has the advantages of no radiation exposure and easy application.[12] Biswal and colleagues first found that the spontaneous low frequency (0.01−0.08 Hz) fluctuations (LFFs) in resting brain have a high correlation within the regions associated with primary motor cortex and suggested that spontaneous LFFs contain physiologically meaningful information in resting-state fMRI. Moreover, the spatial pattern of the LFFs was very similar to the activation pattern of bilateral finger tapping.[13]

Resting-state fMRI has been developed to a new branch of functional neuroimaging and been broadly used in the study of both normal control and metal disorder patients in the aspect of the synchronization of LFFs.[14] Numerous resting-state fMRI studies have revealed high synchronization of LFFs in the bilateral visual areas,[15] the bilateral auditory areas,[16] the language systems[16,17] and the default mode network.[18] Abnormal functional connectivity was found in a wide range of brain disorders including Alzheimer's disease,[19,20] mild cognitive impairment,[21,22] attention deficit hyperactivity disorder,[23–25] depression,[26] schizophrenia[27] and so on. Moreover, some studies have suggested that the spatial distribution of the amplitude of LFF may be related to metabolic correlates of neuronal activity. Several fMRI studies have demonstrated that the amplitude of LFF contains meaningful difference among brain areas and among clinical groups. Biswal *et al.* observed that the amplitude of LFFs in grey matter were higher than that in white matter. Children with attention-deficit/hyperactivity disorder (ADHD) also showed abnormal amplitude of LFFs in anterior cingulated, sensorimotor cortices and inferior frontal cortex.[28] Several research groups have explored the amplitude of LFFs in brain diseases such as schizophrenia,[29] AD,[30] mesial temporal lobe epilepsy[31] and in healthy populations between different brain regions (e.g., visual and auditory regions)[32] or between different physiological states (e.g., eyes closed in rest and eyes opened in rest).[33] Conventional resting-state fMRI studies choose specific frequency band of 0.01−0.1 Hz to examine spontaneous LFF activities and the frequency band was thought to have a high correlation with neuronal fluctuations.[13,34,35] Recently, Zuo and colleagues found that the amplitude of LFFs were different between two sub frequency bands including frequency band slow-5 (0.01−0.027 Hz) and slow-4 (0.027−0.073 Hz). The amplitudes of LFF in slow-4 were higher than that in slow-5 in basal ganglia, thalamus and precuneus.[36] Recently, Han *et al.*[12] showed that there were frequency-dependent changes in amplitude of LFFs in aMCI and observed significant interaction between frequency band and group in the posterior cingulate cortex/precuneus (PCC/PCu), the right parahippocampal gyrus (PHG) and some regions associated with occipital and parietal cortices.

The purpose of our present study was to utilize two approaches called amplitude of low frequency fluctuation (ALFF)[28] and fractional ALFF (fALFF)[37] to the resting-state fMRI study of normal controls and EMCI patients at different frequency bands. The method ALFF can directly measure the total power of a given time course in

a low-frequency range in order to detect the regional intensity of spontaneous fluctuations in BOLD signal. And fALFF gives the result by measuring the power within a specific frequency range divided by the total power in the entire frequency range. These two methods have been used in the resting-state fMRI studies in different groups and different frequency bands.[12,29,36] We want to find (i) whether there were any abnormalities at different frequency bands in the amplitude of LFF between EMCI and normal controls and (ii) whether the two methods have any differences between these two groups.

2. Materials and Methods

2.1. *Subjects*

The subject groups were comprised of 10 early amnestic MCI (EMCI; mean age = 75.35 ± 6.45 years, range 67−88 years, five females) patients and eight healthy controls (mean age = 78.42 ± 9.65 years, range 67−95 years, five females). Data used in this article were provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. All subjects taking part in this study were at the age between 55 and 90, and had the information that was able to provide independent evaluation of the subject's functioning. Moreover, all subjects participated in detailed evaluation at the time of their scans assessing their clinical and neurological status as well as verifying that they still met study criteria. Subjects who had any serious neurological disease (other than incipient AD) or and history of brain lesions or head trauma were excluded and informed consent was obtained from each subject. The functional brain MRI data and corresponding clinical data from baseline and follow-up scans were downloaded before September 5, 2011, from the ADNI publically available database (http://adni.loni.ucla.edu/). Because not all the data provided complete information including education years, Mini Mental State Examination (MMSE), Functional Assessment Questionnaire Total Score (FAQTS), Global Clinical Dementia Rating Scale (CDR) and GDSCALE Total Score, we do not list them in Table 1, which presents the baseline clinical and demographic variables of the two groups.

Table 1. Group demographics at baseline.

	NC	EMCI	p value
Gender (male/female)	3/5	5/5	0.664[a]
Age (years)	67−95 (78.42 ± 9.65)	67−88 (75.35 ± 6.45)	0.456[b]

Data are given as mean ± standard deviation.
Key: EMCI, early amnestic mild cognitive impairment; NC, normal controls.
[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.

2.2. *Data acquisition*

The fMRI data were collected by 3.0-Tesla Philips MRI scanner. Resting-state functional images were obtained using an echo-planar imaging (EPI) sequence and the parameters included repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 80°, number of slices = 48, slice thickness = 3.3 mm and matrix = 64 × 64. All original images files are available to the general scientific community.

2.3. *Image preprocessing and analysis*

All analyses were conducted using a statistical parametric mapping software package (spm8, http://www.fil.ion.ucl.ac.uk/spm/). For each participant, the first ten time points were discarded to avoid transient signal changes before magnetization reached steady-state and to allow subjects to get used to the fMRI scanning noise. The remaining fMRI images were first corrected for within-scan acquisition time differences between slices and then realigned to the first volume to correct for interscan head motions. Next, we spatially normalized images to the standard EPI template. Subjects with head motion exceeding 1.0 mm in any dimension or 1.0° in any angular motion through the resting-state run were excluded from further analysis. Subsequently, the images were spatially smoothed with a 4 mm full width at half maximum (FWHM) Gaussian kernel. To further reduce the effects of confounding factors, we used Resting-State fMRI Data Analysis Toolkit V1.6 (REST, http://restfmri.net/forum/) to remove the linear trends and then to compute ALFF/fALFF at the slow-5 and slow-4 frequency bands.

In the method of ALFF, the time series for each voxel was first transformed to the frequency domain using the Fast Fourier Transform (FFT) and then we obtained the power spectrum. The averaged square root of power spectrum in the predefined frequency band was defined as the ALFF for the given voxel.[28] As an improved method, fractional ALFF (fALFF) computed the fractional of ALFF in a given frequency band over the entire detected frequency range.[37] Previous studies applied the temporal filtering ($0.01\,\text{Hz} < f < 0.08\,\text{Hz}$) to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise such as respiratory and cardiac rhythms.[13,15] While in our study, we did not implement temporal filtering during preprocessing in order to obtain the frequency-dependent changes and we computed the ALFF/fALFF at slow-5 ($0.01-0.027\,\text{Hz}$) and slow-4 ($0.027-0.073\,\text{Hz}$) between these two groups. Moreover, the ALFF/fALFF of each voxel was divided by the individual global mean of ALFF/fALFF within a brain-mask.

2.4. *Statistic analysis*

To compare the effects between groups (NC and EMCI) and frequency bands (slow-4 and slow-5) on ALFF/fALFF, we first performed the one-sample t-test on the maps, respectively. To determine the effects of group, we performed a two-sample t-test between normal controls and EMCI patients on the same frequency band and the masks used in the two-sample t-test were obtained by combining the clusters of two groups with a significant level of $p < 0.05$. All the statistical maps were corrected for multiple comparions to a significant level of $p < 0.05$ using Monte Carlo simulations. To further compare these two methods in different groups and frequency bands, we chose several typical voxels from some regions, including the posterior cingulated cortex (PCC) (Talairach coordinates (−4, −56, 25)), medial prefrontal cortex (MPFC) (Talairach coordinates (−2, 38, 17)), suprasellar cistern (SC) (Talairach coordinates (−1, −2, −18)), ambient cistern (AC) (Talairach coordinates (16, −14, −22)).[37]

3. Results

3.1. *One-sample t-test of ALFF/fALFF*

The one-sample t-test of the original ALFF/fALFF analysis showed significantly higher ALFF/fALFF in the precuneus (PCu), inferior parietal lobe (IPL) and posterior cingulated cortex (PCC) (Figs. 1 and 2), which were components of the default-mode network. Moreover, significantly higher ALFF/fALFF can also been seen in the anterior cingulated cortex (ACC), limbic lobe, insula, cerebellar tonsil, lentiform nucleus, fusiform gyrus, parahippocampa gyrus (PHG), hippocampus, lingual gyrus, thalamus, corpus callosum, supramarginal gyrus, frontal gyres, temporal gyrus and cerebellum. We chose four typical voxels from the brain which were mentioned above and the corresponding t values of these voxels were shown in Fig. 3.

3.2. *Two-sample t-test of ALFF/fALFF*

In the two-sample t-test of the original ALFF/fALFF analysis between two groups, we found that the ALFF of EMCI patients in slow-4 were greater than that of normal controls in the cerebellum, cerebellum posterior lobe, occipital lobe and PCu (Fig. 4). The ALFF of EMCI patients in slow-5 were lower than that of normal controls in the temporal lobe, left cerebrum and middle temporal gyrus (Fig. 5). Brain regions in slow-4 included limbic lobe, cingulated gyrus and corpus callosum which showed significantly lower fALFF in EMCI patients than normal controls (Fig. 6). While in slow-5, the regions frontal lobe and inferior frontal gyrus showed higher fALFF in EMCI patients than normal controls (Fig. 7).

4. Discussion

In our study, we examined changes in the amplitude of LFF between EMCI patients and normal controls at two different frequency bands (slow-4 and slow-5 bands). We demonstrated that many brain areas showed significant difference in ALFF/fALFF between these two groups and between bands slow-4 and slow-5. Moreover, we found that several brain regions including PCu, cerebellum, cingulated gyrus, corpus callosum and some regions in occipital and temporal lobe showed significant difference between frequency band and group, with greater group differences in the slow-5 than that in the slow-4. Our results suggested that the EMCI patients had abnormal amplitude LFF associated with intrinsic brain activity and specific frequency bands.

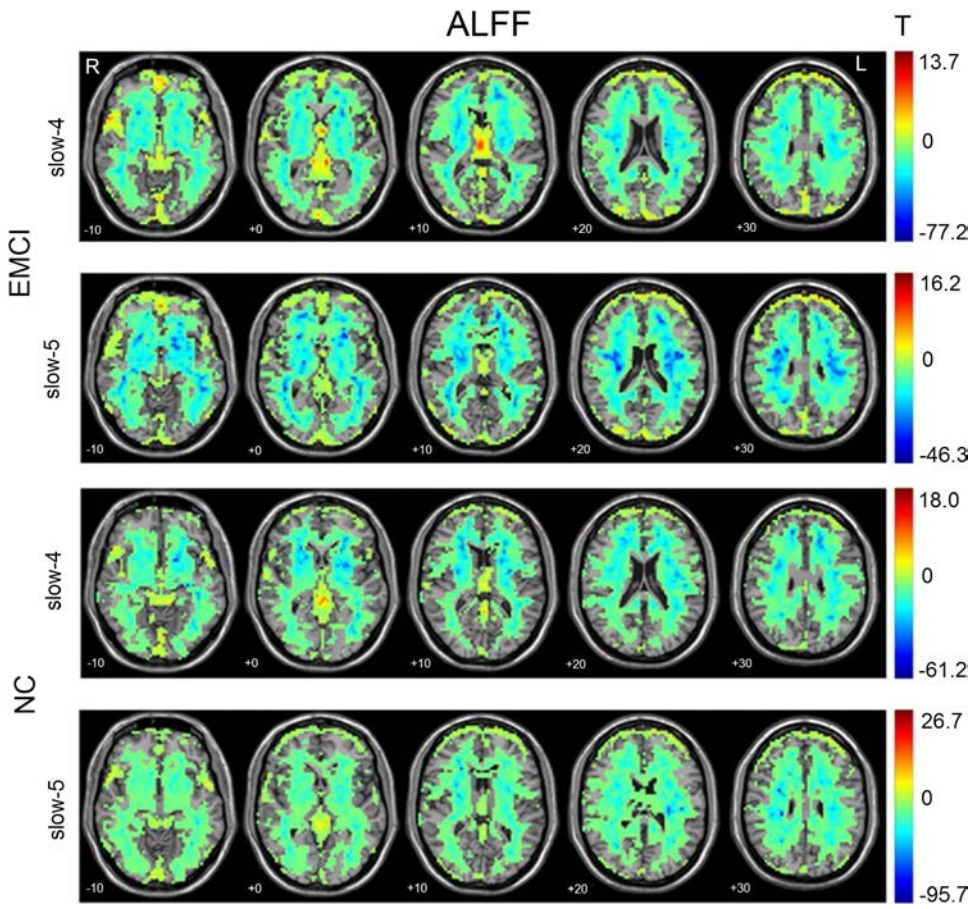


Fig. 1. The results of one-sample t-tests of the original ALFF between band slow-4, band slow-5 and EMCI ($n = 10$, $p < 0.05$, corrected), NC ($n = 8$, $p < 0.05$, corrected).

As mentioned above, the one-sample t-test of the ALFF/fALFF analysis showed higher ALFF/fALFF in the PCu, PCC and IPL (Figs. 1 and 2) and these regions were consistent with previous resting-state fMRI studies[37–39] and they might reflect higher spontaneous neuronal activity during resting state. Comparing Fig. 1 with Fig. 2, we found that the extent and magnitude of activation using fALFF were weaker than using ALFF, and higher ALFF could also been seen in the ventricles, suprasellar cistern and ambient cistern. This indicated that the nonspecific signal components in the cistern area in resting-state fMRI were significantly suppressed using fALFF and these results were consistent with previous study that physiological noise can be effectively suppressed by the fALFF approach.[37] In Fig. 3, we compared the t values of four typical voxels from some special areas in which SC, AC are located in the cistern areas and MPFC, PCC belong to the default mode network. The results showed that the t values of fALFF at SC and AC were significantly lower than that of ALFF, especially in the band slow-4. Moreover, we found from Figs. 3(a) and 3(b) that SC and AC showed significantly higher ALFF in EMCI than that in controls, especially in the band slow-5. While in Figs. 3(c) and 3(d), we found that SC and AC showed significantly higher fALFF in EMCI than that in controls, especially in the band slow-4. Several default-mode network regions including PCC and MPFC showed greater fALFF in EMCI than in controls in the band slow-5. Many previous studies have showed that these regions constitute a structurally and functionally connected neuronal network, which supported the default function of the human brain.[18,40]

In the results of two-sample t-test, we concluded that the abnormalities in spontaneous brain activity in the EMCI patients are different between specific frequency bands. Han and colleagues[12] provided evidence that the band slow-5 was more sensitive in detecting abnormalities in brain

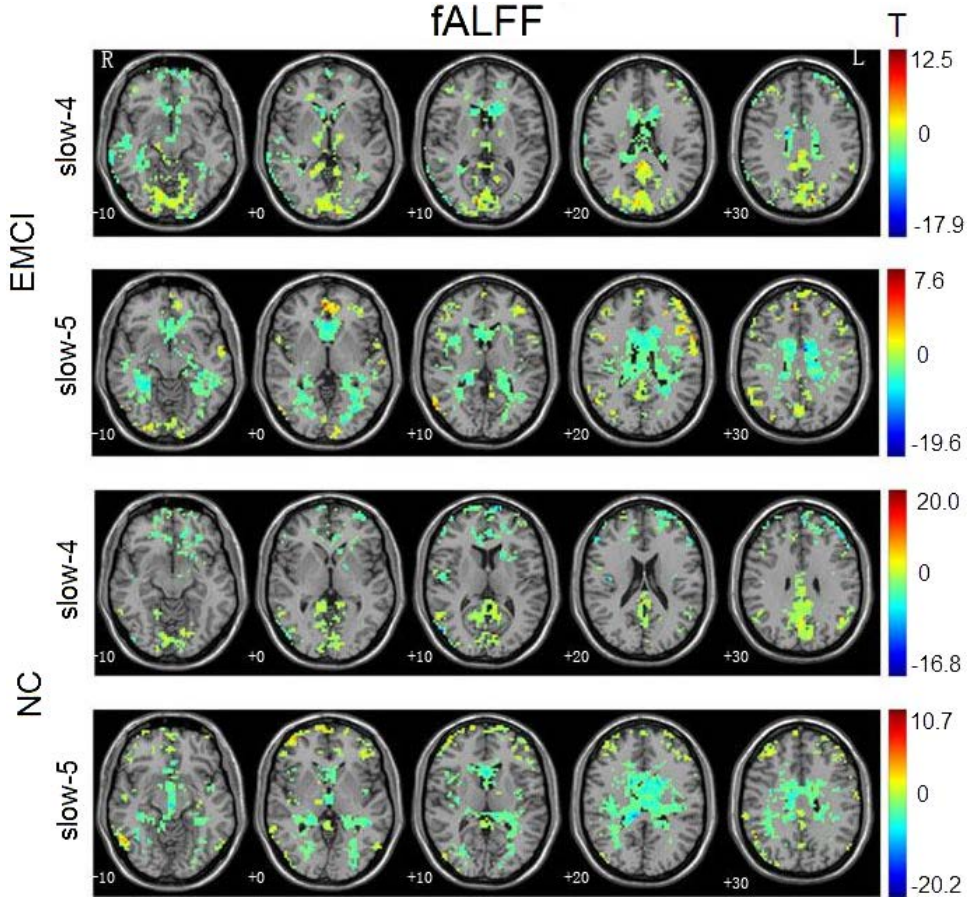
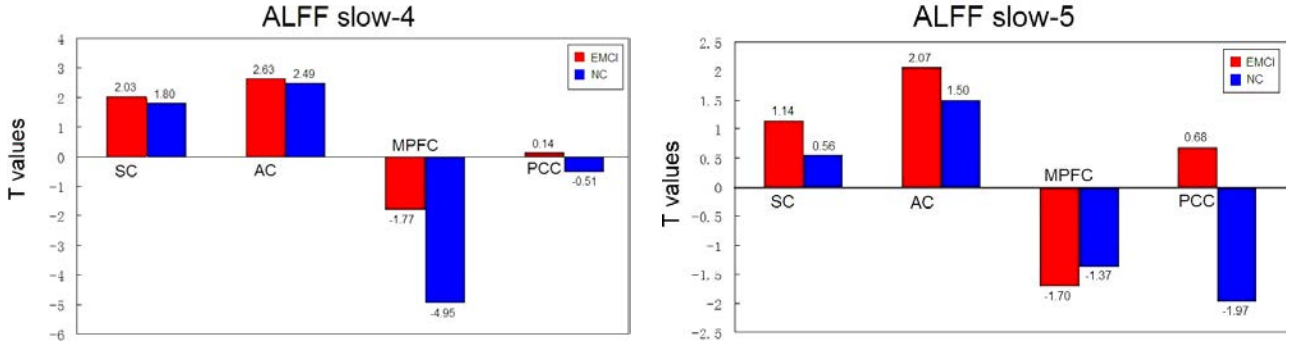
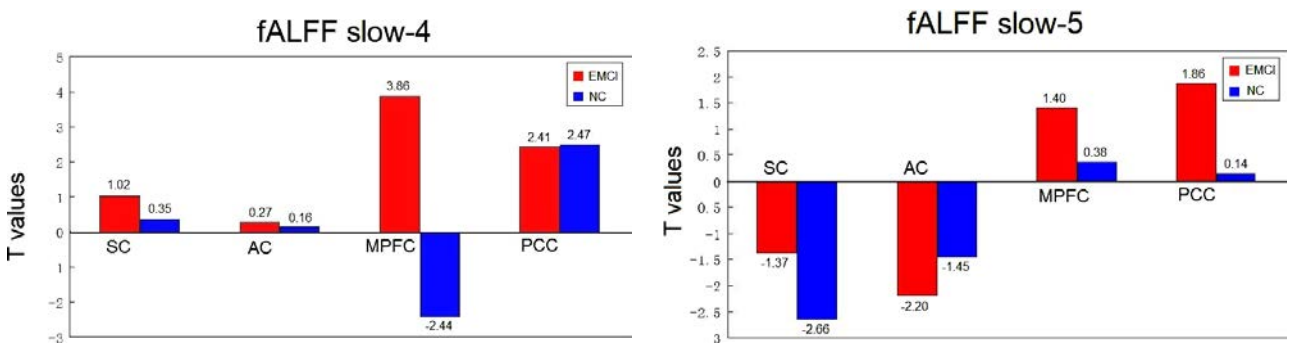


Fig. 2. The results of one-sample t-tests of the original fALFF between band slow-4, band slow-5 and EMCI ($n = 10$, $p < 0.05$, corrected), NC ($n = 8$, $p < 0.05$, corrected).



(a) (b)

Fig. 3. (a) The corresponding t values of a few typical voxels selected from some areas in the EMCI group and normal control group in band slow-4 using ALFF. SC, suprasellar cistern (−1, −2, −18); AC, ambient cistern (16, −14, −22); MPFC, medial prefrontal cortex (−2, 38, 17); PCC, posterior cingulated cortex (−4, −56, 25). (b) The corresponding t values of a few typical voxels selected from some areas in the EMCI group and normal control group in band slow-5 using ALFF. (c) The corresponding t values of a few typical voxels selected from some areas in the EMCI group and normal control group in band slow-4 using fALFF. (d) The corresponding t values of a few typical voxels selected from some areas in the EMCI group and normal control group in band slow-5 using fALFF.



(c) (d)

Fig. 3. (*Continued*)

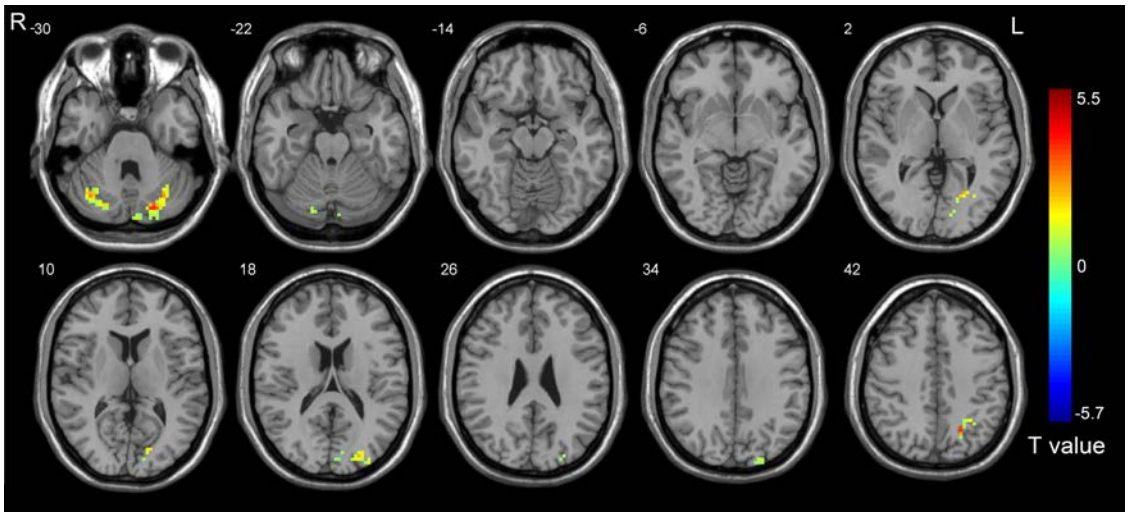


Fig. 4. The main effect for group of ALFF on band slow-4. Hot color shows higher ALFF in the EMCI group than in the control group, whereas blue color shows lower ALFF. The results were obtained by a two-sample t-test ($p < 0.05$).

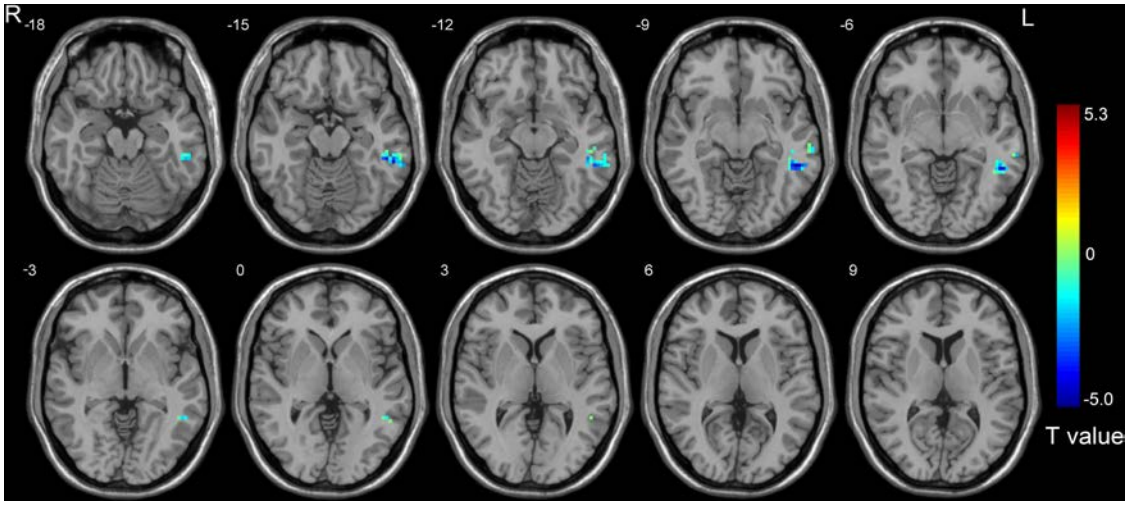


Fig. 5. The main effect for group of ALFF on band slow-5. Hot color shows higher ALFF in the EMCI group than in the control group, whereas blue color shows lower ALFF. The results were obtained by a two-sample t-test ($p < 0.05$).

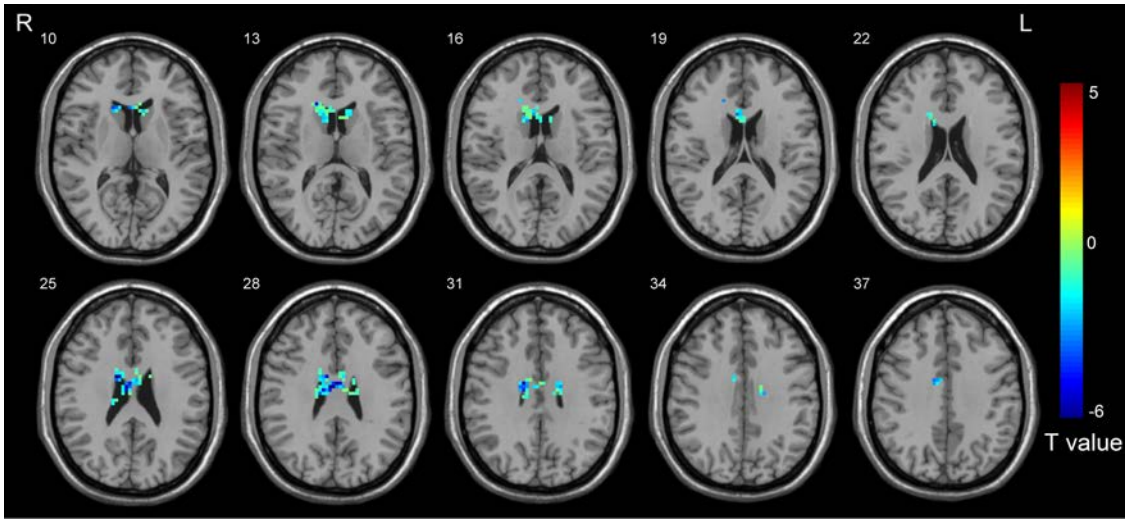


Fig. 6. The main effect for group of fALFF on band slow-4. Hot color shows higher fALFF in the EMCI group than in the control group, whereas blue color shows lower fALFF. The results were obtained by a two-sample t-test ($p < 0.05$).

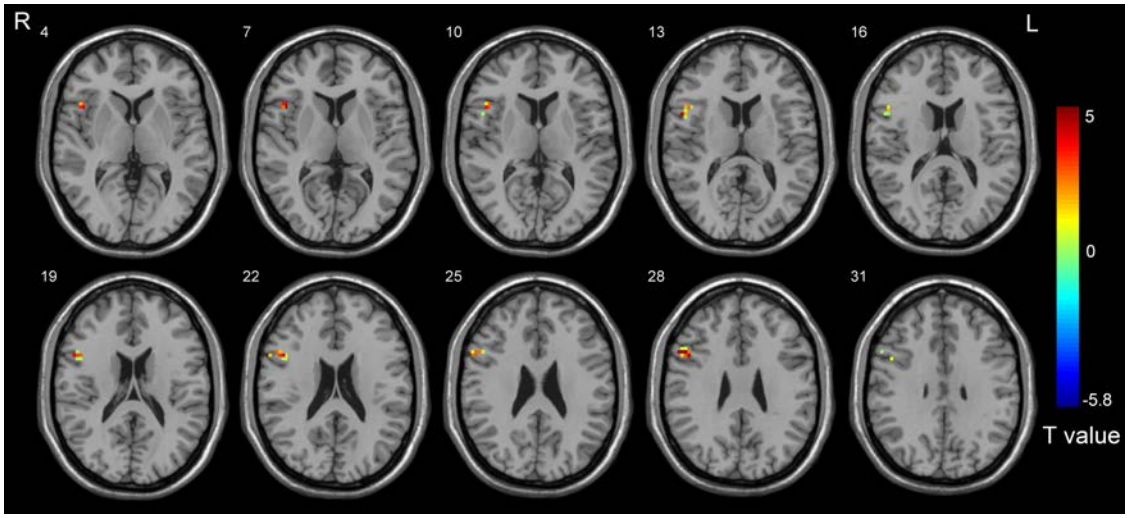


Fig. 7. The main effect for group of fALFF on band slow-5. Hot color shows higher fALFF in the EMCI group than in the control group, whereas blue color shows lower fALFF. The results were obtained by a two-sample t-test ($p < 0.05$).

activity in PCC, PCu and PHG in aMCI patients. Di Martino *et al.*[41] showed greater diagnostic information for children with ADHD in the band slow-4 rather than other bands. Hoptman *et al.*[29] showed that the patients with schizophrenia had widespread abnormalities of amplitude of LFF in the slow-4 frequency band. In the examination of ALFF, our study showed that the EMCI patients had greater increases in ALFF in the PCu, cerebellum posterior lobe, occipital lobe and cerebellum in the band slow-4. While in the band slow-5, we found that the EMCI patients had significant decreases in the temporal lobe, middle temporal gyrus and left cerebrum. Compared with the normal controls, the study showed that the EMCI patients had increased fALFF activity in EMCI patients in the regions including frontal lobe and inferior frontal gyrus in the band slow-5. Meanwhile, we observed that the EMCI patients had decreased fALFF activity in the regions including limbic lobe, cingulated gyrus and corpus callosum in the band slow-4. Thus, our data suggested that there were abnormalities in amplitude of LFFs in patients with EMCI between different frequency bands. Whether these abnormalities are associated with specific frequency bands remains an important question for future work.

In summary, we observed that EMCI patients had abnormal amplitude of LFF in many brain regions between two different frequency bands and more sample data are needed to make these results more convincing. Moreover, further works may help to provide additional information about EMCI among frequency bands.

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