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Cerebral anatomical changes in female asthma patients with and without depression compared to healthy controls and patients with depression

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Abstract

Background: Population-based studies have demonstrated that asthma patients with depression symptoms are more likely to have poor asthma control and worse asthma outcomes. However, the underlying mechanism of the relationship between asthma and depression is still unclear. The present study aimed to examine the cerebral anatomical changes in female asthma patients with and without depression. *Methods*: Using structural magnetic resonance imaging (MRI) and a voxel-based morphometry technique, the primary effects of and the interaction between asthma and depression were analyzed. The cerebral gray matter volume (GMV) was compared between the groups. Correlation analyses between the GMV value of the brain regions and the clinical parameters were completed. *Results*: The interaction effect of asthma and depression was found on the right superior temporal gyrus (STG) and the left middle temporal gyrus. Patients with both asthma and depression showed less GMV in the right STG, the bilateral precuneus, and the right superior frontal gyrus compared to patients with asthma only. The GMV of the right STG showed a decrement form among the asthma only group, healthy controls and asthma plus depression group. In patients with asthma and depression, the volume of the right STG was positively correlated with PD_{20} ($r = 0.714$, $p = 0.047$) and negatively correlated with the nocturnal awakening score in the Asthma Control Test ($r = -0.061$, $p = 0.038$). *Conclusion*: Current findings provided convergent evidence to support the critical role of the right STG in the brain mechanism that mediates asthma and depression.

Keywords

Asthma, cerebral anatomy, depression, structural magnetic resonance imaging, voxel-based morphometry

History

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Introduction

Bronchial asthma (asthma) is a serious global health problem, affecting an estimated 300 million individuals and causing 250 000 annual deaths worldwide [1,2]. Population-based studies have indicated that asthma patients are significantly more likely than those without asthma to have psychological conditions, such as depression [3]. Symptoms, such as wheezing and breathlessness, can prevent patients from enjoying pleasurable activities. This predicament can sometimes lead to a feeling of helplessness, frustration, or even depression. Studies have also demonstrated that asthma patients with depressive symptoms are more likely to have poor asthma control and worse asthma outcomes [4,5]. Previous studies have shown that a patient's psychological status could negatively affect asthma control through a behavioral mechanism, such as decreasing the patient's ability to self-monitor and adhere to treatment [6,7]. However, studies have indicated that a patient's psychological status may affect asthma through a biological mechanism [8,9]. While the change in serotonergic signaling in depression could decrease the cAMP level in airway smooth muscle cells (SMCs) and promote muscle contraction [10,11], understanding the critical role of psychological factors in the brain on influencing asthma symptoms has led to increasing interest.

Using structural magnetic resonance imaging (MRI), Von Leupoldt found that the longer duration of having asthma was associated with increased gray matter volume (GMV) in the brainstem periaqueductal grey (PAG) in patients with mild-to-moderate asthma [12]. Using functional MRI, he also found a down-regulation of insular cortex responses to dyspnea and pain in asthma patients [13]. Additionally, using functional MRI, Rosenkranz found that the anterior cingulate cortex and insula may be hyperresponsive to

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emotional regulation, which may contribute to the dysregulation of peripheral inflammation in individuals with asthma [8]. Because a number of anatomical or functional changes in the brain, in regions such as the cingulate gyri, frontal lobes, cerebellum, and temporal lobes, have been demonstrated in patients with major depression [14–16], some brain regions, such as the anterior cingulate cortex, insula and frontal lobes, may be responsive to depression-related neural changes and may also be important in influencing the expression and perception of asthma symptoms.

First, we explored whether any cerebral change was attributed to the interaction between asthma and depression using structural MRI and Voxel-based morphometry (VBM). VBM is a whole-brain technique using structural MRIs for characterizing regional cerebral volume and tissue concentration differences between two groups of subjects [17]. We hypothesized that asthma and depression may affect the same cerebral regions, such as the anterior cingulate cortex, insula and frontal lobes, and these regions might have different GMVs in asthma patients with or without depression.

Therefore, this study aimed to (1) compare the cerebral GMVs in healthy control patients and patients with or without depression using VBM and (2) explore the correlations between regional GMVs and asthmatic clinical parameters. Because of the higher incidence of depression in female asthma patients, we first studied female patients.

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Methods

Participants

Ten female patients with asthma and depression (AD group) and nine female patients with asthma only (A group) were recruited from the West China Hospital. All of the participants were screened by an experienced psychiatrist using the Chinese Structured Clinical Interview (SCID-IP) for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV, Axis I, patient version) [18]. Asthma was diagnosed according to the Global Initiative for Asthma (GINA) criteria [19]. The following inclusion criteria were applied: (1) between 18 and 50 years of age; (2) Airway hyper-responsiveness (AHR) with inhaled Mch (provocative dose causing a 20% fall in the forced expiratory volume in the first second (FEV_1) [PD_{20}]. <2.5 mg) or documented bronchodilator reversibility in the FEV_1 of >12% predicted and >200 mL; and (3) intermittent to moderate asthma (the asthma severity was determined using the GINA criteria [19]). Depression was determined using the Hamilton Depression Rating Scale (HDRS, 24 items), and a score ≥8 was considered to be the cut-off point for diagnosing depressive symptoms [20]. Thirteen female patients with first-episodes and never-treated major depression (D group) who fulfilled the diagnostic criteria of major depression (as described by the DSM-IV based on the SCID-IP) but did not meet the diagnostic criteria of asthma and 10 healthy female volunteers (NAD group) with no psychiatric or severe medical diseases, including asthma, were recruited as the controls. All of the participants were of Han Chinese descent, right-handed and non-smokers. The following exclusion criteria were used: (1) currently experiencing an acute asthma exacerbation; (2) active alcohol or drug abuse; (3) family history of any mental health disorder or dementia (These people have higher risk for mental disorders other than depression which may affect the cerebral structures of interest); (4) currently pregnant or breast-feeding; (5) history of cancer or other chronic diseases, such as chronic obstructive pulmonary disease, ischemic heart disease, hypertension, diabetes mellitus, or renal insufficiency; and (6) an inability to fully understand, comply with, and/or complete the study. This study was approved by the local institutional review board (IRB). All of the participants provided written informed consent.

Demographic and clinical characteristics and the Asthma Control Test

All of the individuals with asthma were interviewed to collect general and asthmatic characteristics, including age, body mass index (BMI), education level, and asthma age of onset, duration and severity. To assess asthma control, the participants with asthma completed the Asthma Control Test (ACT) [21]. The ACT questionnaire is a validated, self-administered questionnaire that includes five multiple-choice questions pertaining to asthma control over the previous 4 weeks, including limitations in daily activities, episodes of breathlessness, nocturnal awakenings, need for rescue medication, and a self-rating of asthma control. A higher score reflects fewer symptoms and better control.

Measurement of airway hyper-responsiveness and lung function

Airway responsiveness was measured with a methacholine (Mch) challenge, using a standardized dosimeter method. As a safety precaution, the Mch challenge test was administered to patients with a FEV_1 of ≥70% predicted. Based on standardized operating procedures, asthma was diagnosed if the PD_{20} was <2.5 mg or if the bronchodilator reversibility test identified reversibility in the FEV_1. Thus, the pre-bronchodilator values for diagnosing asthma were set as ≥12% and ≥200 mL. The FEV_1 and forced vital capacity (FVC) were measured using a spirometer (Master-Screen Body, Jaeger, Germany).

Voxel-based Morphometry

Image acquisition

All of the participants were scanned using a 3-Tesla Magnetom-TRIO MR scanner (Siemens Medical Solutions, Erlangen, Germany) with a standard head coil. High-resolution, T1-weighted images using a 3D-spoiled gradient echo sequence (SPGR) were acquired for all participants. The image scan 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 = 256 × 256. The final matrix for the T1-weighted images was automatically interpolated in plane to 512 × 512 pixels, which yields an in-plane resolution of $0.47 \times 0.47\ mm^2$. Finally, 156 contiguous coronal slices were acquired.

Image processing and analyses

Image pre-processing and statistical analyses were performed with SPM8 (www.fil.ion.ucl.ac.uk/spm) using the voxel-based

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morphometry toolbox on the Matlab 10.0 platform. (1) A whole-brain template was constructed, and the individual native images of the 42 subjects were normalized to the whole brain template and segmented into gray matter, white matter, and cerebrospinal fluid. (2) A gray matter template was generated from all of the gray matter images obtained in step 1. (3) The native images were segmented again into different tissue types and normalized to the gray matter template. (4) The deformation parameters obtained from the preceding step were applied to the original raw images for all of the subjects to create optimally normalized whole brain images, which were then segmented into gray matter, white matter, and cerebrospinal fluid. (5) The reobtained gray matter images underwent a Jacobian modulation (volume modulation). (6) Finally, the gray matter images were Gaussian-smoothed with a kernel of 6-mm FWHM.

Statistical analysis

To examine the effects of asthma and depression on the regional GMV, an analysis of covariance (ANCOVA) model in SPM8 of the whole-brain GMV was used. Asthma and depression were two factors in the model, and their primary and interaction effects were tested. Patient age and years of education were used as covariates. The group t-test in SPM8 was used to compare the GMVs between groups (A and D, A and AD, A and NAD, AD and D, AD and NAD, D and NAD). The significance level for each group was set at $p < 0.05$ using the AlphaSim correction (a combination of threshold of $p < 0.001$ and a minimum cluster size of 12 voxels). According to the analysis from the first two steps, the most related regions were found. In the AD and A groups, the volume of interest (VOI) function (spm_regions.m) in SPM8 was used to extract the eigenvariate GMV values within the cluster in the most related differential regions based on a former analysis. These values were used for Spearman's correlation analysis of the clinical parameters using SPSS version 13.0 (SPSS Inc, Chicago, IL) statistical software.

Results

Demographic and clinical characteristics

The demographic information for all of the participants is presented in Table 1. There were no statistically significant differences in age and years of education among the A, AD, D, and NAD groups. The differences between any two groups were not statistically significant ($p > 0.05$).

No significant differences were found in the general characteristics, asthma characteristics, and ACT scores (either total or for each section) between groups A and AD. The exception was longer asthma duration when comparing groups A and AD (Table 2).

Table 1. Baseline characteristics of participants.

	A	AD	D	NAD	*F* value	*p* Value
n	9	10	13	10		
Age (years)	33.1 ± 9.6	35.9 ± 8.2	30.9 ± 9.1	29.8 ± 7.5	0.990	0.408
Years of education	11.7 ± 4.0	12.0 ± 3.5	13.2 ± 2.3	14.1 ± 2.4	1.324	0.281

The differences between any two groups are not significant.
A = asthma, AD = asthma and depression, D = major depression, NAD = health control.

Voxel-based analysis of gray matter changes

The interaction between asthma and depression was found in the right superior temporal gyrus (STG) and the left middle temporal gyrus (MTG). The primary effect of asthma was found for the GMV in the right STG, left middle frontal gyrus (MFG), and right angular gyrus. The primary effect of depression was found in the left paracentral lobule. All of the cluster sizes, Montreal Neurologic Institute (MNI) coordinates, which determine the brain structures, and the *f* and *p* values for the above cerebral regions are shown in Table 3.

In the D group, there was less GMV in the left MFG and right inferior frontal gyrus compared to the NAD group, while in the A group, there was an increased GMV in the right STG and left inferior occipital gyrus. Compared to the NAD controls, the AD patients had a reduced GMV in four cerebral regions, including the right thalamus, right superior frontal gyrus, right STG, and left STG, while there was no increase in GMV in the AD patients. The D group had less GMV in the left MFG and left superior frontal gyrus (SFG) than the A patients, while the AD patients had less GMV in the left MFG than the D patients. The AD patients had less GMV in the right STG, right precuneus/angular gyrus, right SFG, and left precuneus compared to the A group. There was no region with increased GMV in the AD patients compared to the A patients. All of the cluster sizes, MNI coordinates, and *T* and *P* values for the above cerebral regions are shown in Table 4.

For all of the cerebral regions that exhibited primary or interaction effects and differences in the GMV in the between-group comparisons, the right STG was the only region in which the GMV was simultaneously the primary effect of asthma and the interaction effect between asthma and depression. The right STG was also the only region that had a decreased GMV in the A, NAD, and AD groups. Therefore, we assumed that the right STG might be the most likely region to link asthma and depression.

Correlation analyses for the right superior temporal gyrus GMV and clinical parameters

Correlation analyses for the right STG GMV and the clinical parameters were performed separately for the A and AD groups. For the A group, there was no significant correlation between the right STG volume and patient age, education level, asthma characteristics, ACT score, PD_{20}, or lung function values. In the AD group, the right STG volume positively correlated with the PD_{20} (correlation coefficient, 0.714; *p* value, 0.047) and negatively correlated with the score for nocturnal awakening (correlation coefficient, −0.661; *p* value, 0.038), while no significant correlation was present among age, education level, asthma characteristics, scores for the other four ACT questions and the lung function values (Table 5; Figure 1).

Discussion

In our study, although we did not demonstrate that the anterior cingulate cortex, insula or frontal lobes were involved in the

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Table 2. Comparison of general characteristics, asthma characteristics and ACT score between only asthma and asthma plus depression groups.

	A ($n=9$)	AD ($n=10$)	*F*/Z value	*p* Value
BMI (kg/m^2)	21.7 ± 2.4	22.3 ± 2.3	0.257	0.619
Asthma onset age (years)	25.4 ± 12.0	32.1 ± 12.8	1.360	0.260
Asthma duration (months)	105 ± 73.8(13)	13.4 ± 19.2(5)	−3.087	0.002
Asthma severity			–	–
Intermittent	1	0		
Mild	2	5		
Moderate	6	5		
ACT	16.7 ± 4.7	16.8 ± 4.1	0.004	0.948
Activity limitations	3.2 ± 1.0	3.0 ± 1.3	0.169	0.686
Breathlessness	3.1 ± 1.5	3.7 ± 1.1	1.035	0.323
Nocturnal awakening	2.7 ± 1.7	3.0 ± 1.3	0.235	0.634
Rescue medication	4.7 ± 1.0	4.7 ± 0.9	0.006	0.941
Self-rating of asthma control	3.0 ± 1.0	2.4 ± 1.3	1.188	0.291
Lung function				
FEV_1%	88.9 ± 8.1	86.8 ± 14.0	0.121	0.733
FVC%	95.5 ± 7.7	100.5 ± 7.0	1.902	0.190
FEV_1/FVC%	82.2 ± 9.4	74.0 ± 9.0	3.085	0.101
PD_{20}	0.98 ± 1.10[a]	1.08 ± 0.79[b]	0.034	0.857
HDRS score	3.8 ± 2.2	14 ± 3.5	56.3	0.000

A = asthma, AD = asthma and depression.
[a]In A group, 5 of 9 subjects had the Mch challenge test.
[b]In AD group, 8 of 10 subjects had the Mch challenge test.

Table 3. Cerebral regions of which the primary effect and interaction effect of asthma and depression was/were on.

	Brain regions	Voxel	MNI coordinates (x, y, z)	*F* value	*p* Value
Primary effect of asthma	Right superior temporal gyrus	246	42, −24, −6	17.06	0.000
	Left middle frontal gyrus	118	−25.5, −10.5, 39	19.60	0.000
	Right angular gyrus	76	49.5, −76.5, 36	17.95	0.000
Primary effect of depression	Left Paracentral lobule	19	−15, −19.5, 60	17.88	0.000
Interaction of asthma and depression	Right superior temporal gyrus	87	39, −40.5, 7.5	17.36	0.000
	Left middle temporal gyrus	24	−42, −43.5, −6	17.66	0.000

Table 4. Cerebral regions with statistically different gray matter volume between each two groups.

	Brain regions	Voxel	MNI coordinates (x, y, z)	*T* value	*p* Value
Comparison between two groups (former > latter)					
NAD > D	Left middle frontal gyrus	17	−27, −1.5, 61.5	3.88	0.001
	Right inferior frontal gyrus	34	24, 63, 27	4.28	0.000
		33	37.5, 57, 24	4.47	0.000
A > NAD	Right superior temporal gyrus	93	45, −43.5, 6	4.29	0.000
	Left inferior occipital gyrus	38	−43.5, −70.5, −7.5	4.80	0.000
NAD > AD	Right thalamus	160	12, −13.5, −3	5.14	0.000
	Right superior frontal gyrus	73	24, 1.5, 58.5	4.16	0.000
	Right superior temporal gyrus	17	57, −51, 15	4.48	0.000
	Left superior temporal gyrus	28	−54, −48, 27	4.32	0.000
A > D	Left middle frontal gyrus	50	−13.5, −4.5, 54	4.60	0.000
	Left superior frontal gyrus	46	−24, 51, 39	4.21	0.000
D > AD	Left middle frontal gyrus	56	−27, 4.5, 42	4.81	0.000
A > AD	Right superior temporal gyrus	955	37.5, −37.5, 7.5	5.32	0.000
	Right Precuneus/angular gyrus	284	46.5, −76.5, 36	5.52	0.000
	Right superior frontal gyrus	95	24, 0, 63	4.94	0.000
	Left precuneus	28	−18, −61.5, 46.5	4.04	0.001

neural mechanism linking asthma and depression as we hypothesized, some other regions were found to play a role in this process.

The analyses of the effect of asthma and depression on cerebral regions showed that the right STG and left MTG have interaction effect with asthma and depression. The right STG was also found to be the primary area affected by asthma, and a between-group comparison showed differences in the GMV in the right STG among the A, AD and NAD groups. In contrast, the left MTG was not the primary area affected by asthma or depression, and no GMV difference in the left MTG was found among the groups.

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Table 5. Correlation analysis on gray matter volume of RSTG and clinical parameters.

	A		AD	
	Correlation coefficient	*p* Value	Correlation coefficient	*p* Value
Age	0.226	0.559	0.578	0.080
Education	−0.511	0.160	0.235	0.514
Duration	−0.403	0.282	0.226	0.531
Severity	0.568	0.111	0.244	0.497
ACT	−0.552	0.123	−0.563	0.090
Activity limitations	−0.448	0.227	−0.386	0.270
Breathlessness	−0.332	0.382	−0.142	0.696
Nocturnal awakening	−0.616	0.078	−0.661	0.038
Rescue medication	−0.548	0.127	−0.290	0.416
Self-rating of asthma control	−0.364	0.336	−0.064	0.862
HDRS	−0.641	0.063	0.170	0.639
FEV_1	0.071	0.879	−0.200	0.606
FVC	0.536	0.215	−0.600	0.088
FEV_1/FVC	−0.536	0.215	−0.100	0.798
PD_{20}	−0.100	0.873*	0.714	0.047[$]

A = asthma, AD = asthma and depression.
*In A group, 5 of 9 subjects had the Mch challenge test.
[$]In AD group, 8 of 10 subjects had the Mch challenge test.

The STG is the region known to be associated with social cognitive function [14,22] and is also thought to play a major role in perception in concert with the amygdala, orbitofrontal cortex, and anterior cingulate cortex [23–25]. Previous studies have found a decreased GMV in the right STG of severe major depressive patients compared to healthy controls [15]. Although no study thus far has reported an abnormal structural change in the STG of asthma patients, several studies on the brain circuitry of other pulmonary diseases have shown STG involvement. For example, patients with obstructive sleep apnea syndrome (OSAS) have reduced function in the left STG compared to controls [26]. In addition, the STG has also been implicated in voluntary expiratory efforts in an earlier study [27]

Further between-group comparison found that the GMV in the right STG in the A-group patients was greater than the NAD group. Considering the STG is related to sensation, we speculated that the increased GMV in the right STGs of A-group patients compared to the NAD group may be the result of the normal brain's compensatory response to recurrent asthma symptoms to achieve a relatively appropriate symptom perception level toward stimuli. However, the GMV in the right STG was found to be decreased in the AD patients compared to the NAD and A patients. Because previous studies have implicated right STG dysfunction in major depression [14–16], the reduced GMV in the right STG in patients with asthma and depression may also be explained by depression-related dysfunction of right STG that may overwhelm the compensatory response to asthma. If the increased GMV in the right STG in asthma only patients is related to maintaining appropriate symptom perception as we speculated, the decreased GMV in the right STG in patients with asthma and depression may associated to inappropriate symptom perception, hypersensitivity, or blunted perception. Actually, this abnormal symptom perception in asthma patients with depression has already been demonstrated in several previous studies [28–30]. There is also another possibility that the structural brain changes between these patient groups may be caused by a certain genetic variability. However, there was no reported data on the genetic differences between asthma patients with or without depression.

Furthermore, the present study found that in patients with asthma and depression, the GMV in the right STG positively correlated with the PD_{20}, which means that the decreased GMV in the STG was related to the increased AHR. Two possible mechanisms could explain this correlation. First, as previously discussed, the decreased GMV in the right STG may lead to abnormal symptom perception toward the stimulus. Therefore, the increased AHR in patients with asthma and depression could be the result of inappropriately increased symptom perception to Mch. Second, depression may affect the PD_{20} through a biological mechanism. A previous study has found that emotional stress may lead to hyper-responsiveness in certain brain regions, leading to the dysregulation of peripheral inflammation in individuals with asthma [8]. The present study also found that the GMV in the right STG negatively correlated with the ACT nocturnal symptom score in patients with asthma and depression, indicating that the decreased GMV in the STG was related to fewer nocturnal symptoms in these patients. Because the ACT is a subjective tool, the ''fewer nocturnal symptoms'' may really be fewer symptoms or a diminished symptom perception. As discussed before, previous studies have already demonstrated abnormal symptom perception in asthma patients with depression. Thus, explaining the ''fewer nocturnal symptoms'' as a blunted symptom perception is more reasonable. As for why only nocturnal awakening on the ACT was associated with a change in the right STG, this finding was thought to be consistent with the clinical characteristic of asthma that symptoms often occur or are exacerbated at night. In addition, a higher neuronal activity in the brain overnight, especially during sleep, which could regulate the airway and sensation, could explain why symptoms are present only at night. In our study, the asthma duration in patients with only asthma was longer than in patients with asthma and depression. A previous brain MRI study of asthma patients showed that longer asthma duration was associated with an increased GMV in the PAG [12]. However, we did not find a correlation between asthma duration and the GMV in the right STG in the patients with asthma only or asthma and depression.

In addition to the right STG findings, the present study found that the GMV of the left MFG was the primary effect of asthma and the interaction effect of asthma and depression. The left MFG was thought to be related to the brain's ability to coordinate different information [31]. Although, no study thus far has shown an association between the MFG and asthma, a reduced GMV in the left MFG has been reported in patients with OSAS [32]. In addition to the left MFG, there are other regions that are only found to have different GMVs in one or two two-groups comparisons, such as the right thalamus, right IFG, left IOG, bilateral precuneus and SFG. Although discussing the limited findings related to these regions is difficult, the findings indicate a wide range of structural brain changes in patients with asthma and depression.

Three limitations should be considered when interpreting the findings of our study. Firstly, because female asthma

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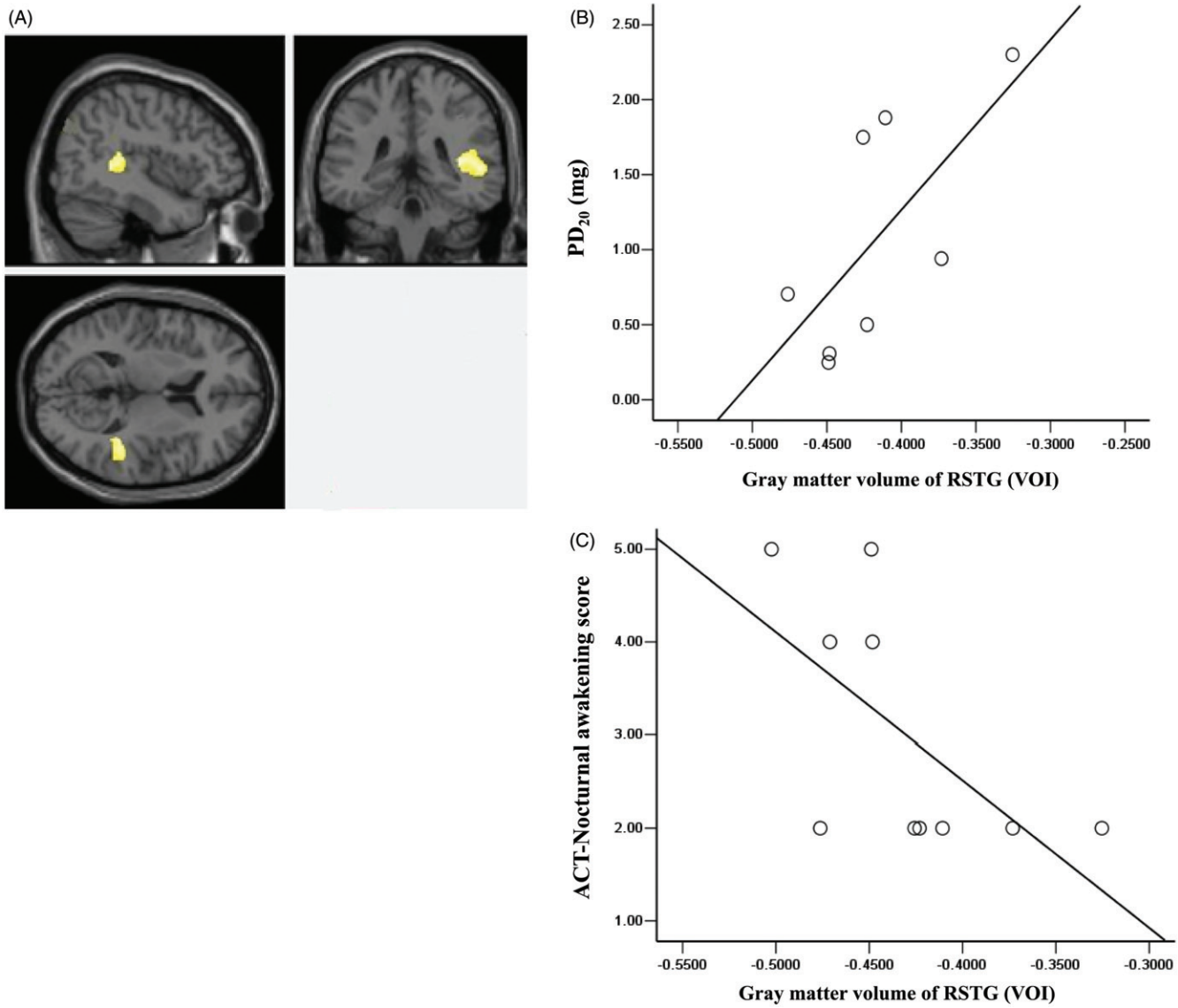


Figure 1. Right STG gray matter volume in relation to PD_{20} and ACT score of nocturnal awakening. A: AD patients showed less gray matter volume in right STG compared to A patients. B: In AD group, the gray matter volume of right STG was positively related to PD_{20}. C: In AD group, the gray matter volume of right STG was negatively related to the score of ACT nocturnal awakening.

patients are more susceptible to depression than males, we only studied female patients and healthy controls to avoid the possible effect of gender on brain structures in a relatively limited sample population. Future studies with larger sample populations that include male patients are required. Secondly, our study focused on women, but we didn't assess the menopausal status or hormone levels which may also play a role in the depression and brain function of women. Thirdly, because this study is first to explore the brain circuitry, structural brain changes alone cannot lead to definitive conclusions regarding the underlying mechanism linking asthma and depression. In this regard, future functional MRI studies with specific stimuli, such as induced dyspnea and emotion pictures, are necessary.

Conclusion

In summary, using the VBM method, we found structural changes in the right STG of female patients with depression and asthma compared to female patients with asthma only and healthy controls. The reduced GMV in the right STG was associated with an increased AHR and fewer nocturnal symptoms. These findings demonstrate that the right superior temporal gyrus might play a critical role in the brain mechanism that links asthma and depression. Future studies using symptom-perception functional MRI and molecular analysis of peripheral inflammation are necessary in asthmatic patients with depression.

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Declaration of interest

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LW, YJ, SL designed the experiments. LW, TW, SZL, ZL, YM, XX, YY performed the experiments. LW, SZL, ZL, YM, SL analyzed the data. SL contributed analysis tools. LW, YJ, SL wrote the paper.

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