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Original Article

Altered intrinsic brain activities in patients with transient ischemic attack using amplitude of low-frequency fluctuation: a resting-state fMRI study

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Abstract: *Objective:* Various neuroimaging studies reported that transient ischemic attack (TIA) was associated with brain morphology changes, whereas the intrinsic brain activity changes in TIA patients remain unknown. The purpose of the study was to investigate alterations of spontaneous brain activity in TIA patients using the amplitude of low-frequency fluctuation (ALFF) method and its correlation with clinical features. *Methods:* A total of 25 patients with TIA (15 males and 10 females) and 25 healthy controls (HCs) (15 males and 5 females) closely matched in age, sex, and education underwent resting-state functional magnetic resonance imaging scans. The ALFF method was used to assess spontaneous brain activities. Patients with TIA were distinguished from HCs by receiver operating characteristic (ROC) curve. The relationships between the mean ALFF signal values in many brain regions and clinical features in TIA patients were calculated by Pearson correlation analysis. *Results:* TIA patients had significantly lower ALFF values in the left cerebellum posterior lobe and right precentral/postcentral gyrus relative to the HCs. In contrast, the higher ALFF values in TIA patients were observed in the right prefrontal gyrus. However, no relationships were found between the mean ALFF signal values of the different areas and clinical manifestations in TIA patients. *Conclusion:* Our results demonstrated that TIA patients showed abnormal intrinsic brain activities in many brain regions related to motor control and cognition function, which might offer some useful information to explore neural mechanisms of TIA patients.

Keywords: Transient ischemic attack, ALFF, blood oxygenation level-dependent, resting state, functional magnetic resonance imaging

A transient ischemic attack (TIA) or "mini stroke" is a common cerebrovascular disease caused by a temporary disruption in the blood supply to part of the brain and it is characterized by temporary loss of vision, difficult speaking, and weakness on one side of the body. According to a recent survey performed in China, the prevalence of TIA in hypertension patients was 67.5% [1]. Approximately, 1.7% of TIA patients occurs in ischemic stroke [2]. There are a variety of risk factors for TIA including hypertension [3], and family history of stroke or TIA [4]. TIA is also associated with impairment of physical activity [5] and cognition [6]. At present, Ticagrelor and Aspirin are the main treatment methods for TIA patients [7, 8]. Magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) have been used to explore the pathologic changes of brain. A neuroimaging study demonstrated that TIA patients with lesion exhibited higher lactate/NAA ratio compared with individuals, involved who were in a healthcare experimentation (control group). Moreover, choline (Cho)-to-creatine (Cr) ratio showed a positive relationship with regional cerebral blood flow (rCBF) value [9]. Besides, another research reported that TIA patients were associated with a perfusion abnormal region in relative mean transit time using perfusion MRI [10] Tong et al. reported that TIA patients showed decrease of fractional anisotropy ratio (rFA) in the lesions of specific brain regions [11]. A recent study demonstrated that TIA patients exhibited decreased levels of frac-

Table 1. Demographics and clinical measurements by group

Condition	TIA	HC	t	*P*-value*
Male/female	15/10	15/10	N/A	> 0.99
Age (years)	60..48±3.45	60.60±3.55	-0.121	0.904
Weight (kg)	65.76±4.94	66.08±5.03	-0.227	0.821
Handedness	25R	25R	N/A	> 0.99
Duration of TIA (days)	11.60±5.37	N/A	N/A	N/A

*P < 0.05 Independent t-tests comparing two groups. Abbreviations: HC, healthy control; N/A, not applicable;

tional anisotropy (FA) in forceps minor, anterior thalamic radiations, cingulum, inferior fronto-occipital fasciculus (IFOF), and corticospinal tract compared with to control group [12]. Meanwhile, Zamboni et al. reported that TIA patients were associated with frontal white matter hyperintensities (WMHs) and decreased fractional anisotropy (FA) [13].

Functional MRI (fMRI) was successfully applied to evaluate changes in brain's activity in TIA patients. Guo et al. demonstrated that TIA patients exhibited lower regional homogeneity (ReHo) values in prefrontal cortex and anterior cingulate cortex [14]. Another research reported that TIA patients were associated with the disrupted resting-state functional networks, such as default mode network (DMN) and self-referential network [15]. However, it is still unclear whether the altered spontaneous low-frequency fluctuations in blood oxygen level-dependent (BOLD) occur in TIA patients. The amplitude of low-frequency fluctuation (ALFF), can be used to investigate spontaneous neuronal activity in the BOLD fMRI signal. Besides, spontaneous low-frequency fluctuations in BOLD fMRI signals are correlated with spontaneous activities [16, 17]. Several neuroimaging studies demonstrated that ALFF method has been successfully applied to assess the spontaneous neuronal activities of brain in various diseases (e.g., glaucoma [18], blindness [19], high myopia [20], etc. Thus, the ALFF method has proved to be a reliable and effective resting-state fMRI technique.

Here, the aim of this study was to investigate the different intrinsic activities of brain in TIA patients using the ALFF method. Moreover, the relationship between mean ALFF values in different brain regions and their clinical features in TIA patients was explored by Pearson correlation coefficient.

Participants and methods

Participants

A total of 25 patients with TIA (15 males and 10 females) were recruited from the Neurology Department of the Jiujiang Affiliated Hospital of Nanchang University. All TIA patients were associated with any syndrome of focal neurological dysfunction ascribable to a vascular territory and lasting < 24 h [21]; The exclusion criteria for TIA in the study were presented as follows: 1) with a history of cerebral hemorrhage, and stroke; 2) with other psychiatric disorders such as depression, dementia, etc.; 3) TIA patients with a long history of aspirin therapy, etc; 4) with cardiovascular system diseases such as heart disease and hypertension.

Twenty-five healthy controls (15 males and 10 females) participated in the study and were matched in age, sex, and education level to subjects in the TIA group. All HCs met the following criteria: 1) no psychiatric disorders (depression, bipolar disorder, and so on); and 2) had to be able to be scanned with a MRI (e.g., no cardiac pacemaker or implanted metal devices, and so on).

This study was approved by the Ethics Committee of Jiujiang Affiliated Hospital of Nanchang University. Informed consent was obtained from all donors prior to their donation, and the research methods complied with the principles of the Declaration of Helsinki.

MRI parameters

MRI scanning was performed on a 3-Tesla MR scanner (Trio, Siemens, Munich, Germany). The functional data were obtained with spoiled gradient-recalled echo sequence with the parameters, 176 images (repetition time = 1,900 ms, echo time = 2.26 ms, thickness = 1.0 mm, gap = 0.5 mm, acquisition matrix = 256 × 256, field of view = 250 mm × 250 mm, flip angle = 9°) covering the whole brain were obtained. Finally, 240 functional images (repetition time = 2,000 ms, echo time = 30 ms, thickness = 4.0 mm, gap = 1.2 mm, acquisition matrix = 64 × 64, flip angle = 90°, field of view = 220 mm × 220 mm, 29 axial slices with gradient-recalled echo-pla-

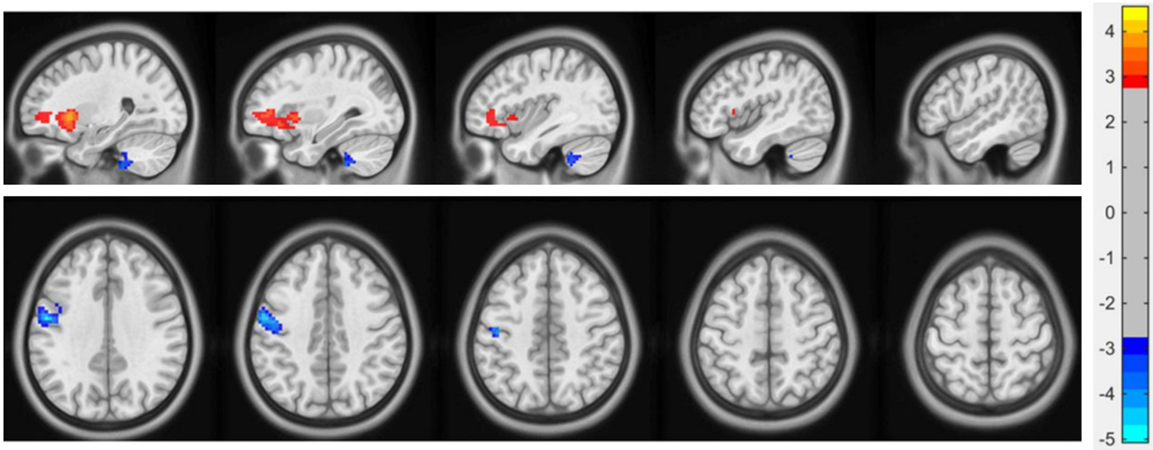

Figure 1. Spontaneous brain activity in the TIAs versus HCs. Significant activity differences were observed in the Left Cerebellum Posterior Lobe, right precentral/postcentral gyrus, right prefrontal gyrus. The red or yellow denotes higher ALFF values, and the blue areas indicate lower ALFF values (P < 0.01 for multiple comparisons using Gaussian Random Field (GRF) theory, z > 2.3, P < 0.01, cluster > 40 voxels, FDR corrected). Abbreviations: ALFF, amplitude of low-frequency fluctuation; TIA, transient ischemic attack; HC, healthy controls; FDR, false discovery rate.

Table 2. Brain areas with significantly different ALFF values between groups

Brain regions/conditions	Left/right	MNI coordinates			Cluster size	t-value
		X	Y	Z		
TIA < HCs						
Cerebellum Posterior Lobe	Left	-49	-67	-43	557	-4.432
Precentral/Postcentral Gyrus	Right	51	-12	48	80	-4.074
TIA > HCs						
Prefrontal gyrus	Right	26	19	2	548	4.324

Notes: The statistical threshold was set at the voxel level with P < 0.05 for multiple comparisons using Gaussian Random Field (GRF) theory (z > 2.3, P < 0.01, cluster > 40 voxels, FDR corrected). Abbreviations: ALFF, amplitude of low-frequency fluctuation; TIA, transient ischemic attack; HCs, healthy controls; MNI, Montreal Neurological Institute; FDR, false discovery rate; L, left; R, right.

nar imaging pulse sequence) covering the whole brain were obtained.

fMRI data analysis

Functional data were preprocessed using DPARSFA (http://rfmri.org/DPARSF) [22] using Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2013a (Math Works, Natick, MA, USA) and included the following steps: 1) The first ten volumes of each subject were discarded due to the possible instability of the initial MRI signal and to permit the participants to adapt to the scanning environment; 2) The remaining 230 volumes of functional BOLD images were corrected for slice timing effects and motion. Individual T1-weighted MPRAGE structural images were registered to the mean fMRI data, and then the resulting aligned T1-weighted images were segmented using the diffeomorphic anatomical registration through the exponentiated Lie algebra toolbox for improving spatial precision in normalization of fMRI data.

ALFF analysis

To calculate ALFF, first, the remaining data were smoothed with a Gaussian kernel of 6 × 6 × 6 mm^3 full-width at half-maximum (FWHM). Second, the fMRI images were detrended and band pass-filtered (0.01-0.08 Hz) to reduce the effects of low-frequency drift and physiological high-frequency respiratory and cardiac noise. Then we converted the smoothed signal of each voxel from time domain to frequency domain via Fast Fourier Transform (FFT) to obtain the power spectrum. Finally, all the ALFF maps were divided by the mean value of each ALFF map.

Statistical analysis

For the clinical measurements, including the duration of the onset of TIA were analyzed in

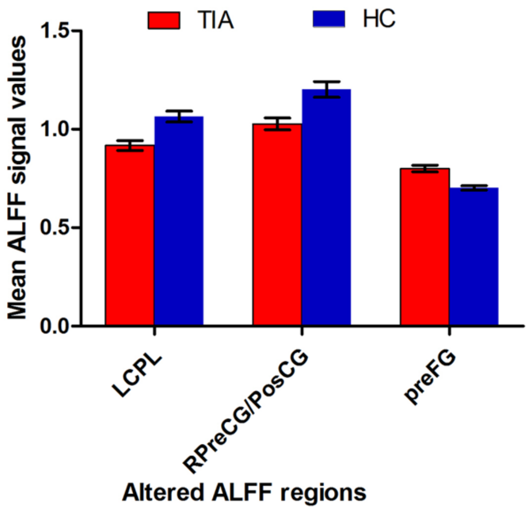

Figure 2. The mean values of altered ALFF values between the TIAs and HC groups. Abbreviations: ALFF, amplitude of low-frequency fluctuation; TIA, transient ischemic attack; HC, healthy controls.

the study withindependent sample T tests using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). ($P < 0.05$ significant differences).

The two-sample t-tests were used to examine the difference in the zALFF maps between the TIA group and the HCs, using the SPM8 toolkit after controlling for the effects of age and sex. ($P < 0.01$ for multiple comparisons using Gaussian Random Field (GRF) theory $z > 2.3$, $P < 0.01$, cluster > 40 voxels, FDR corrected).

The mean ALFF values in the different brain regions between two groups were analyzed by the receiver operating characteristic (ROC) curves method. Pearson correlation was used to evaluate the relationship between the mean ALFF values in different brain regions in the TIA group and behavioral performances were obtained ($P < 0.05$ significant differences).

Results

Demographics and visual measurements

There were no differences in weight ($P = 0.821$) or age ($P = 0.904$) between the two groups ($p > 0.05$). The mean ± standard deviation of the duration of TIA was 11.60±5.37 days (**Table 1**).

ALFF differences

Compared with HCs, TIA patients had significantly lower ALFF values in the left cerebellum posterior lobe and right precentral/postcentral gyrus; (**Figure 1** [blue] and **Table 2**). In contrast, higher ALFF values in the TIA patients groups were observed in the right prefrontal gyrus. (**Figure 1** [red] and **Table 2**). ($P < 0.01$ for multiple comparisons using Gaussian Random Field (GRF) theory, $z > 2.3$, $P < 0.01$, cluster > 40 voxels, FDR corrected). The mean values of altered ALFF values between the two groups were shown with a histogram (**Figure 2**). In the TIA group, there were no correlation between the mean ALFF values in different brain regions and their clinical manifestations ($p > 0.05$).

Receiver operating characteristic curve

We hypothesized that the ALFF differences between the TIA and HC groups might be useful diagnostic markers. Besides, the mean ALFF values in the different brain regions were analyzed by the receiver operating characteristic (ROC) curves method. The areas under the ROC curve (AUCs) for ALFF values were as follows: Left Cerebellum Posterior Lobe (0.790), right precentral/postcentral gyrus (0.738); (**Figure 3A**, TIAs < HCs) right prefrontal gyrus (0.834). (**Figure 3B**, TIAs > HCs).

Discussion

In our study, compared with the control group, TIA patients had significantly lower ALFF values in the posterior lobe of left cerebellum and right precentral/postcentral gyrus in comparison with control group. In contrast, the higher ALFF values in TIA patients was observed in the right prefrontal gyrus.

The postcentral gyrus is located in the primary somatosensory cortex (S1), playing a critical role in sensation [23]. Besides, the precentral gyrus is located in the posterior frontal lobe, which is a part of primary motor cortex. A previous neuroimaging study reported that TIA patients exhibited the hyperfunction of the contralesional motor network [24]. Meanwhile, another study demonstrated that the chronic stage stroke was associated with motor deficits [25]. Moreover, reduced FA in voxels of transcallosal motor and ipsilesional corticospinal fibers occurred in TIA patients [26]. Based on the achieved results, we found that TIA patients significantly exhibited lower ALFF values in the right precentral/postcentr-

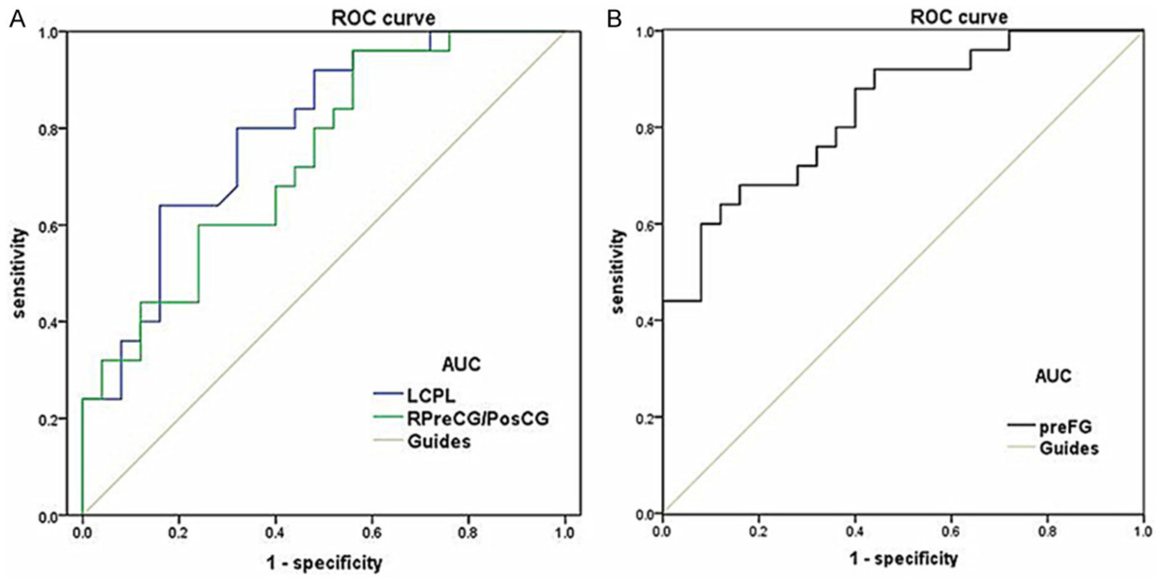

Figure 3. ROC curve analysis of the mean ALFF values for altered brain regions. The areas under the ROC curve were 0.790 ($p < 0.001$; 95% CI: 0.665-0.914) for LCPL; RPreCG/PosCG (0.738) ($p = 0.004$; 95% CI: 0.602-0.874); (TIAs < HCs) (A) preFG (0.834) ($p < 0.001$; 95% CI: 0.724-0.943), (TIAs > HCs) (B).

al gyrus, reflecting the dysfunction of brain regions. As we all know, the TIA patients were significantly more likely to have hypertension, which may significantly increase the risk of stroke [27]. Thus, we speculated that the TIA patients might associate with impaired motor control.

The frontal gyrus is a part of frontal lobe, playing a critical role in cognition and emotion activities. In addition, the frontal gyrus is involved in attentional capture [28], and cognition [29]. Several previous neuroimaging studies reported that TIA patients associated with the declining the level of cognition [30-32]. However, Rooij et al. expressed that TIA patients associated with persistent cognitive impairment [33]. In the present study, it was revealed that TIA patients had higher ALFF values in the right prefrontal gyrus, indicating the hyperfunction of the brain regions. Therefore, we speculated that TIA patients might be associate with dysfunction of cognition.

It is well-known that the cerebellum is involved in motor control [34]. Besides, the cerebellum plays a significant role in the cognition function [35]. Our result suggested that the ALFF values were remarkably decreased in TIA patients' posterior lobe of left cerebellum, which might reflect the dysfunction of motor coordination. Thus, it can be concluded that TIA might lead to the dysfunction of motor control.

In summary, our results suggested that TIA patients exhibited abnormal spontaneous neural activity in many brain regions, which closely associated with motor control and cognition function, leading to present precious clinical information to explore the neural mechanisms in TIA patients.

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Disclosure of conflict of interest

None.

Abbreviations

ROC, receiver operating characteristic; ALFF, amplitude of low-frequency fluctuation; CI, confidence interval; TIA, transient ischemic attack; HCs, healthy controls; LCPL, Left Cerebellum Posterior Lobe; RPreCG/PosCG, right Precentral/Postcentral Gyrus; RpreFG, prefrontal gyrus.

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