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Altered brain network integrity in patients with asthma: A structural connectomic diffusion tensor imaging study

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ABSTRACT

Brain functional deficits had been reported in asthma patients. These deficits may be related to treatment resistance, inaccurate self-assessment and poor self-management. However, changes of the structural brain network in asthma patients remain largely unclear. Diffusion tensor imaging were acquired from 54 asthmatic patients and 44 controls. Then we calculated all the participants' structural network metrics. All the participants underwent the test of Hamilton Rating Scale for Depression and Anxiety as well as a lung function. Multiple linear correlation analyses were conducted. At the global level, asthma patients had a higher path length and lower global efficiency than controls, implying a shift toward regular networks. At the local level, asthma patients exhibited abnormal nodal connectivity with other nodes involved the fronto-limbic regions. Our findings highlight more locally segregated but less efficiently integrated structural networks, particularly involving frontal-limbic networks, in asthmatic patients. These findings provide important evidence to support the role of brain networks in the pathophysiology of asthma.

1. Introduction

Asthma is a serious global health problem characterized by airway inflammation, airway hyperresponsiveness and airway wall remodelling (Bahadori et al., 2009). Although asthma is a lung disease, it also affects other systems, especially the brain. For example, psychological comorbidity in asthmatic patients is common (Chen et al., 2014; Gao et al., 2015; Opolski and Wilson, 2005), leading to treatment resistance, inaccurate self-assessment and poor self-management (Choi et al., 2014; Frieri et al., 2015; Letitre et al., 2014). However, where and how the brain is affected in patients with asthma remains unclear.

Previous functional imaging studies have shown asthma-specific abnormal functional connectivity between the insular cortex and periaqueductal grey matter (von Leupoldt et al., 2009v). Furthermore, the anterior cingulate cortex and insula appear to be critical components of the circuitry associated with asthma-related symptom aggravation (Rosenkranz et al., 2005; Rosenkranz et al., 2012; Rosenkranz and Davidson, 2009; Xiong et al., 2016). Using voxel-based morphometry, prior studies have found grey matter alterations, including increased grey matter volume in the periaqueductal grey matter and decreased grey matter volume in the superior temporal gyrus, superior frontal gyrus and precuneus, which may be involved in integrating physiological function with external sensation, cognition and emotion (Wang et al., 2014). These findings suggested altered brain changes, especially involving the frontal and limbic system (Rosenkranz et al., 2005; Rosenkranz et al., 2012; Rosenkranz and Davidson, 2009; von

Abbreviations: AAL, automated anatomical labelling; AHR, hyper-responsiveness; AUC, area under the curve; BMI, body mass index; *Cp*, clustering coefficient; DTI, diffusion tensor imaging; *Eglob*, global efficiency; *Eloc*, local efficiency; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; HRSA, Hmilton Rating Scale for Anxiety; HRSD, Hmilton Rating Scale for Depression; *Lp*, characteristic path length; Mch, methacholine; MRI, magnetic resonance imaging; PANDA, pipeline for analyzing brain diffusion images; γ, normalized clustering coefficient; λ, normalized characteristic path length; TBSS, tract-based spatial statistics

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Leupoldt et al., 2009v; Xiong et al., 2016), in patients with asthma. However, the features of brain networks in patients with asthma remain largely unknown. In particular, the patterns of the white matter integrity at the network modular level have not been previously studied in asthma. Such investigations are important to help us understand the brain changes that are related to the pathophysiology of asthma. These studies can provide relatively invariant brain characteristics to help researchers understand how brain function is affected by disruptions in its structure (Passingham et al., 2002; Sporns et al., 2005).

Emerging analytic methods based on graph theory can be used to quantitatively analyse complex networks, which can help investigators interpret biological mechanisms at the network modular level (Bullmore and Sporns, 2009; Lui et al., 2016). Structural connectivity, as measured in vivo by MRI, typically reflects fibre bundles that connect different regions. These bundles are the infrastructure that underlies functional connectivity (Chen et al., 2017; Park and Friston, 2013). Studies of structural connectivity networks have been well established in mental disorders (Cao et al., 2013; Chen et al., 2016; Korgaonkar et al., 2014; Nucifora et al., 2007) and show good reproducibility (Bonilha et al., 2015). In the present study, we calculated three parameters related to nodal centrality. Measures of nodal centrality are based on the idea that they may act as important controls of information flow (Goh et al., 2003). Nodal degree is defined as the number of edges connecting a node to the remaining nodes in a network. Nodal efficiency reflects the ability of a node to spread information to the rest of the nodes in a network. Nodal betweenness captures the influence of a given node over information flow between all of the other nodes in a network(Rubinov and Sporns, 2010; Zhang et al., 2011). These three measures are correlated with each other, e.g., a node with a high degree tends to have high nodal efficiency and betweenness, and all of these measures reflect the importance of a node in a network (Hagmann et al., 2008; Zhang et al., 2011). Furthermore, anatomically central nodes often facilitate brain integration and become the infrastructure of functionally central nodes (Rubinov and Sporns, 2010). Thus, altered nodal centralities are associated with changes in the integrity of information flow and changes in regional function (Suo et al., 2015; Zhao et al., 2016).

By using fibre tractography and graph theoretic analysis, the present study aimed to investigate the connectivity of altered white matter in asthma and further explore its relationship with patients' clinical symptoms. Based on previous imaging studies of asthma, we assumed that asthma would have an abnormal brain white integrity involving the cortical-limbic system. Furthermore, these abnormal findings may be associated with asthmatic clinical symptoms. The findings could provide objective evidence to help to understand the importance role of brain networks in the pathophysiology of asthma.

2. Methods

2.1. Participants

Fifty-four asthma patients were recruited as outpatients of West China Hospital. A total of 44 healthy controls matched for age and sex were recruited via advertisements. Asthma was diagnosed according to the Global Initiative for Asthma (GINA) criteria (http://ginasthma.org/). All the patients with asthma were firstly interviewed by an experienced psychiatrist (Yao Gong) using the Structured Clinical Interview for DSM-IV (SCID)-Patient Version. No psychiatric disorders were found in patients. Healthy controls were recruited and screened using the SCID-Non-Patient Version to confirm the lifetime absence of psychiatric and neurological illness. Further, to explore whether change of brain network in patients with asthma might contribute to the increased risk for psychiatric disorders, we use Hamilton Rating Scale for Depression and Anxiety (HRSD and HRSA) to measure the motional status for patients and controls. All subjects underwent an MRI scan. MRI were inspected by an experienced neuroradiologist, and no gross abnormalities were observed in either group. This study was approved by the local institutional review board. All subjects fully understood the experiment and provided written informed consent.

The following inclusion criteria were applied: (1) age between 18 and 60 years; (2) airway hyper-responsiveness (AHR) with inhaled methacholine (Mch) (provocative dose causing a 20% fall in the force expiratory volume in the first second (FEV1) or bronchodilator reversibility in the FEV1 more than 12% predicted and more than 200 ml); and (3) intermittent to moderate asthma (the severity of asthma was determined using the GINA criteria).

The following exclusion criteria were used: (1) Asthmatic patient was at acute attack rather than stable episode; (2) Participant had alcohol or drug abuse; (3) Participant had mental health disorder, dementia or neurologic disorders; (4) Participant was current pregnancy or breast-feeding; and (5) Participant had cancer or other chronic diseases, such as chronic obstructive pulmonary disease, ischaemic heart disease, hypertension, diabetes mellitus, or renal insufficiency.

All patients were interviewed to collect their general and asthmatic characteristics, including age, gender, body mass index (BMI), education level, and age of onset, duration and severity of asthma. Airway responsiveness was measured with a Much challenge using the standardized dosimeter method. Based on standardized operating procedures, asthma was diagnosed if the PD_{20} was 2.5 mg or the bronchodilator reversibility test identified reversibility in the FEV_1. Asthma diagnosis was confirmed a significant post-bronchodilator response as an improvement in FEV1 values greater than 12% and 200 ml. The FEV_1 and forced vital capacity (FVC) were measured using a spirometer (Master-Screen Body, Jaeger, Germany).

2.2. Image acquisition

All participants were scanned using a 3-TeslaMagnetom-TRIO MR scanner (Siemens Medical Solutions, Erlangen, Germany) with an 8-channel phased array coil.

DTI acquisition involved a single-shot, spin-echo planar imaging sequence in contiguous axial planes that covered the whole cerebral and cerebellum. Diffusion-sensitizing gradients were applied in 20 non-collinear directions and were acquired without diffusion weighting (b = 0). The imaging parameters were set to the following values: TR = 6800 ms, TE = 93 ms, b-value = 1000s/mm^2, slice thickness = 3 mm, and 50 slices. The matrix resolution was 128 × 128 at acquisition and was reconstructed to 256 × 256 voxels. The voxel size was 1.8 × 1.8 × 3 mm^3.

High-resolution T1-weighted images using a 3D-spoiled gradient echo sequence (SPGR) were acquired for all participants. The imaging parameters were as follows: TR = 8.5 ms; TE = 3.93 ms; flip angle = 12°; slice thickness = 1 mm; single shot; field of view (FOV) = 24 × 24 cm; and matrix size = 256 × 256 voxels. The final matrix for the T1-weighted images was automatically interpolated in-plane to 512 × 512pixels, which yielded an in-plane resolution of 0.47 × 0.47 mm^2. Finally, 156 contiguous coronal slices were acquired.

2.3. Network metrics

Graph theory analysis didn't cover the cerebellum for the reasons that we focused on the cerebral white matter, and also previous imaging studies (Bian et al., 2018; Opolski and Wilson, 2005; Rosenkranz et al., 2012; von Leupoldt et al., 2009v; Wang et al., 2014) about asthma reported no abnormalities in the cerebellum. Besides, it could increase the sensitivity to detect the brain abnormality by only covering the whole cerebral brain during data processing. Detail of data preprocessing and graph theory analysis see supplementary materials. In the present study, we calculated both the global and regional network measures for brain DTI networks. The global measures included (1) small-world parameters, including the clustering coefficient (C_p), characteristic path length (L_p), normalized clustering coefficient (γ),

normalized characteristic pathlength (λ), and small-worldness (σ); (2) network efficiency measures including the local efficiency (*Eloc*) and global efficiency (*Eglob*). Regional measures included three nodal centrality metrics: degree, efficiency, and betweenness.

2.4. Statistical analysis

Differences in network metrics: To investigate between-group differences, nonparametric permutation tests were performed on the AUC for each network metric. First, we calculated the between-group difference in the mean values of each network metric. To test the null hypothesis that the observed group differences could occur by chance, we randomly reallocated all of the mean values of each network metric into two groups and recomputed the mean difference between the two randomized groups. This randomization procedure was repeated 10,000 times, and the 95th percentile of each distribution was used as the critical value for a two-tailed test of the null hypothesis with a probability of a type I error of 0.05. Notably, before the permutation tests, multiple linear regression analyses were performed to remove the confounding effects of age and gender for each network metric.

Relationships between network measures and clinical variables: In the exploratory analysis, we further assessed the relationships between these metrics and clinical measures (HRSD, HRSA, lung function parameters) via multiple linear regression analyses with age, gender, and tobacco use as confounding factors in some patients.

3. Results

3.1. Demographic and clinical characteristics

There were no statistical differences in age, gender, years of education or BMI between patients and controls. Four in 47 patients and 7 in 36 controls had a history of mild to moderate tobacco use ($p = 0.15$). Compared to controls, asthma patients showed worse lung function (FEV_1%, $p < 0.01$; FEV_1/FVC%, $p < 0.01$). The patients' HRSD scores were higher than those of controls ($p = 0.04$). However, no participants had comorbid psychiatric and neurologic disease. For more details, see Table 1.

3.2. Asthma-related alterations in small-world properties

Both asthma patients and controls showed small-world architecture in brain structural networks, implying a balance between structural segregation and integration (Fig. 1). The asthma group showed significantly lower values for *Eglob* ($P = 0.016$) and significantly higher values for γ ($P = 0.028$), λ ($P = 0.012$), L_p ($P = 0.018$) and σ ($P = 0.044$) (Fig. 2). The small-world network is economical, because it has the characteristics of higher *Cp* comparable to regular network and lesser *Lp* comparable to random regular network. So higher values in normalized *Cp* (γ), normalized *Lp* (λ) indicated a shift toward regular networks.

Table 1
Demographic and clinical measures.

	Group	Number	Mean	SD	P-value
Age (years)	Controls	44	38.64	10.35	0.99
	Asthma	54	38.67	10.46	
Gender (male/female)	Controls	12/32	-	-	0.08
	Asthma	24/30	-	-	
Education(years)	Controls	42	12.76	4.58	0.24
	Asthma	52	10.77	3.85	
BMI(kg/m^2)	Controls	43	23.44	3.28	0.94
	Asthma	54	23.39	3.00	
FEV_1%	Controls	22	2.71	0.57	< 0.01
	Asthma	50	2.19	0.7	
FVC%	Controls	22	3.32	0.72	0.25
	Asthma	50	3.09	0.76	
FEV_1/FVC%	Controls	22	81.92	6.77	< 0.01
	Asthma	50	70.21	13.77	
HRSD score	Controls	15	2.27	3.65	0.04
	Asthma	38	5.47	2.26	
HRSA score	Controls	15	2.80	4.07	0.13
	Asthma	38	5.00	5.73	
Severity of illness	Asthma	48	2.25	0.99	-
Duration of illness (years)	Asthma	48	8.47	10.72	-

3.3. Asthma-related alterations in regional nodal characteristics

Asthma patients exhibited altered nodal centralities, i.e., increased centralities in the right inferior frontal gyrus (triangular part), left inferior frontal gyrus (orbital part), left parahippocampal gyrus and right middle temporal gyrus (temporal pole) and decreased centralities in the left inferior frontal gyrus (opercular part), left middle cingulum and right supramarginal gyrus ($P < 0.05$, FDR corrected). These differences thus involved the bilateral frontal, right temporal, and right parietal cortices as well as the limbic system (Table 2, Fig. 3).

3.4. Relationships between network measures and clinical variables

In the exploratory study with smaller sample size, correlation analysis showed that the degree of the right middle temporal gyrus (temporal pole) was negatively correlated with the HRSD and HRSA scores. The betweenness of the right inferior frontal gyrus (triangular part) and degree of the left inferior frontal gyrus (opercular part) were negatively correlated with the FEV_1 (Fig. 4). We did the correlational analysis between duration of illness and network metric, severity of asthma and network metric. However, it didn't show significant findings.

4. Discussion

To our knowledge, this is the first study to explore the differences in structural connectivity networks between asthmatic patients and controls. At the global level, the asthma group showed significantly lower values in *Eglob* and significantly higher values in γ, λ, L_p and σ, indicating more segregated but less efficient processing. At the nodal level, the findings revealed abnormal nodal centralities that involved the fronto-limbic network, a key neural circuit for emotional processing. In the further exploratory analysis with a smaller sample size, we explored the relationship between the altered white matter network and clinical symptom using the limited data. Findings showed the nodal degree of the right middle temporal gyrus (temporal pole) was negatively correlated with the HRSD and HRSA scores. The nodal betweenness of the right inferior frontal gyrus (triangular part) and nodal degree of the left inferior frontal gyrus (opercular part) were negatively correlated with the FEV_1. These findings provide novel insights into white matter connectivity in asthma, but exact neuromechanism underlying the asthma needs further study.

It is interesting that patients with asthma showed a shift from small-world networks toward regular networks, which has been found in several neuropsychiatric disorders, such as post-traumatic stress disorder (Suo et al., 2015), attention-deficit/hyperactivity disorder (Wang et al., 2009), and temporal lobe epilepsy (Bernhardt et al., 2011). The regularization process is generally associated with a lower signal propagation speed as well as reduced synchronizability and computational power (Strogatz, 2001). As is known, hypoxia with low energy metabolism of the brain are common in asthmatic patients (Moraes et al., 2012), possibly affecting internal and external information processing in asthma (Rosenkranz et al., 2012). The present study indicated that the overall efficiency was abnormally reduced at the white matter network level, suggesting that the corresponding information processing capacity was reduced in patients with asthma.

The present study found decreased nodal centrality in the inferior frontal gyrus and cingulate and increased nodal centrality in the

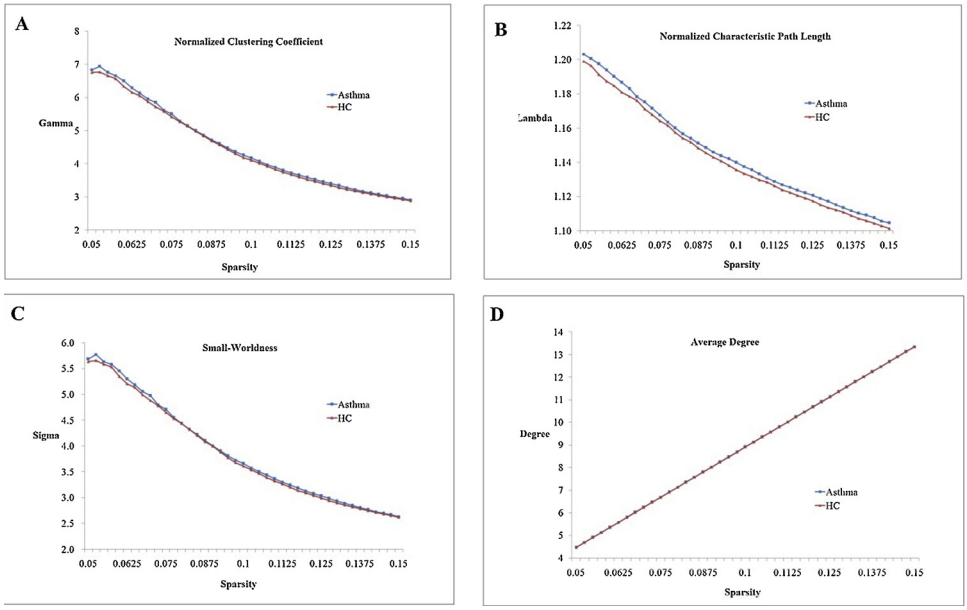

Fig. 1. Key small-world parameters of the DTI connectome as a function of the sparsity threshold. In this study, the small-world regime was defined as $0.05 < S < 0.15$. Both the asthma group and healthy control (HC) group showed (A) a normalized clustering coefficient greater than 1, (B) a normalized characteristic path length approximately equal to 1, and (C) an individual sigma values larger than 1, indicating that both groups exhibited a small-world topology. (D) The average degree of all nodes across the thresholded networks was larger than 4.5.

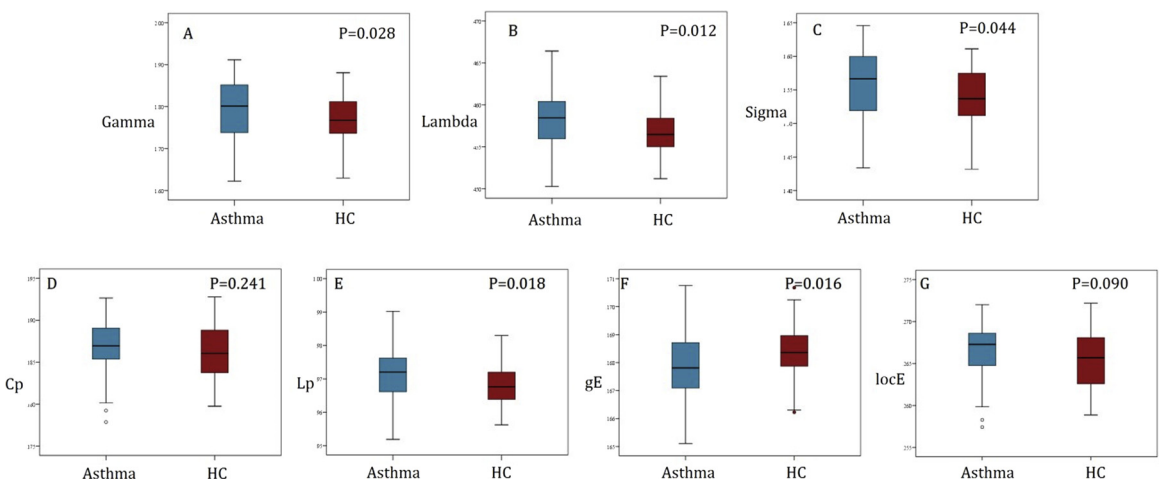

Fig. 2. Differences in the topological properties of the brain functional connectome between the asthma and HC groups.

Table 2
Regions showing abnormal nodal centralities.

	P value, FDR-corrected, < 0.05		
Brain areas	Nodal Degree	Nodal Efficiency	Nodal Betweenness
Asthma > HC	-	-	-
right inferior frontal gyrus (triangular part)	-	-	0.0010
left inferior frontal gyrus (orbital part)	0.0009	-	-
left parahippocampal gyrus	-	-	0.0010
right middle temporal gyrus (temporal pole)	0.0004	0.0001	-
Asthma < HC	-		-
left inferior frontal gyrus (opercular part)		0.0010	-
left middle cingulum	0.0003	0.0014	-
right supramarginal gyrus	-	-	0.0012

parahippocampus involving the fronto-limbic regions. These findings are in accordance with MRI findings from nonspecific deep white matter and subcortical hyperintensities in asthma (Passingham et al., 2002; Wang et al., 2014), indicating damage to the white matter. Besides, a recent study investigated the neuromechanism underlying cognitive impairments of asthma by using tract-based spatial statistics (TBSS) approach and found the asthmatic patients displayed executive dysfunction which was closely correlated with white matter abnormalities (Bian et al., 2018). Our findings are also supported by previous fMRI, VBM and TBSS studies, which found abnormalities in the anterior cingulate cortex and superior frontal gyrus (Bian et al., 2018; Rosenkranz et al., 2005; Wang et al., 2014). Decreased nodal centrality in the inferior frontal gyrus and cingulate reflects the low importance of these regions in the network, while increased nodal centrality in parahippocampus represents easier communication with other brain regions. In summary, these abnormal nodal centralities

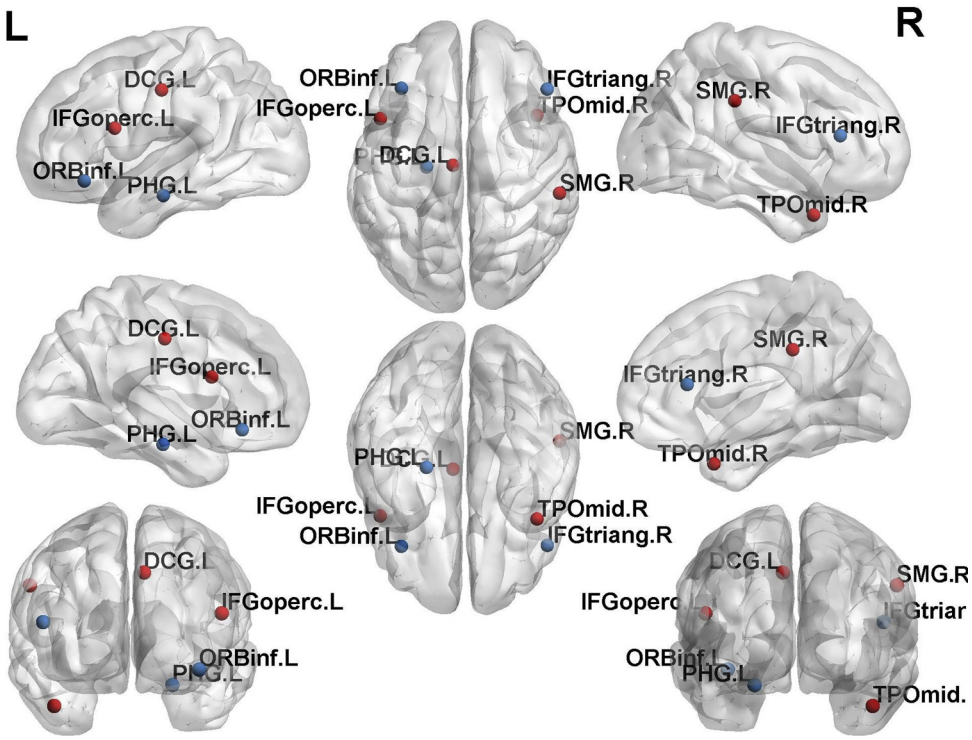

Fig. 3. Increased nodal centrality (hot colours) was found in the right inferior frontal gyrus (triangular part), left inferior frontal gyrus (orbital part), left parahippocampal gyrus and right middle temporal gyrus (temporal pole). Decreased nodal centrality (cold colours) was found in the left inferior frontal gyrus (opercular part), left middle cingulum and right supramarginal gyrus ($P < 0.05$, FDR-corrected).

indicate abnormal information flow and altered brain function.

Similarly, previous structural and functional graph theoretic studies have found altered nodal centralities within the fronto-limbic regions in patients with emotional deficits, such as depressive disorder (Korgaonkar et al., 2014; Wang et al., 2017; Zhang et al., 2011), bipolar disorder (Leow et al., 2013) or seasonal affective disorder (Borchardt et al., 2015). Although the asthma patients included in this study had no comorbid mental illnesses, the depression scores of these patients were higher than of normal controls. Correlation analysis further indicated an association between partial node abnormalities and clinical measurements, i.e., asthmatic anxiety, depression scores, and respiratory function parameters. However, it remains unknown whether fronto-limbic system abnormalities in asthma will give rise to the high incidence of mental illness in asthma patients. This result provides new clues for future studies on the interactions between asthma, mood disorders, and respiratory function.

Our study had several limitations. First, although 54 patients and 44 controls were enrolled in the study and all subjects underwent DTI

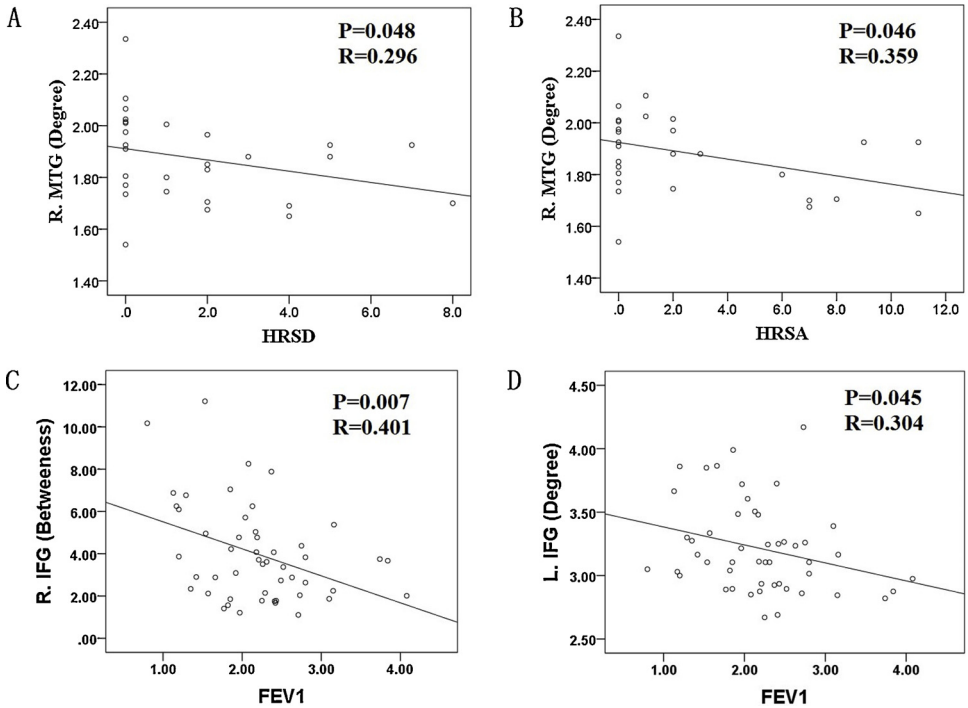

Fig. 4. Scatter plots of the nodal centralities compared to the HRSD, HRSA (Hamilton Rating Scale for Depression and Anxiety, respectively) scores and FEV_1 (forced expiratory volume in the first second).

scans, not all participants complied with the collection of all clinical data because of the longtime interview, questionnaire and MRI scan. Second, the participants are not well matched for gender because of limited data, but no significant difference between patients and controls. Third, our parcellation scheme divided the whole brain into 90 areas based on the anatomical AAL template. However, different parcellation schemes will cause certain variations. Fourth, we used a probability-based approach, which has advantages in tracking crossing fibres compared with using deterministic tractography (Behrens et al., 2007). However, probabilistic tracking may introduce spurious WM connections between regions that are not biologically connected. However, we removed connections with an average probability less than 0.001. Last, although in the exploratory analysis, we found several relationships between abnormal imaging features and clinical symptoms, it should be caution with the statistical significance differences because of the limited small sample size. Future studies need more fine and exhaustive data to further explore the relationship between the imaging features and emotional and respiratory symptoms.

5. Conclusion

In conclusion, our study provides the first report on connectome-level differences in structural networks between asthmatic patients and healthy controls. Our findings highlight the greater local segregation but less efficient integration of structural networks in patients with asthma, in particular the fronto-limbic networks. These findings deepen our understanding of brain changes in the pathophysiology of asthma.

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