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Original Article

Alterations of spontaneous brain activity in patients with asthma using amplitude of low-frequency fluctuation: a resting-state fMRI study

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Abstract: Objective: Many previous studies demonstrated that the hypoxia led to the abnormal spontaneous brain activity, whereas the intrinsic brain activity changes in asthma patients remain unknown. The study aimed to evaluate the alterations of spontaneous brain activity in asthma patients using amplitude of low-frequency fluctuation (ALFF) method and its relationships with clinical features. Methods: A total of 27 patienits with asthma (17 males and 10 females) and 27 healthy controls (HCs) (17 males and 10 females) closely matched in age, sex, and education underwent resting-state functional magnetic resonance imaging scans. The ALFF method was applied to assess spontaneous brain activity changes. Patients with asthma 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 asthma patients were calculated by pearson correlation analysis. Results: Compared with HCs, the asthma patients had significantly lower ALFF in the bilateral cerebellum anterior lobe/brainstem/thalamus/putamen/posterior cingulate cortex/middle cingulate cortex/lingual gyrus (BA 18, 19, 23, 30) and left middle occipital gyrus (BA 18); In contract, the asthma patients showed higher ALFF values in the left cerebellum posterior lobe, left middle temporal gyrus (BA 20, 37), right middle temporal gyrus (BA 20, 21), left superior temporal gyrus (BA 53) and bilateral superior frontal gyrus/precentral gyrus (BA 4, 6, 8, 9). However, no relationship was found between the mean ALFF signal values of the different brain areas and the clinical manifestations in asthma patients. Conclusion: We demonstrated that asthma patients had abnormal spontaneous activities in many brain regions related to respiratory control and emotion control function, which might provide some useful informations to explain the neural mechanisms of clinical features including hypoxia, dyspnea and depression in asthma patients.

Keywords: ALFF, asthma, blood oxygenation level dependent, resting state, functional magnetic resonance imaging

Introduction

Asthma is a common disease of respiratory system characterized by paroxysmal dyspnea. According to the recent survey, the prevalence of the asthma is 8.4% in the United States [1]. The occurrence of asthma is associated with a variety of risk factors such as family history of asthma [2], genetic [3] and environmental factors, [4] et al. The main clinical symptoms of asthma are wheezing, shortness of breath, chest tightness and coughing. Moreover, the asthma is showed to be associated with other diseases such as obstructive sleep apnea and asthma [5], rhinosinusitis [6], et al. Severe asthma will lead to hypoxia. Besides, the chronic asthma patients may be accompanied by psychological problems [7].

As we all know, the dyspnea is a threatening cardinal symptom in asthma patients. Dyspnea has bad influence on the lung function. Meanwhile, the dyspnea affects the cerebral function activity. A previous study demonstrated that health subject who was treated with air hunger showed activation in the insular cortex [8].

Table 1. Demographics and clinical measurements by group

Condition	Asthma	HC	t	*P*-value*
Male/female	17/10	17/10	N/A	> 0.99
Age (years)	51.62±5.20	51.26±5.27	0.260	0.796
Weight (kg)	63.56±7.12	63.18±6.68	0.197	0.845
Handedness	27R	27R	N/A	> 0.99
Duration of asthma (years)	27±6.21	N/A	N/A	N/A

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

Meanwhile, the lesions of the right insular cortex patients showed the reduced sensitivity for the perception of dyspnea [9]. Other study reported that the dyspnea showed the many brain regions activation including limbic and paralimbic loci [10]. Moreover, von Leupoldt A et al. found that the dyspnea and pain showed the similar emotion-related human brain network [11]. A recent study exhibited that the health subjects with dyspnea were associated with the emotion-related brain areas activated, which might indicate development of unfavorable health behaviors in patients suffering from dyspnea [12]. Functional magnetic resonance imaging (fMRI) has been successfully applied to evaluate the brain function changes in asthma patients. A previous study demonstrated that asthma patients showed increased activity in insular cortex and decreased activity in periaqueductal gray (PAG) [13]. Meanwhile, other research exhibited that the duration of the asthma was correlated with the increased gray matter volume (GMV) in the brainstem PAG [14]. Wang L et al. found that asthma patients with depression showed the less GMV in the right superior temporal gyrus and the bilateral precuneus using a voxel-based morphometry method [15]. Moreover, the asthma patients with depressive symptoms were associated with the decreased regional homogeneity in the right insula [16]. A recent research exhibited that the asthma patients showed the smaller hippocampal volumes than health subjects [17]. Although the abovementioned researches revealed the abnormalities of the brain activity and structure in asthma patients. The understanding of the spontaneous brain activity changes in asthma patients at rest remains unknown.

The amplitude of low-frequency fluctuation (ALFF) can be used to detect the spontaneous neuronal activity in blood oxygenation level dependent (BOLD) signal. The blood oxygenation level dependent signal changes can reflect the changes in the neuronal and physiological activities to some extent. A previous study demonstrated that the spontaneous low-frequency (0.01-0.08 Hz) fluctuations showed highly correlation between the right and left primary motor cortex at rest [18]. Besides, spontaneous low-frequency fluctuations of blood oxygena-level-dependent (BOLD) fMRI signals are correlated with the spontaneous neuronal activities [19, 20]. In our previous studies, the ALFF method had been successfully applied to investigate the spontaneous brain activities in various diseases such as glaucoma [21], blindness [22], leukoaraiosis [23] and alzheimer's disease [24] et al. Thus, ALFF is considered to be a reliable and sensitive measurement, which can be used to evaluate spontaneous neural activity accurately.

Here, our study aimed to investigate the changes of baseline brain activity in asthma patients compared health subjects using ALFF method and its relationship with the clinical manifestations. We hypothesized that the significant different ALFF values in many brain regions which was closely related to their clinical manifestation in asthma patients.

Materials and methods

Subjects

A total of 27 patients with asthma (17 males and 10 females) were recruited from the Jiangxi Provincial People's Hospital, Nanchang, People's Republic of China. The diagnostic criteria of bronchial asthma were: 1) patients with the intermittent hypoxia, wheezing symptom; 2) than 20% decrease in forced expiratory volume (FEV) in 1 within 1 h; 3) without respiratory infection and other respiratory disease; 4) without psychiatric disorders and cerebral infarction diseases.

Twenty-seven healthy controls (17 males, 10 females) with age-, sex-, and education status-matched to subjects in the asthma group participated in the study. All healthy controls met the following criteria: 1) no psychiatric disor-

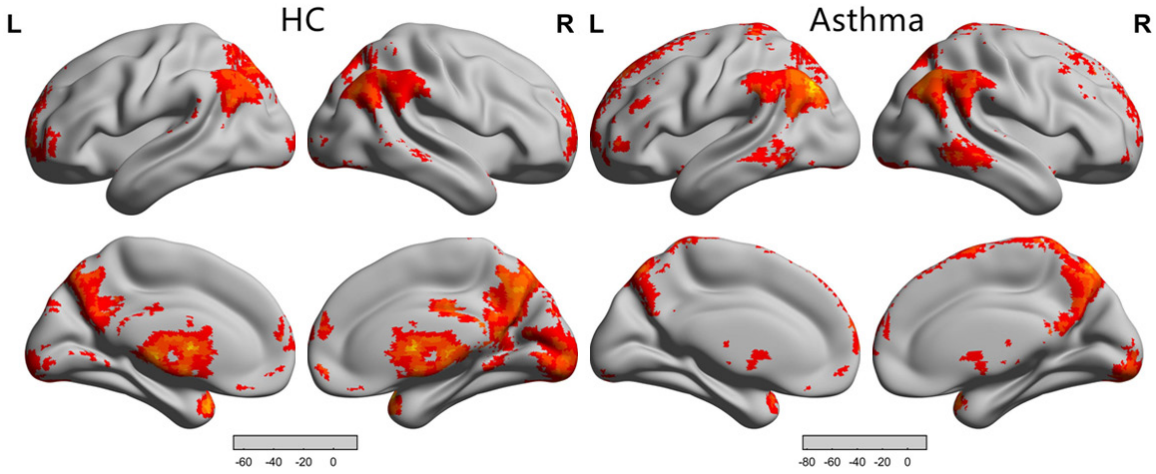

Figure 1. One sample t-test results. Within-group ALFF maps within the HC (left) and asthma (right) groups ($P < 0.001$, FDR corrected). Abbreviations: ALFF, amplitude of low-frequency fluctuation; BA, Brodmann area; HCs, healthy controls; FDR, false discovery rate.

ders (depression, bipolar disorder, sleep disorder, and so on); and 2) be able to be scanned with MRI (eg, no cardiac pacemaker or implanted metal devices, and so on). All research methods followed the Declaration of Helsinki and conformed to the principles of medical ethics of Jiangxi Provincial People's Hospital, Nanchang, People's Republic of China. All volunteers participated in the study voluntarily and were informed of the purposes, methods, and potential risks before signing an informed consent form.

MRI parameters

MRI scanning was performed on a 3-Tesla MR scanner (Trio, Siemens, Munich, Germany). The T1 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°) 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-planar imaging pulse sequence).

fMRI data analysis

Functional data were preprocessed using DPARSFA (http://rfmri.org/DPARSF) [25] 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. The first ten volumes were discarded due to magnetization equilibration. After the head motion correction, the fMRI images were spatially normalized to the Montreal Neurological Institute space criteria using the standard echo-planar imaging template and resampling the images at a resolution of 3 mm × 3 mm × 3 mm. 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 cumulative clinical measurements, including the age and weight in two groups were analyzed in the study with independent sample T test using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). ($P < 0.05$ significant differences).

For the asthma and HCs, a one-sample t-test ($P < 0.001$, FDR corrected) was performed to

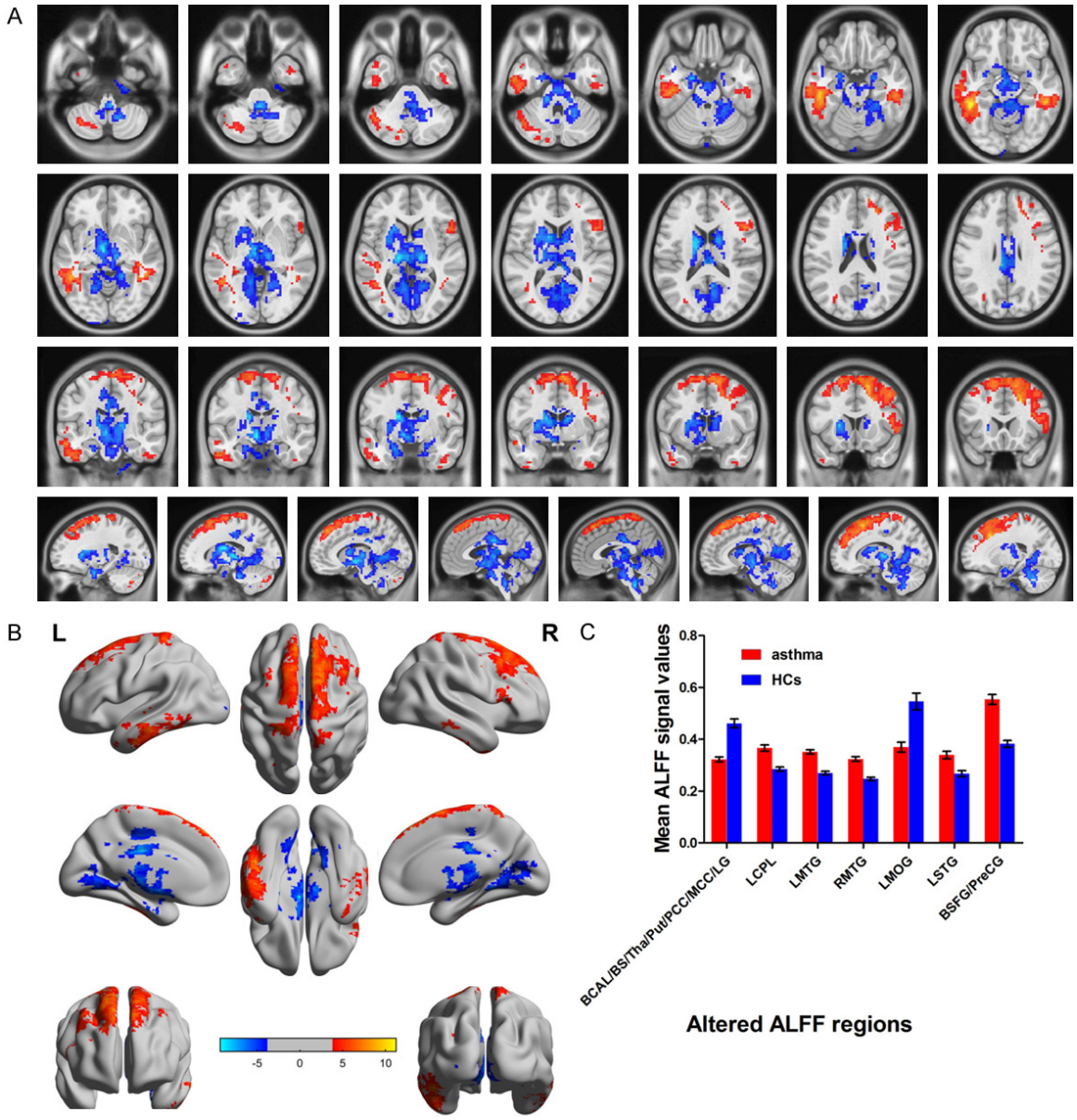

Figure 2. Spontaneous brain activity in the asthma versus HCs. Significant activity differences were observed in the bilateral cerebellum anterior lobe/brainstem/thalamus/putamen/posterior cingulate cortex/middle cingulate cortex/lingual gyrus and left middle occipital gyrus, left cerebellum posterior lobe, left middle temporal gyrus, right middle temporal gyrus, left superior temporal gyrus and bilateral superior frontal gyrus/precentral gyrus. The red or yellow denotes higher ALFF values, and the blue areas indicate lower ALFF values, respectively ($P < 0.01$ for multiple Comparisons using Gaussian Random Field (GRF) theory, $z > 2.3$, $P < 0.01$, cluster > 40 voxels, FDR corrected). A, B. The mean values of altered ALFF values between the asthma and HC groups. C. Abbreviations: ALFF, amplitude of low-frequency fluctuation; HC, healthy controls; FDR, false discovery rate; BCAL, bilateral cerebellum anterior lobe; BS, brainstem; Tha, thalamus; Put, putamen; PCC, posterior cingulate cortex; MCC, middle cingulate cortex; LG, lingual gyrus; LMOG, left middle occipital gyrus; LCPL, left cerebellum posterior lobe; LMTG, left middle temporal gyrus; RMTG, right middle temporal gyrus; LSTG, left superior temporal gyrus; BSFG, bilateral superior frontal gyrus; PreCG, precentral gyrus.

extract the ALFF values across the subjects within each group. And then, statistical analysis was performed with a general linear model analysis using the SPM8 toolkit to investigate the ALFF signal group differences in resting state between two groups, 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).

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

Brain areas	MNI coordinates			Voxels	BA	L/R	Peak T values
	x	y	z				
Asthma group < HCs							
Cerebellum Anterior Lobe/Brainstem/Thalamus/Putamen/Posterior Cingulate cortex/Middle Cingulate cortex/Lingual Gyrus	-6	-12	-9	4813	18, 19, 23, 30	B	-9.329
Middle Occipital Gyrus	-27	-96	0	56	18	L	-4.213
Asthma group > HCs							
Cerebellum Posterior Lobe	-45	-60	-36	248		L	6.978
Middle Temporal Gyrus	-45	-36	-18	997	20, 37	L	11.25
Middle Temporal Gyrus	51	-36	-15	413	20, 21	R	8.809
Superior Temporal Gyrus	-42	-30	3	53	53	L	5.283
Superior Frontal Gyrus/Precentral Gyrus	21	24	39	3621	4, 6, 8, 9	B	9.185

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, FDRcorrected). Abbreviations: ALFF, amplitude of low-frequency fluctuation; BA, Brodmann area; HCs, healthy controls; MNI, Montreal Neurological Institute; FDR, false discovery rate; L, left; R, right; B, bilateral.

The mean ALFF values in the different brain regions between two groups were analyzed by receiver operating characteristic (ROC) curves method. Meanwhile, Pearson correlation was used to evaluate the relationship between the mean ALFF values in different brain regions in asthma group and behavioral performances using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). ($P < 0.05$ significant differences).

Results

Demographics and visual measurements

We did not find any differences in weight ($P = 0.845$) and age ($P = 0.796$) between the two groups ($P > 0.05$). The mean ± standard deviation of the duration of asthma was 27±6.21 years. (The more details were showed in the **Table 1**).

ALFF differences

Intra-group comparison within the asthma and HC groups (**Figure 1**). Compared with HCs, asthma patients had significantly lower ALFF in the bilateral cerebellum anterior lobe/brainstem/thalamus/putamen/posterior cingulate cortex/middle cingulate cortex/lingual gyrus (BA 18, 19, 23, 30) and left middle occipital gyrus (BA 18) (**Figure 2A** and **2B** [blue] and **Table 2**). In contrast, higher ALFF values in the asthma patients groups were observed in the left cerebellum posterior lobe, left middle temporal gyrus (BA 20, 37), right middle temporal gyrus (BA 20, 21), left superior temporal gyrus (BA 53) and bilateral superior frontal gyrus/precentral gyrus (BA 4, 6, 8, 9). (**Figure 2A** and **2B** [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 between the two groups were shown with a histogram (**Figure 2C**). In the asthma group, we did not find any 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 asthma and HC groups might be useful diagnostic markers. Besides, the mean ALFF values in the different brain regions were analyzed by receiver operating characteristic (ROC) curves method. The areas under the ROC curve (AUCs) for ALFF values were as follows: left cerebellum posterior lobe (0.865), left middle temporal gyrus (BA 20, 37) (0.954), right middle temporal gyrus (BA 20, 21) (0.944), left superior temporal gyrus (BA 53) (0.809) and bilateral superior frontal gyrus/precentral gyrus (BA 4, 6, 8, 9) (0.943) (**Figure 3A**, astham > HCs); bilateral cerebellum anterior lobe/brainstem/thalamus/putamen/posterior cingulate cortex/middle cingulate cortex/lingual gyrus (BA 18, 19, 23, 30) (0.933) and left middle occipital gyrus (BA 18) (0.840) (**Figure 3B**, astham < HCs).

Discussion

The aim of our study was to investigate the spontaneous brain activity changes in asthma patients using ALFF method. We demonstrated that the asthma patients showed lower ALFF values in the bilateral cerebellum anterior lobe/

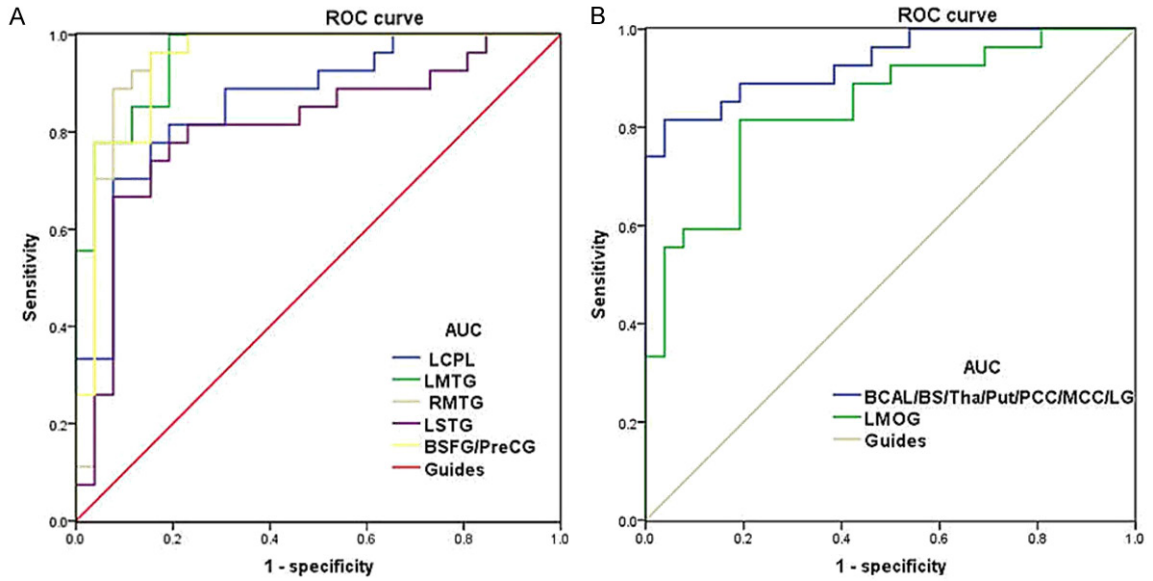

Figure 3. ROC curve analysis of the mean ALFF values for altered brain regions. Notes: The areas under the ROC curve were 0.865, ($P < 0.001$; 95% CI: 0.766-0.963) for left Cerebellum Posterior Lobe, left Middle Temporal Gyrus (0.954) ($P < 0.001$; 95% CI: 0.905-1.000), Right Middle Temporal Gyrus (BA 20, 21) (0.944) ($P < 0.001$; 95% CI: 0.873-1.000), left Superior Temporal Gyrus (0.809) ($P < 0.001$; 95% CI: 0.686-0.933) and Bilateral Superior Frontal Gyrus/Precentral Gyrus (BA 4, 6, 8, 9) (0.943) ($P < 0.001$; 95% CI: 0.878-1.000), (asthma > HCs) (A); Bilateral Cerebellum Anterior Lobe/Brainstem/Thalamus/Putamen/Posterior Cingulate cortex/Middle Cingulate cortex/Lingual Gyrus (BA 18, 19, 23, 30) (0.933) ($P < 0.001$; 95% CI: 0.868-0.998) and left Middle Occipital Gyrus (BA 18) (0.840) ($P < 0.001$; 95% CI: 0.734-0.947) (asthma < HCs) (B). Abbreviations: ROC, receiver operating characteristic; ALFF, amplitude of low-frequency fluctuation; CI, confidence interval; HCs, healthy controls; BCAL, bilateral cerebellum anterior lobe; BS, brainstem; Tha, thalamus; Put, putamen; PCC, posterior cingulate cortex; MCC, middle cingulate cortex; LG, lingual gyrus; LMOG, left middle occipital gyrus; LCPL, left cerebellum posterior lobe; LMTG, left middle temporal gyrus; RMTG, right middle temporal gyrus; LSTG, left superior temporal gyrus; BSFG, bilateral superior frontal gyrus; PreCG, precentral gyrus.

brainstem/thalamus/putamen/posterior cingulate cortex/middle cingulate cortex/lingual gyrus (BA 18, 19, 23, 30), left middle occipital gyrus (BA 18) compared wtih health controls. Meanwhile, the asthma patients showed higher ALFF values in the left cerebellum posterior lobe, left middle temporal gyrus (BA 20, 37), right middle temporal gyrus (BA 20, 21), left superior temporal gyrus (BA 53) and bilateral superior frontal gyrus/precentral gyrus (BA 4, 6, 8, 9).

The analysis of the decreased ALFF values in asthma

The brainstem is located at the posterior part of the brain, which include midbrain, pons and medulla oblongata. The brainstem plays a critical role in the regulation ofcardiac [26, 27] and respiratory control [28]. A previous study demonstrated that the health subjects showed the acivity in the dorsal rostral pons with stimulation respiration with carbon dioxide [29]. Moreover, A recent study exhibited that the periaqueductal grey (PAG) located in the midbrain was closely related to the respiratory control [30]. The asthma patients might have associated with chronic hypoxia [31]. In our study, we found that the asthma patients showed the significant lower ALFF values in the bilateral brainstem, which might indicate the dysfunction of the brainstem in asthma patients. The imparirment of the brainstem might relate to the dysfunction of respiratory control and dyspnea in asthma patients.

The thalamus is located in the forebrain, which play a critical role in the spatial visual processing [32] and pain [33]. Meanwhle, the thalamus is closely related to the regulation of respiratory [34, 35]. Douglas RM et al. found that the chronic intermittent hypoxia would lead to the decrease the N-acetyl aspartate/creatine (NAA/Cr) ratio in neonatal mouse thalamus [36]. In our study, we demonstrated that asthma patients showed the decreased ALFF val-

ues in the bilateral thalamus, which might reflect the dysfunction of the thalamus in the asthma patients. The intermittent hypoxia in asthma patients might lead to the dysfunction of the thalamus.

The putamen is located at the forebrain, which is the outside of the part of the basal ganglia. A previous study exhibited that the health subject who was stimulated respiration by carbon dioxide showed the posterior putamen activated [29]. Meanwhile, Molina F et al. demonstrated that the short-term hypoxia had bad influence on the angiogenic pathway in rat caudate putamen [37]. In our study, we found that the asthma patients showed the marked decreased ALFF values in the bilateral putamen. Thus, we speculated that the asthma may lead to the dysfunction of the putamen.

The cingulate cortex is located in the medial aspect of the cerebral cortex, which is the crucial part of the limbic system. The cingulate cortex plays an important role in the decision making [38] and negative affect [39]. A previous study demonstrated that the posterior cingulate cortex (PCC) was showed to be associated with emotion processes [40]. Meanwhile, Yang R et al. exhibited that the major depressive disorder patients showed the significant decreased functional connectivity in PCC [41]. Moreover, many previous researches found that asthma patients were affected by psychological problem [42, 43]. These negative emotions may be caused by asthma symptoms [44]. The occurrence of the depression may be related to dyspnea in asthma patients [45]. Yan X et al. demonstrated that the high altitude residents who lived in the chronic hypoxia environment exhibited the decreased gray matter volume at the left cingulated [46]. Esser RW et al. demonstrated that the COPD patients showed the decreased gray matter in PCC [47]. In support of these findings, we also found that the asthma patients showed the lower ALFF values in the PCC and middle cingulate cortex, which might indicate the dysfunction of the cingulate cortex. Thus, we speculated that the impairment of the cingulate cortex may be related to the negative emotion caused by the dyspnea symptoms.

The lingual gyrus is a part of the occipital lobe, which play an important role in processing vision. Besides, the lingual gyrus is involved in the reading processing [48]. Pescosolido N et al. demonstrated that the the hypobaric hypoxia might lead to the impaired visual function [49]. The children cerebral hypoxia was associated with the visual defects [50]. Zhang J et al. found that the COPD patients showed the decreased ALFF in the right lingual gyrus [51]. In support of these findings, our results suggested that the asthma patients showed the decreased ALFF values in the bilateral lingual gyrus and left middle occipital gyrus, which reflected the dysfunction of the occipital gyrus. Therefore, we speculated that asthma might lead to the dysfunction of occipital gyrus.

The analysis of the increased ALFF values in asthma

The superior frontal gyrus (SFG) is situated in the superior part of the prefrontal cortex, which play a key role in cognition [52]. Besides, the SFG is involved in the cognitive network and default mode network (DMN) [53]. Schneider S et al. found that acute hypoxia might lead to the activation in the right SFG [54]. In our study, we found that the asthma patients showed the marked increased ALFF values in the bilateral superior frontal gyrus, which might indicate the hyperactivity of the SFG. We speculated that the hyperactivity of the SFG might be related to the hypoxia symptom in asthma patients.

The precentral gyrus is located in the surface of the posterior frontal lobe, which is involved in the primary motor cortex. A previous study reported that the high altitude subject who was exposed to the hypoxia-reoxygenation environment showed the increased functional connectivity in the right postcentral gyrus [55]. In our study, we found that the asthma patients showed the significant increased ALFF values in the bilateral precentral gyrus. We suggested that the hyperactivity of the precentral gyrus might be related to hypoxia caused by dyspnea in asthma patients.

Conclusion

In summary, we demonstrated that the asthma patients had abnormal spontaneous activities in many brain regions related to respiratory control and emotion control function, which might provide some useful informations to explain the neural mechanisms of clinical features including hypoxia, dyspnea and depression in asthma patients.

Acknowledgements

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Disclosure of conflict of interest

None.

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