Front. Med. 2020, 14(6): 792–801
https://doi.org/10.1007/s11684-020-0745-1

RESEARCH ARTICLE

Cerebral regional and network characteristics in asthma patients: a resting-state fMRI study

Siyi Li[1,*], Peilin Lv[2,*], Min He[3,*], Wenjing Zhang[1], Jieke Liu[4], Yao Gong[5], Ting Wang[3], Qiyong Gong[1], Yulin Ji (✉)[3], Su Lui (✉)[1]

[1]Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu 610041, China; [2]Department of Anesthesiology, West China Hospital of Sichuan University, Chengdu 610041, China; [3]Department of Respiratory Medicine, West China Hospital, Sichuan University, Chengdu 610041, China; [4]Department of Radiology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu 610041, China; [5]Department of Geriatric Psychiatry, The Fourth People's Hospital of Chengdu, Chengdu 610036, China

Abstract **Asthma is a serious health problem that involves not only the respiratory system but also the central nervous system. Previous studies identified either regional or network alterations in patients with asthma, but inconsistent results were obtained. A key question remains unclear: are the regional and neural network deficits related or are they two independent characteristics in asthma? Answering this question is the aim of this study. By collecting resting-state functional magnetic resonance imaging from 39 patients with asthma and 40 matched health controls, brain functional measures including regional activity (amplitude of low-frequency fluctuations) and neural network function (degree centrality (DC) and functional connectivity) were calculated to systematically characterize the functional alterations. Patients exhibited regional abnormities in the left angular gyrus, right precuneus, and inferior temporal gyrus within the default mode network. Network abnormalities involved both the sensorimotor network and visual network with key regions including the superior frontal gyrus and occipital lobes. Altered DC in the lingual gyrus was correlated with the degree of airway obstruction. This study elucidated different patterns of regional and network changes, thereby suggesting that the two parameters reflect different brain characteristics of asthma. These findings provide evidence for further understanding the potential cerebral alterations in the pathophysiology of asthma.**

Keywords asthma; brain; regional activation; functional connectivity; resting-state fMRI

Introduction

Asthma is one of the most serious and chronic respiratory diseases that also affects the central nervous system [1–5]. Previous studies have illustrated functional changes and their implications in the brains of asthma patients by using functional MRI (fMRI), which is a noninvasive method that aims to improve our understanding of human brain function *in vivo* [6]. Regional functional changes, including altered activation in the insula, anterior cingulate cortex, and superior frontal gyrus, were observed in patients with asthma, and these specific functional changes are related to emotional pathway and pulmonary symptoms in the respiratory system [5,7,8]. In addition to regional function, fMRI studies have demonstrated a close connection between lung function and neural network changes in patients with asthma. For example, altered degree centrality (DC) values, which are the measure of the node influence across whole brain functional connections at the voxel level [9], have been detected in various brain regions in patients with asthma [10]. Functional connectivity (FC) changes across limbic circuits were also found during perceived dyspnea and pain in patients with asthma [11].

The abovementioned evidence suggests that brain functional changes involve both regional and network levels in asthma. However, the relationship between

Received July 4, 2019; accepted December 18, 2019
Correspondence: Su Lui, lusuwcums@tom.com;
Yulin Ji, jiyulin427@163.com

*These authors contributed equally to this study.

regional functional changes and network disorganization remains unclear. Different patterns of changes have been detected using varying analytic approaches. Regional functional changes have been detected in various brain areas, including the anterior cingulate cortex, insular lobe, and frontal lobe [1,7,8], while altered neural networks are located in the default mode network, cortical-basal ganglia network, frontoparietal network, and sensorimotor network, which affect areas including the temporal gyrus, parietal lobe, basal ganglia nuclei, and part of the cerebellum [10,12,13]. The varied findings at both regional and network levels may be affected by studied samples, methodologies, and therapy selections. Moreover, regional and network changes show associations with different clinical ratings. Functional changes in the anterior cingulate cortex and insular cortex are closely related to emotional performance with depression and stress [1,8], while the neural network in the brainstem, periaqueductal gray, and limbic system is correlated with airway inflammation, dyspnea, and pain of the respiratory system in asthma [11,14]. Regional functional changes can influence the global network in brain disorders such as schizophrenia [15–19]. Different regional and network patterns reflect specific pathophysiology mechanisms and can potentially be used as biomarkers and treatment targets for schizophrenia. However, whether regional functional changes also lead to neural network deficits in asthma remains largely unknown, and this information is crucial to clarify the biological characteristics of the disease and further develop clinical diagnosis and treatment.

Therefore, the current resting-state fMRI (rs-fMRI) study will explore brain functional changes at both the regional and network levels in patients with asthma. Metrics include amplitude of low-frequency fluctuation (ALFF, reflecting the spontaneous neural activity of the cerebral cortex) [20], DC, and FC. The relationship between functional measures and asthma-related clinical symptoms was analyzed to determine associations between functional brain changes and clinical ratings. Emotional correlation analysis with fMRI metrics was carried out based on the previous findings with processing of emotional information in patients with asthma [1]. We hypothesized that a potential difference existed in brain functional changes and clinical performance at the regional and whole brain levels in patients with asthma, and regional abnormalities may be associated with network disorganization.

Materials and methods

Participants

This study was approved by the Ethical Committee of West China Hospital of Sichuan University. All participants volunteered for the study and provided written informed consent. We recruited 39 patients who demonstrated evidence of either bronchodilator reversibility or bronchial hyperresponsiveness and were diagnosed with asthma according to the Global Initiative for Asthma (GINA) criteria. Forty healthy controls (HCs) matched in age and sex without a history of asthma or other significant medical conditions were also enrolled. The inclusion criteria for patients were as follows: (1) age between 18 and 60 years, (2) right-handed, (3) airway hyperresponsiveness with inhaled methacholine (provocative dose causing a 20% fall in the forced expiratory volume in the first second (FEV_1)) or bronchodilator reversibility in the FEV_1 more than 12% predicted and more than 200 mL, and (4) moderate asthma classified according to the GINA criteria. Exclusion of criteria for all participants included the following: (1) age of younger than 18 years or older than 60 years, (2) history of cancer or other chronic diseases, (3) current pregnancy or breastfeeding, (4) history of psychiatric disorders as revealed by using the Structured Clinical Interview for DSM-IV (SCID)-Patient Version, (5) currently experiencing an acute asthma exacerbation, and (6) history of substance abuse or dependence.

Demographic and clinical data acquisition

All of the participants were interviewed to collect demographic data, including age, gender, years of education, and body mass index (BMI). For recruited patients with asthma, additional clinical information, including illness duration and severity of asthma, was recorded. Lung function measures, including FEV_1 and forced vital capacity (FVC), were tested by a spirometer (MasterScreen Body, Jaeger, Germany). To determine whether brain functional alterations in patients with asthma may contribute to the increased risk for psychiatric moods, we collected the Hamilton Rating Scale for Depression and Anxiety (HRSD and HRSA, respectively) to measure the emotional status of patients.

Image data acquisition

MRI data were collected on a whole-body 3.0 T MR scanner (Siemens Trio, Erlangen, Germany) with a 12-channel phase array head coil. Rs-fMRI data were acquired with an EPI protocol: TR = 2000 ms, TE = 30 ms, flip angle = 90°, matrix = 64 × 64, field of view = 240 mm × 240 mm, 30 slices with 5 mm slice thickness, and voxel size = 3.75 mm × 3.75 mm × 5 mm. The duration of rs-fMRI scanning was 7 min, and each functional run contained 200 volumes. A high-resolution T1-weighted anatomical image was acquired using a 3D-spoiled gradient echo sequence (SPGR; TR = 8.5 ms, TE = 3.93 ms, flip angle = 12°, 156 sagittal slices with thickness = 1 mm, FOV = 240 mm × 240 mm, and data matrix = 256 × 256) for normalization of rs-fMRI data.

Data preprocessing

We preprocessed rs-fMRI data using Data Processing Assistant for Resting-State fMRI (version 2.3) software, and this software was implemented within the MATLAB toolbox. The first 10 volumes were discarded to achieve steady-state longitudinal magnetization, and the remaining data were processed with the following steps: slice timing, head motion correction, spatial normalization, and smoothing with a Gaussian kernel of 4 mm full width at half maximum (FWHM). After the above steps were completed, fMRI images were spatially normalized to Montreal Neurological Institute space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra to resample the images and achieve a voxel resolution of 3 mm × 3 mm × 3 mm [21]. We removed the linear trend to correct the scanner drift, and the bandpass filtering range was set at 0.01–0.08 Hz to reduce the effects of low-frequency drift and high-frequency physiological noise.

To obtain ALFF values, we transformed the time series to the frequency domain to achieve the power spectrum by using fast Fourier transformation. The measure of the ALFF from each voxel was yielded by transforming the square root from power and averaging from 0.01 Hz to 0.08 Hz. Finally, the ALFF of each voxel was divided by the global mean ALFF value, which was standardized across all subjects.

DC is a reliable centrality metric across the entire brain network. DC values were calculated using REST software (Resting-State fMRI Data Analysis Toolkit V1.8) [22]. First, we computed the time series of all brain voxels using Pearson's correlation coefficients (r). Second, by setting a predefined gray matter mask, we obtained an FC correlation matrix between the time series of one voxel and the time courses of all other voxels. Third, we defined the thresholding of each correlation at $r > 0.25$ to remove the effects caused by noises [23]. Finally, we converted the individual voxel-wise DC into a z-score map, and yielded DC data were smoothed spatially with a Gaussian kernel of 6 mm FWHM.

FC revealed the specific configurations of connected regions [24]. FC values were computed by using the same software with DC values in the REST package toolkit. First, we selected the regions of interest (ROIs) based on the comparison results of ALFF and DC values between patients with asthma and HCs. Second, the representative time series of each ROI was obtained by averaging the preprocessed rs-fMRI data from all voxels in the ROI in each individual. Finally, FC values were computed using Pearson correlation coefficients between the time series of each ROI and whole brain, resulting in a z-score map of FC in each subject.

Statistical analysis

Statistical analytic processes of the comparison of ALFF, DC, and FC values between patients with asthma and HCs were performed in REST software with two-sample T test analysis. Additionally, age, gender, and education years were added as covariates. In all image statistical analyses, AlphaSim was used to correct for multiple comparisons when testing for statistical significance. The AlphaSim calculation was also performed in REST software on the basis of the statistical map of two groups and a predefined mask file. An actual smoothness kernel was estimated to ensure the accuracy of the results. The threshold of a false-positive detection for our study was set to $P < 0.05$ using a minimum cluster size of five contiguous voxels.

Peak values of functional measures of brain regions that were significantly different between groups were extracted. Pearson correlation analysis between altered functional metrics and asthma-specific clinical indices, including illness duration, severity of illness score, FEV_1, FVC, FEV_1/FVC, and psychiatric score of HRSD and HRSA, was conducted using SPSS Statistics software (version 24.0). The significance level was set to $P < 0.05$.

Results

Demographics

The demographic information showed no significant differences in age (patients, 34.54; HCs, 33.90), gender (male/female: patients, 11/28; HCs, 10/30), education years (patients, 11.46; HCs, 12.80), and BMI (patients, 23.1; HCs, 21.41) between patients with asthma and HCs ($P > 0.05$). In patients with asthma, the mean FEV_1 and FVC were 2.28 and 3.12, respectively, and the mean percentage of FEV_1/FVC was 71.88. The mean duration of illness for patients was 5.88 years, and the mean severity of illness score was 2.29. HRSD and HRSA were evaluated separately, resulting in mean scores of 7.62 and 6.03, respectively, in patients with asthma (Table 1).

Imaging findings

In rs-fMRI analysis, we found regional functional alterations in the cerebrum within the default mode network measured with ALFF values. Compared with HCs, patients with asthma showed decreased ALFF values in the left angular gyrus and right precuneus, while ALFF values were increased in the right inferior temporal gyrus ($P < 0.05$, corrected by AlphaSim calculation; Table 2 and Fig. 1).

Network alterations were evaluated with DC values.

Table 1 Demographics and clinical characteristics of study participants

	Asthma patients		HCs[a]		*P*
	Mean	SD	Mean	SD	
Age (year)	34.54	9.05	33.9	8.01	0.54
Gender (male/female)	11/28	–	10/30	–	0.53
Education (year)	11.46	3.71	12.8	4.21	0.62
BMI[b] (kg/m^2)	23.10	2.80	21.41	2.83	0.76
HRSD[c] score	7.62	6.84			
HRSA[d] score	6.03	5.17			
FEV_1[e] (%)	2.28	0.57			
FVC[f] (%)	3.12	0.57			
FEV_1/FVC (%)	71.88	13.58			
Severity of illness score	2.29	1.06			
Duration of illness (year)	5.88	8.05			

[a] HCs, healthy controls; [b] BMI, body mass index; [c] HRSD, Hamilton Rating Scale for Depression; [d] HRSA, Hamilton Rating Scale for Anxiety; [e] FEV_1, forced expiratory volume in the first second; [f] FVC, forced vital capacity.

Table 2 Amplitude of low-frequency fluctuation and degree centrality of significant brain areas with comparisons between patients with asthma and healthy controls

	Brain areas	*x*	*y*	*z*	Voxels	*T*	*P*
ALFF[a]							
Patients<HCs[b]	Left angular gyrus	−45	−69	30	149	3.93	<0.05
	Right precuneus	3	−54	18	165	3.53	<0.05
Patients>HCs	Right inferior temporal gyrus	54	−3	−33	105	3.18	<0.05
Degree centrality							
Patients<HCs	Left caudate	−12	9	3	110	3.94	<0.05
	Left lingual gyrus	−15	−87	−18	472	4.07	<0.05
	Right middle occipital gyrus	39	−72	12	398	3.92	<0.05

[a] ALFF, amplitude of low-frequency fluctuation; [b] HCs, healthy controls.

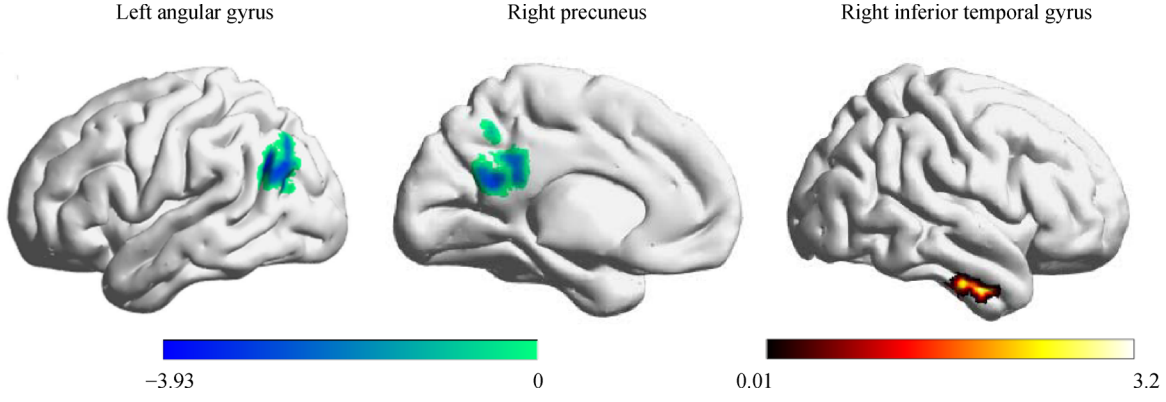

Fig. 1 Patients with asthma showed decreased amplitude of low-frequency fluctuation (ALFF) values in the left angular gyrus and right precuneus (green and blue) and increased ALFF values in the right inferior temporal gyrus (red and yellow).

Compared with HCs, patients had decreased DC changes in the left caudate, left lingual gyrus, and right middle occipital gyrus extending to the right inferior occipital gyrus ($P < 0.05$, corrected by AlphaSim calculation; Table 2 and Fig. 2). DC alterations showed no overlap of anatomic areas with regional functional changes.

To further determine the difference between regional and network changes, we performed FC analysis by selecting seeds based on brain regions with altered ALFF or DC values. By comparing patients with asthma with HCs in subsequent network analysis based on DC results, we detected widespread decreased FC consistent with DC

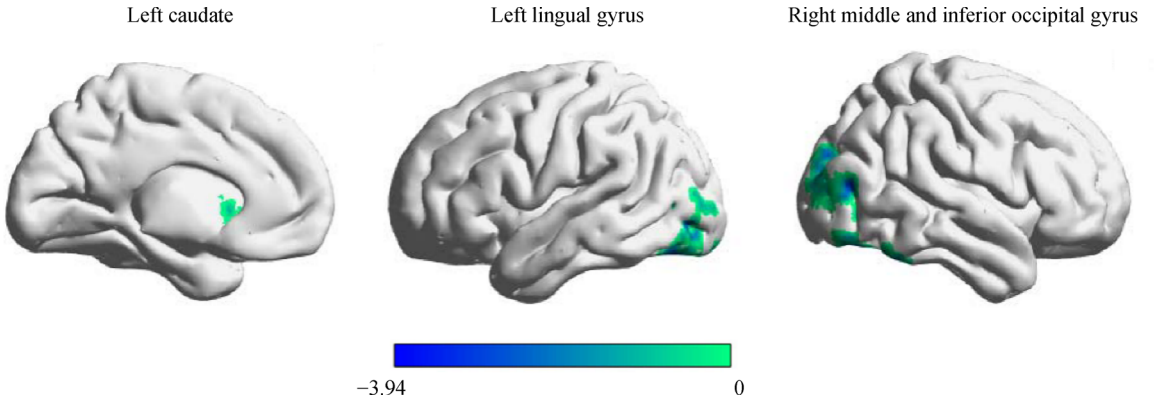

Fig. 2 Patients with asthma showed decreased degree centrality in the left caudate, left lingual gyrus, and right middle occipital gyrus, extending to the right inferior occipital gyrus (green and blue).

findings. Decreased FC was found between the left caudate seed and left superior frontal gyrus and right inferior occipital gyrus in patients with asthma and between the left lingual gyrus seed and left superior frontal gyrus, as well as between the right middle occipital gyrus seed and left superior frontal gyrus ($P < 0.05$, corrected by AlphaSim calculation; Table 3 and Fig. 3), which mostly involved the sensorimotor network and visual network. No significant FC was detected between seeds with regional ALFF changes and other brain regions.

Correlation with clinical ratings

A positive correlation was found between DC of the left lingual gyrus and FEV_1/FVC ($r = 0.442$, $P = 0.009$; Fig. 4), indicating that decreased DC was associated with severe

Table 3 Decreased functional connectivity of significant brain areas with comparisons between patients with asthma and healthy controls

Seed	Connected area	*x*	*y*	*z*	Voxels	*T*	*P*
Left caudate	Left superior frontal gyrus	−9	−9	78	511	3.83	<0.05
	Right inferior occipital gyrus	45	−78	−18	755	4.28	<0.05
Left lingual gyrus	Left superior frontal gyrus	−4	33	33	185	3.50	<0.05
Right middle occipital gyrus	Left superior frontal gyrus	−12	28	40	146	3.23	<0.05

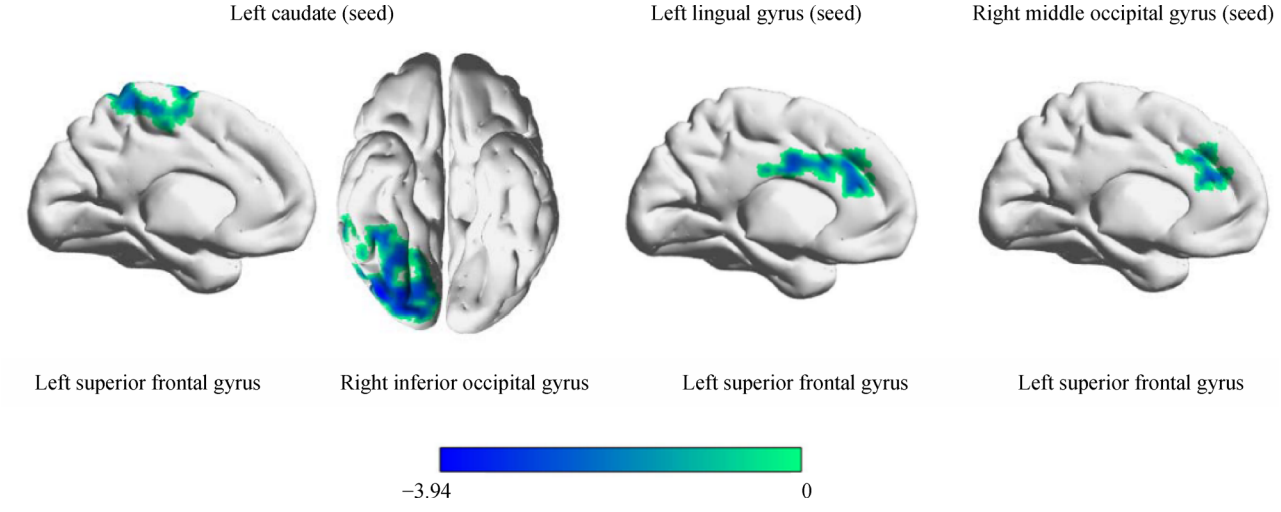

Fig. 3 Patients with asthma showed decreased functional connectivity between left caudate seed and left superior frontal gyrus and right inferior occipital gyrus; between left lingual gyrus seed and left superior frontal gyrus; and between right middle occipital gyrus seed and left superior frontal gyrus (green and blue).

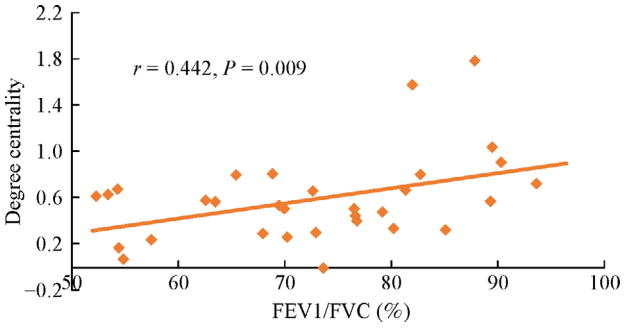

Fig. 4 Degree centrality of left lingual was positively correlated with FEV_1/FVC (%) in patients with asthma (FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity).

airway obstruction. No significant correlation was detected between other rs-fMRI measures and asthmatic clinical data and emotional data.

Discussion

By analyzing the metrics of ALFF, DC, and FC, our rs-fMRI study revealed that regional functional changes were located in regions that differed from those with network changes. Regional functional changes included both decreased and increased activation within the default mode network in patients with asthma, while the network deficits included the cortical cortex and subcortical regions involving the left caudate, lingual gyrus, and right middle occipital gyrus. No significant correlation between ALFF and clinical symptoms was detected. Further FC analysis strengthened the decreased network alterations in asthma with decreased FC between DC-based seeds and the left superior frontal gyrus and right occipital gyrus in the sensorimotor network and visual network, respectively. Moreover, we detected the relationship between brain fMRI measures and lung functional index with a positive correlation between DC in the left lingual gyrus and FEV_1/FVC. Altogether, these findings suggested that regional and neural network deficits are independent characteristics in patients with asthma, which may reflect different aspects of the pathophysiology of asthma.

ALFF is a reliable metric with good performance in demonstrating spontaneous activities of the brain cortex at rest [20,25]. We observed regional brain functional changes with decreased ALFF in the left angular gyrus and right precuneus and increased ALFF located in the right inferior temporal gyrus. The angular gyrus, precuneus, and temporal lobe are usually classified as the default mode network in many network organizations [26–28]. The default mode network is considered a higher-level cognitive network and consists of brain regions that typically activate during resting-state but deactivate during the performance of a particular task [29,30]. The altered regional abnormalities within the default mode network implied spontaneous changes in the central nervous system affected by asthma. Previous studies demonstrated reduced gray matter volume in the angular gyrus within patients with asthma and reduced gray matter volume and cortical thickness in the precuneus in patients with chronic obstructive pulmonary disease (COPD) [31–33]. We also detected the regional changes in the left angular gyrus with fractional ALFF (Supplementary Table S1), which further demonstrated the stable change of this area affected by asthma. The consistent alterations in brain structure and function may imply their important roles in the participation of pathophysiology in asthma-related cerebral changes. The only increased ALFF alteration was located in the right inferior temporal gyrus; thus, the high activation in patients with asthma was similar to the changes in the COPD-related brain function study [34]. This area is correlated with chronic pain symptoms, such as chronic back pain [35,36], which is considered a key component engaging in the chronic pain sensory process [13]. This finding might explain the association of lasting symptoms in patients with asthma. Regional abnormalities exhibited independent changes within the default mode network, which suggested that the spontaneous changes in cerebral regional function in the central nervous system originated from asthma illness.

Unlike regional functional changes, the network deficits reflect cortical and subcortical changes involving the left caudate, lingual gyrus, and right occipital gyrus. No overlapping brain areas in ALFF and DC illustrated the inconsistency between regional and network changes in patients with asthma. The widespread decreased brain connectivity provided evidence for the impaired central nervous system in patients with asthma. Altered brain functional changes in the lingual gyrus have been reported among high-altitude residents [37–39], and brain connectivity changes in the lingual gyrus could be related to hypoxia in asthma. We also found a positive correlation between DC of the left lingual gyrus and FEV_1/FVC, which suggested that decreased DC was correlated with heavy airway obstruction. The direct relationship between brain functional measures and the lung functional index strengthens asthma-related impairments in the central nervous system. The caudate is believed to play a key role in cognitive neural circuits [40], which may be correlated with degenerated cognitive function in patients with asthma [41]. Structural studies in COPD also reported decreased gray matter volume and density in the caudate [42,43]. Simultaneous changes in caudate structure and function suggested consistent subcortical alterations in asthma. Abnormalities in the bilateral occipital gyrus were detected in both CT and MRI examinations during asthma attacks [44–46], and visible structural changes enhance the

influence of asthma on the cerebrum. The functional alterations in asthma and patients with COPD by using regional homogeneity (reflecting regional signal synchrony strength) [47] and FC analysis were consistent with our findings [48]. These aberrant functional changes demonstrated the crucial network nodes influenced by asthma.

We further calculated the seed-based FC to explore whether the ALFF or DC can affect the connectivity strength, which reflects the relationship between regional and network function in an intuitive way. We did not find significant FC based on seeds with ALFF alteration, which implied that regional function alterations exerted limited effects on network function. Moreover, widespread FC alterations in patients with asthma based on seeds with DC alteration provided evidence supporting decreased network function. Selected FC seeds (including the left caudate, lingual gyrus, and right middle occipital gyrus) from the DC results and the network exerted decreased FC, mainly involving the superior frontal gyrus and occipital lobe. The superior frontal gyrus is an important brain region in the sensorimotor network [49,50], and an altered sensorimotor network is associated with altered respiratory amplitude in patients with asthma [51]. We detected decreased FC in three seeds from the DC results and the superior frontal gyrus, which highlighted the crucial role of the superior frontal gyrus in asthma-specific neural abnormalities. Reduced gray matter volume in the superior frontal gyrus has been elucidated [31] and locally segregated but less efficiently integrated into the frontal lobe with structural organization [52]. Respiratory system measures, including ratings of breathlessness, airway inflammation, and asthma control degree, are all associated with brain functional alterations in this area [31,53]. Patients with COPD also demonstrated activation in the same brain area [34], indicating the interrelation between respiratory system damage and functional changes in the superior frontal gyrus within the sensorimotor network. Except for the relation between network changes and clinical features, a previous study found direct evidence of neuroinflammation with increased levels of tumor necrosis factor α and interleukin-1 β in the superior frontal gyrus and significant neuronal loss in the asthmatic mouse brain [54]. Our results also showed the importance of the occipital gyrus with decreased FC between the left caudate and right inferior occipital gyrus, as well as decreased FC between the right middle occipital gyrus and left superior frontal gyrus. The occipital cortex is associated with visual processing, and occipital degeneration participated in the visual deficits in some patients with asthma, as reflected in previous studies [45,55–57]. The consistent results in our study hinted at the impaired visual network affected by asthma. Beyond this finding, the occipital lobe is a brain area with high vascular density. Therefore, functional changes may also be possible due to abnormal ventilation in poor asthma control patients [58–60]. The widespread decreased neural network exhibited different alterations with regional function, and the sensorimotor network and visual network are the core changes in the network influenced by asthma. These findings demonstrated different cerebral regional and network patterns, and those patterns reflected specific characteristics related to respiratory symptoms and secondary changes in patients with asthma, which could be potential biomarkers in helping us understand the neural pathophysiology of asthma and selection of treatment.

Although we found different regional and network characteristics with mostly widespread decreases in brain functional changes in asthma patients with ALFF, DC, and FC, some limitations should be considered in three perspectives. First, we recruited both patients and HCs with more females than males, and the gender bias could sway our results with more female features. Further studies with large sample sizes, including gender-balanced patients, are needed. Second, our cross-sectional study could not reflect asthma progression with dynamic functional abnormalities, and a longitudinal study is required in the future to display the progression of brain alterations in asthma. Finally, we did not exclude the confounding effects of medication, which could affect the asthma control condition exhibited in brain activities.

In conclusion, by using functional measures with ALFF, DC, and FC, this study reflected different patterns of brain functional changes at the regional and network levels in patients with asthma. Regional abnormalities reflected independent changes within the default mode network, which implied regional deficits with spontaneous changes in the central nervous system affected by asthma. Network characteristics were detected with widespread decreased functional alterations across the whole brain, and they were mostly involved with changes in sensorimotor and visual network. The correlation between network abnormalities and airway obstruction degree reflected that brain damage was associated with impaired respiratory system originating from asthma. This study is helpful in extending our understanding of the neuropathophysiology of asthma.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Nos. 81671664 and 81621003), National Program for Support of Top-notch Young Professionals (No. W02070140), Fundamental Research Funds for the Central Universities (No. 2018SCUH0011), Science and Technology Project of the Health Commission of Sichuan Province (No. 18ZD035), Sichuan Science and Technology Program (No. 2019YJ0155), and 1·3·5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (Nos. ZYYC08001 and ZYJC18020).

Compliance with ethics guidelines

Siyi Li, Peilin Lv, Min He, Wenjing Zhang, Jieke Liu, Yao Gong, Ting Wang, Qiyong Gong, Yulin Ji, and Su Lui declare that they have no conflict of interest. This study was approved by the Ethical Committee of West China Hospital of Sichuan University, and all procedures followed were in accordance with the ethical standards.

Electronic Supplementary Material Supplementary material is available in the online version of this article at https://doi.org/10.1007/s11684-020-0745-1 and is accessible for authorized users.

References

1. Rosenkranz MA, Davidson RJ. Affective neural circuitry and mind-body influences in asthma. Neuroimage 2009; 47(3): 972–980
2. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. PLoS One 2012; 7(8): e40921
3. Parker J, Wolansky LJ, Khatry D, Geba GP, Molfino NA. Brain magnetic resonance imaging in adults with asthma. Contemp Clin Trials 2011; 32(1): 86–89
4. Barr J, Katz Y, Barzilay B, Lahat E. 'Respiratory epilepsy'–does it exist? Clin Neurol Neurosurg 1998; 100(3): 196–198
5. Ritz T, Kroll JL, Patel SV, Chen JR, Yezhuvath US, Aslan S, Khan DA, Pinkham AE, Rosenfield D, Brown ES. Central nervous system signatures of affect in asthma: associations with emotion-induced bronchoconstriction, airway inflammation, and asthma control. J Appl Physiol 2019; 126(6): 1725–1736
6. Pattinson K. Functional brain imaging in respiratory medicine. Thorax 2015; 70(6): 598–600
7. Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, Bosch JA, Sheridan JF, Davidson RJ. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc Natl Acad Sci USA 2005; 102(37): 13319–13324
8. Busse WW. The brain and asthma: what are the linkages? Chem Immunol Allergy 2012; 98: 14–31
9. Zuo XN, Ehmke R, Mennes M, Imperati D, Castellanos FX, Sporns O, Milham MP. Network centrality in the human functional connectome. Cereb Cortex 2012; 22(8): 1862–1875
10. Li QG, Zhou FQ, Huang X, Zhou X, Liu C, Zhang T, Li HY, Wu XR, Wang J. Alterations of resting-state functional network centrality in patients with asthma: evidence from a voxel-wise degree centrality analysis. Neuroreport 2018; 29(14): 1151–1156
11. von Leupoldt A, Sommer T, Kegat S, Eippert F, Baumann HJ, Klose H, Dahme B, Büchel C. Down-regulation of insular cortex responses to dyspnea and pain in asthma. Am J Respir Crit Care Med 2009; 180(3): 232–238
12. Xiong X, Zhu H, Wang T, Ji Y. Altered intrinsic regional brain activity in female asthmatics with or without depressive symptoms: a resting-state functional magnetic resonance imaging study. J Asthma 2016; 53(9): 922–929
13. Zhang Y, Yang Y, Bian R, Yin Y, Hou Z, Yue Y, Xu Z, Yuan Y. Abnormal functional connectivity of ventral anterior insula in asthmatic patients with depression. Neural Plast 2017; 2017: 7838035
14. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry 2009; 66(5): 407–414
15. Liu S, Li A, Liu Y, Yan H, Wang M, Sun Y, Fan L, Song M, Xu K, Chen J, Chen Y, Wang H, Guo H, Wan P, Lv L, Yang Y, Li P, Lu L, Yan J, Wang H, Zhang H, Wu H, Ning Y, Zhang D, Jiang T, Liu B. Polygenic effects of schizophrenia on hippocampal grey matter volume and hippocampus-medial prefrontal cortex functional connectivity. Br J Psychiatry 2019 Jun 6. [Epub ahead of print] doi: 10.1192/bjp.2019.127
16. Lavigne KM, Menon M, Woodward TS. Functional brain networks underlying evidence integration and delusions in schizophrenia. Schizophr Bull 2020; 46(1): 175– 183
17. Fu Z, Tu Y, Di X, Du Y, Pearlson GD, Turner JA, Biswal BB, Zhang Z, Calhoun VD, Characterizing dynamic amplitude of low-frequency fluctuation and its relationship with dynamic functional connectivity: an application to schizophrenia. Neuroimage 2018; 180(Pt B): 619–631
18. Zhou C, Tang X, You W, Wang X, Zhang X, Zhang X, Yu M. Altered patterns of the fractional amplitude of low-frequency fluctuation and functional connectivity between deficit and non-deficit schizophrenia. Front Psychiatry 2019; 10: 680
19. Lui S, Deng W, Huang X, Jiang L, Ma X, Chen H, Zhang T, Li X, Li D, Zou L, Tang H, Zhou XJ, Mechelli A, Collier DA, Sweeney JA, Li T, Gong Q. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am J Psychiatry 2009; 166(2): 196–205
20. Zuo XN, Di Martino A, Kelly C, Shehzad ZE, Gee DG, Klein DF, Castellanos FX, Biswal BB, Milham MP. The oscillating brain: complex and reliable. Neuroimage 2010; 49(2): 1432–1445
21. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007; 38(1): 95–113
22. Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, Tian LX, Jiang TZ, Wang YF. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 2007; 29(2): 83–91
23. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci 2009; 29 (6): 1860–1873
24. Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP. Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. Neuroimage 2010; 49(3): 2163–2177
25. Bu X, Hu X, Zhang L, Li B, Zhou M, Lu L, Hu X, Li H, Yang Y, Tang W, Gong Q, Huang X. Investigating the predictive value of different resting-state functional MRI parameters in obsessive-compulsive disorder. Transl Psychiatry 2019; 9(1): 17
26. Bellana B, Liu Z, Anderson JAE, Moscovitch M, Grady CL.

Laterality effects in functional connectivity of the angular gyrus during rest and episodic retrieval. Neuropsychologia 2016; 80: 24–34

27. Foster BL, Rangarajan V, Shirer WR, Parvizi J. Intrinsic and task-dependent coupling of neuronal population activity in human parietal cortex. Neuron 2015; 86(2): 578–590
28. Ciaramelli E, Grady CL, Moscovitch M. Top-down and bottom-up attention to memory: a hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. Neuropsychologia 2008; 46(7): 1828–1851
29. Davey CG, Harrison BJ. The brain's center of gravity: how the default mode network helps us to understand the self. World Psychiatry 2018; 17(3): 278–279
30. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001; 98(2): 676–682
31. Wang L, Wang T, Liu S, Liang Z, Meng Y, Xiong X, Yang Y, Lui S, Ji Y. Cerebral anatomical changes in female asthma patients with and without depression compared to healthy controls and patients with depression. J Asthma 2014; 51(9): 927–933
32. Chen J, Lin IT, Zhang H, Lin J, Zheng S, Fan M, Zhang J. Reduced cortical thickness, surface area in patients with chronic obstructive pulmonary disease: a surface-based morphometry and neuropsychological study. Brain Imaging Behav 2016; 10(2): 464–476
33. Wang C, Ding Y, Shen B, Gao D, An J, Peng K, Hou G, Zou L, Jiang M, Qiu S. Altered gray matter volume in stable chronic obstructive pulmonary disease with subclinical cognitive impairment: an exploratory study. Neurotox Res 2017; 31(4): 453–463
34. Herigstad M, Hayen A, Evans E, Hardinge FM, Davies RJ, Wiech K, Pattinson KTS. Dyspnea-related cues engage the prefrontal cortex: evidence from functional brain imaging in COPD. Chest 2015; 148(4): 953–961
35. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006; 26(47): 12165–12173
36. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 2010; 66(1): 149–160
37. Yan X, Zhang J, Gong Q, Weng X. Prolonged high-altitude residence impacts verbal working memory: an fMRI study. Exp Brain Res 2011; 208(3): 437–445
38. Wei W, Wang X, Gong Q, Fan M, Zhang J. Cortical thickness of native Tibetans in the Qinghai-Tibetan Plateau. AJNR Am J Neuroradiol 2017; 38(3): 553–560
39. Yan X, Zhang J, Gong Q, Weng X. Cerebrovascular reactivity among native-raised high altitude residents: an fMRI study. BMC Neurosci 2011; 12(1): 94
40. Jaspers E, Balsters JH, Kassraian Fard P, Mantini D, Wenderoth N. Corticostriatal connectivity fingerprints: probability maps based on resting-state functional connectivity. Hum Brain Mapp 2017; 38(3): 1478–1491
41. Ray M, Sano M, Wisnivesky JP, Wolf MS, Federman AD. Asthma control and cognitive function in a cohort of elderly adults. J Am Geriatr Soc 2015; 63(4): 684–691
42. Zhang H, Wang X, Lin J, Sun Y, Huang Y, Yang T, Zheng S, Fan M, Zhang J. Reduced regional gray matter volume in patients with chronic obstructive pulmonary disease: a voxel-based morphometry study. AJNR Am J Neuroradiol 2013; 34(2): 334–339
43. Zhang H, Wang X, Lin J, Sun Y, Huang Y, Yang T, Zheng S, Fan M, Zhang J. Grey and white matter abnormalities in chronic obstructive pulmonary disease: a case-control study. BMJ Open 2012; 2(2): e000844
44. Kurahashi H, Okumura A, Koide T, Ando Y, Hirata H, Magota M, Watabane K. Posterior reversible encephalopathy syndrome in a child with bronchial asthma. Brain Dev 2006; 28(8): 544–546
45. Givre SJ, Mindel JS. Presumed bilateral occipital neurosarcoidosis. A case report. J Neuroophthalmol 1998; 18(1): 32–35
46. Tyvaert L, Devos P, Deloizy M, Belhadia A, Stekelorom T. Peripheral and central neurological manifestations in a case of Churg Strauss syndrome. Rev Neurol (Paris) 2004; 160(1): 89–92 (in French)
47. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. Neuroimage 2004; 22(1): 394–400
48. Xin H, Li H, Yu H, Yu J, Zhang J, Wang W, Peng D. Disrupted resting-state spontaneous neural activity in stable COPD. Int J Chron Obstruct Pulmon Dis 2019; 14: 499–508
49. Li W, Qin W, Liu H, Fan L, Wang J, Jiang T, Yu C. Subregions of the human superior frontal gyrus and their connections. Neuroimage 2013; 78: 46–58
50. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, Fischl B, Liu H, Buckner RL. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011; 106(3): 1125–1165
51. Liu Y, Qin W, Li R, Yu S, He Y, Xie Y. Investigation on the neural mechanism of hypnosis-based respiratory control using functional MRI. Contrast Media Mol Imaging 2018; 2018: 8182542
52. Gao X, Xiao Y, Lv P, Zhang W, Gong Y, Wang T, Gong Q, Ji Y, Lui S. Altered brain network integrity in patients with asthma: a structural connectomic diffusion tensor imaging study. Respir Physiol Neurobiol 2019; 266: 89–94
53. Herigstad M, Faull OK, Hayen A, Evans E, Hardinge FM, Wiech K, Pattinson KTS. Treating breathlessness via the brain: changes in brain activity over a course of pulmonary rehabilitation. Eur Respir J 2017; 50(3): 1701029
54. Xia MX, Ding X, Qi J, Gu J, Hu G, Sun XL. Inhaled budesonide protects against chronic asthma-induced neuroinflammation in mouse brain. J Neuroimmunol 2014; 273(1-2): 53–57
55. Millington RS, James-Galton M, Maia Da Silva MN, Plant GT, Bridge H. Lateralized occipital degeneration in posterior cortical atrophy predicts visual field deficits. Neuroimage Clin 2017; 14: 242–249
56. Heo W, Kim JS, Chung CK, Lee SK. Relationship between cortical resection and visual function after occipital lobe epilepsy surgery. J Neurosurg 2018; 129(2): 524–532
57. Snyder SL, Buchsbaum MS, Krishna RC. Unusual visual symptoms and Ganser-like state due to cerebral injury: a case study using (18) F-deoxyglucose positron emission tomography. Behav Neurol 1998; 11(1): 51–54
58. Madjar C, Gauthier CJ, Bellec P, Birn RM, Brooks JC, Hoge RD. Task-related BOLD responses and resting-state functional connectivity during physiological clamping of end-tidal CO_2. Neuroimage

2012; 61(1): 41–49

59. O'Herron P, Chhatbar PY, Levy M, Shen Z, Schramm AE, Lu Z, Kara P. Neural correlates of single-vessel haemodynamic responses *in vivo*. Nature 2016; 534(7607): 378–382

60. Miners S, Moulding H, de Silva R, Love S. Reduced vascular endothelial growth factor and capillary density in the occipital cortex in dementia with Lewy bodies. Brain Pathol 2014; 24(4): 334–343