Brain Network Study of Attentional Cognitive Impairment in Children with Bronchial Asthma

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Abstract

Bronchial asthma is a common clinical disease in pediatrics. It affects brain function and causes cognitive impairment due to long-term hypoxia in the brain. Studies have shown attention deficits in asthma children, but lack the basis for brain studies. Functional magnetic resonance imaging (fMRI) based on functional connectivity analysis was used in this study, and 31 asthma children and typically developing children (TDC) were compared in degree centricity (DC), voxel-mirrored homotopic connectivity (VMHC) and continuous performance test (CPT). The study found that the correct number of CPT in the asthma group was significantly lower than the TDC group. And the reaction time in the asthma group was significantly longer than the TDC group. Compared with TDC group, asthma children exhibited lower DC value in the right superior frontal gyrus (after FDR correction, $P<0.05$). Meanwhile, asthma children exhibited lower VMHC value in bilateral superior frontal gyrus and bilateral superior parietal lobule (after FDR correction, $P<0.05$). The study found that the impaired functions of superior frontal gyrus and superior parietal lobule were related to the attention deficit of asthma children which were the key nodes of the default network and the dorsal attention network. This study will provide objective indicators for the evaluation of attention in asthma children and provide scientific basis for early clinical intervention.

Introduction

Bronchial asthma is a complex multifactorial airway disease characterized by chronic airway inflammation, reversible airway obstruction, inflammatory exudation and airway hyperresponsiveness[1]. By the end of 2014, the number of asthma patients worldwide has increased to 334 million[2] and is expected to increase to 400 million by 2025[3], making asthma a serious public health problem. In asthma attacks, bronchial smooth muscle contraction and airway swelling cause airflow restriction, leading to insufficient oxygen intake in vital organs. The brain is most sensitive to hypoxia, and long-term hypoxia will affect brain function and cause cognitive impairment[4]. In a variety of cognitive functions, attention is the basis of other cognitive functions. Any advanced cognitive function requires attention participation, and the defect of attention function leads to difficulties in making and executing plans and completing tasks[5]. Attention deficit is the main cause of school-age children's learning difficulties and academic performance decline. However, the current clinical assessment methods for cognitive impairment of attention mainly rely on behavioral and assessment scales collected by clinicians, which are subjective to a certain extent, so it is very necessary to find an objective and accurate evaluation index in clinical diagnosis and treatment.

Previous studies have confirmed that children with bronchial asthma have obvious cognitive impairment of attention. Guo et al.[6] established a chronic asthma model in adolescent mice, and found that the impairment of attention and memory function in adolescent mice was related to chronic intermittent hypoxia caused by asthma through a controlled study, suggesting that asthma may cause cognitive impairment in children. Bender et al.[7] used drugs to control nocturnal asthma attacks to conduct therapeutic experimental studies, and found that patients with nocturnal asthma attacks might have impaired daytime cognitive functions, which were mainly reflected in higher neurocognitive functions such as attention. These studies confirmed the existence of attention cognitive deficit in bronchial asthma, but did not further study the brain mechanism of attention cognitive deficit in asthma patients, which limited the clinical application of asthma treatment.

As an emerging functional imaging technology, functional magnetic resonance imaging (fMRI) has the advantages of non-invasive, non-radioactive and high spatial resolution, and has been widely used in basic and clinical studies[8,9]. At present, there are few studies on attentional impairment of bronchial asthma by using fMRI. Zhang et al.[10] conducted a comparative study of 39 asthma patients and 60 healthy controls and found that the regional homogeneity of bilateral occipital lobe and bilateral sensorimotor area of asthma patients significantly enhanced, and asthma patients had enhanced regional homogeneity in bilateral occipital lobe, left paracentral lobule and right sensorimotor area after group cognitive behavioral therapy intervention which indicated the cognitive level of attention improved. Wang et al.[11] found that decreased gray matter volume of right superior temporal gyrus in asthmatic patients was associated with attention deficit.These studies suggested that attentional cognitive impairment was associated with functional abnormalities in multiple brain regions. In order to study the brain mechanism of attentional cognitive impairment, it is necessary to combine the functional connectivity of brain regions. Therefore, this study adopted the two algorithms of degree centrality (DC)[12] and voxel-mirrored homotopic connectivity (VMHC)[13] based on functional connectivity to analyze and explore which brain regions are related to asthma attention impairment.

This study will combine fMRI brain network and attentional behavior analysis, study the characteristics of center brain regions and homotopic connectivity between the two hemispheres, explore the correlation between abnormal brain function connection and clinical symptoms, and look for reliable clinical objective indicators for attention. The results of this study would provide a better way for the early assessment of asthma children's attention deficit.

Materials And Methods

Participants

The asthma group included 31 children aged (8.98±1.52yrs, 17 boys and 14 girls) who were diagnosed by specialist from Changzhou Children’s Hospital of Nantong University during January 2020 to September 2021. The diagnostic criteria were according to the guidelines for diagnosis and prevention of bronchial asthma in children (2016 edition)[14]. All children met the following criteria: (1) Recurrent wheezing, coughing, shortness of breath and chest tightness are mostly related to contact with allergens, cold air, physical and chemical irritation, respiratory tract infection, exercise and hyperventilation (such as laughter and crying), and often occur or worsen at night and/or early morning. (2) When the attack occurs, scattered or diffuse asthma can be heard in both lungs, mainly in expiratory phase, and prolonged in expiratory phase. (3) The above symptoms and signs are effective with anti-asthma treatment, or relieved by themselves. (4) Wheezing, coughing, shortness of breath and chest tightness caused by other diseases is excluded.

The TDC group included 31 children (8.31± 1.39yrs, 16 boys and 15 girls) from an ordinary school in Changzhou. And all the asthma and normal children should also meet the following criteria: (1) IQ>80 measured by the Wechsler Intelligence Scale for Children 4th edition-Chinese version[15]. (2) Right-handedness. (3) Older than 5-year-old. (4) Having no medical history related to neural and mental diseases. The study was approved by ethics committee of Changzhou Children's Hospital of Nantong University (2020-008). Informed consent was obtained from the parent of every participant, and all the participants agreed to join in the study.

Image acquisition

The images were acquired by using a Siemens 1.5-Tesla Magnetom Avanto scanner. The children were asked to close eyes, remain calm and awake status. Rs-fMRI data were acquired to use an echo-planar imaging sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip angle = 90°, 18 axial slices, thickness/gap = 6.0/1.2 mm, field of view (FOV) = 240 × 240 mm, matrix = 64 × 64, 180 time points. High-resolution T1-weighted three-dimensional (3D) images used the following parameters: TR = 414 ms, TE = 11 ms, flip angle = 90°, thickness/gap = 5.0/1.5 mm, FOV = 240 mm × 240 mm, in-plane resolution = 256 × 256[16].

Data analysis

The first ten time points of fMRI data were discarded for avoiding the signal changes before the magnetization reached a steady state and make the children get used to the noises. Then the data were preprocessed using the Data Processing Assistant for Resting-State fMRI Advanced Edition (DPARSFA) V4.3 software package[17]. DPARSFA is a widely used analytic tool. The preprocessing included the following procedures: 1) slice timing correction; 2) head motion correction; 3) spatial normalization to a standard template (Montreal Neurological Institute, MNI) and re-sampling (3×3×3 mm^3); 4) removal of linear trend; 5) DC and VMHC calculation; 6) spatial smoothing with a Gaussian kernel of 6 mm full width at half maximum[16].

Continue performance test (CPT)

CPT is a Go/Nogo task to test children's attentional behavior. The stimulus content includes the Arabic numeral 0~9. We make the number 1 as the cue, the 9 after 1 as the Go stimulus, the other numbers after 1 as the Nogo stimulus, and the other numbers after not-1 as the distraction stimulus. The stimulus consists of 400 numbers, among which the sequence of numbers 1 to 9 is 20%, the sequence of numbers 1 to not-9 is 20%, the sequence of numbers not-1 to 9 is 20%, and the probability of other numbers appearing randomly. Children were asked to respond to the "9" button that appeared immediately after "1" and not to press any other number. The stimulus lasted 200 ms with a stimulus interval of 1300ms. The stimulus appeared in the center of the monochrome CRT display. The US e-prime software was used to control the presentation of stimuli and automatically record behavioral results.

Statistical analysis

The comparison of CPT between two groups used the measure of two-sample t-test by the software of SPSS 22.0. In the fMRI study，participants with head motion > 3 mm of translation or 3° of rotation in any direction were discarded and all the participants were eligible. Two-sample t-test was performed as a measure of comparing the resting-state DC and VMHC between the two groups by DPARSFA. The t-test results were corrected by FDR multiple comparison ($P<0.05$, cluster size≥10). And the results of two-sample *t*-tests were overlaid on the Ch2 template.

Results

The comparison of attention behavior

The correct number of continuous performance test (CPT) in the asthma group was significantly lower than the TDC group (34.62±2.73 vs 36.76±2.40, $P=0.001$, $t=-3.57$, Figure 1). And the reaction time in the asthma group was significantly longer than the TDC group (479.73±76.86 vs 428.58±71.27, $P=0.004$, $t=2.97$, Figure 1).

The comparison of DC and VMHC value between asthma and TDC group

Compared with TDC group, asthma children exhibited lower DC value in the right superior frontal gyrus (after FDR correction, $P<0.05$, Table 1 & Figure 2).

Compared with TDC group, asthma children exhibited lower VMHC value in bilateral superior frontal gyrus and bilateral superior parietal lobule (after FDR correction, $P<0.05$, Table 1 & Figure 3).

Table 1
The comparison of DC and VMHC value between asthma and TDC group

Brain regions	Voxels (mm^3)	Brodman's area	MNI coordinates			t value
			x	y	z	
Decreased DC						
right superior frontal gyrus	13	6	21	-9	78	-8.01
Decreased VMHC						
right superior frontal gyrus	90	6	18	-3	75	-6.12
left superior frontal gyrus	90	6	-18	-3	75	-6.12
right superior parietal lobule	14	7	21	-54	75	-5.18
left superior parietal lobule	14	7	-21	-54	75	-5.18

Note: Two sample t-test ($P<0.05$, after FDR correction); MNI: Montreal Neurological Institute; t value: Negative areas meant the DC or VMHC value of asthma group was lower than the TDC group

Discussion

DC and VMHC are two commonly used indexes to study brain networks. DC reflects the centrality of the brain region in the whole brain. The higher the degree of centrality, the more connections it has with other brain regions, and the more important it is in the whole brain[18]. VMHC reflects the connection strength of homotopic brain regions in the whole brain. The more coincident the bilateral homotopic regions are, the higher the values of VMHC are[19]. In this study, we used these two indexes to study the brain network in hypoxia children, in order to find the early indicators for the assessment of attentional cognitive impairment.

This study found that the correct number of CPT in asthma children was significantly lower than normal children, and the reaction time in asthma children was significantly longer than normal children. The CPT results suggested asthma children existed attention deficit, which was consistent with previous studies[20,21]. In order to further research the brain mechanisms of asthma's attention deficit, the brain network analysis methods of fMRI were used in the study.

This study found that the DC value of right superior frontal gyrus in asthma children was lower than that in normal children, and the VMHC value between left and right superior frontal gyrus was lower than that in normal children. The superior frontal gyrus, located in the upper prefrontal lobe, has long been considered as a complex cellular area[22]. The superior frontal gyrus has been reported to be involved in many cognitive and motor control tasks, especially the posterior superior frontal gyrus which contains the supplementary motor area and is mainly involved in motor tasks [23,24]. The lateral part of superior frontal gyrus is mainly involved in executive task and attentional task in working memory[25,26]. The medial part of the superior frontal gyrus, which is activated during cognition-related tasks, is part of the default network[27,28]. Studies have found that DMN is involved in the regulation of attention and cognitive behavior. When performing attention-related tasks, DMN brain regions are activated. DMN activity antagonizes dorsal attention network, which also reflects the influence of DMN on attentional cognition. When the human brain is completing a specific task, more attention is used to concentrate on the task, and the functional activity of DMN decreases. While in the resting state, when no specific task is performed, the attention is more used to observe the external environment, and the functional activity of DMN is significantly increased, which enables the "monitoring" and "exploration" of the environment[29,30]. In this study, the DC value of the right superior frontal gyrus and the VMHC value of asthma children between the bilateral superior frontal gyrus were both lower than normal children, which also reflected the effect of this default network brain region on attentional cognition. In asthma children, the functional connection between the right superior frontal gyrus and other brain regions was decreased, as well as the VMHC between the two sides of the superior frontal gyrus was decreased, which weakened the effect of the superior frontal gyrus on attentional cognition, leading to the impairment of attentional cognition in asthma children.

The VMHC value of bilateral superior parietal lobule of asthma children was lower than normal children. The superior parietal lobule is an important node of the dorsal attention network, which has similar functions with the intraparietal suleus, the core brain region of the dorsal attention network, receiving visual information input and participating in the regulation of spatial orientation. Specifically, the intrapietal sulcus is mainly involved in the endogenous attention shift caused by the change of target features but unchanged spatial position, while the superior parietal lobule is mainly related to the exogenous attention shift caused by the target spatial movement[31,32,33]. The dorsal attention network, also known as the visuospatial attention network, is responsible for the management of spatial attention and visual movement, and participates in the top-down (endogenous) goal-oriented attention orientation[34]. The dorsal attention network is involved in attentional switching and spatial attention control during the adjustment of visual attention function[35]. Therefore, as an important component of the dorsal attention network, the superior parietal lobule is directly related to attentional cognition. In this study, the VMHC value of bilateral superior parietal lobule in asthma was lower than normal children, also confirmed that the attentional deficit in asthma children was associated with the functional impairment of the superior parietal lobule. The functional connection between the two homotopy brain regions was weakened, which impaired the function of the superior parietal lobule to regulate attention and could not accurately complete the exogenous attention transfer, leading to the decrease of the attention level of asthma children.

In conclusion, this study found that the attentional behavior of asthma children was lower than that of normal children, and the impaired functions of superior frontal gyrus and superior parietal lobule were related to the attention deficit of asthma children. This study explored the possible mechanism of attention deficit in asthmatic children through the study of brain network, and found that the attention dificit was related to the damage of the key nodes of the default network and the dorsal attention network. This study will provide objective indicators for the evaluation of attention in asthmat children and provide scientific basis for early clinical intervention.

Declarations

Author contributions

K.J. and L.Z. designed the study, conducted the analysis, and drafted the initial manuscript; Y.H., C.Q. and J.W. were involved in the acquisition of the data; Y.G., Q.S. and Y.C. contributed to the conduct of the study; J.X. and J.Z. designed the study, reviewed and revised the manuscript. All authors reviewed the manuscript and approved the final version.

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Competing interests

The authors declare no competing interests.

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Figures

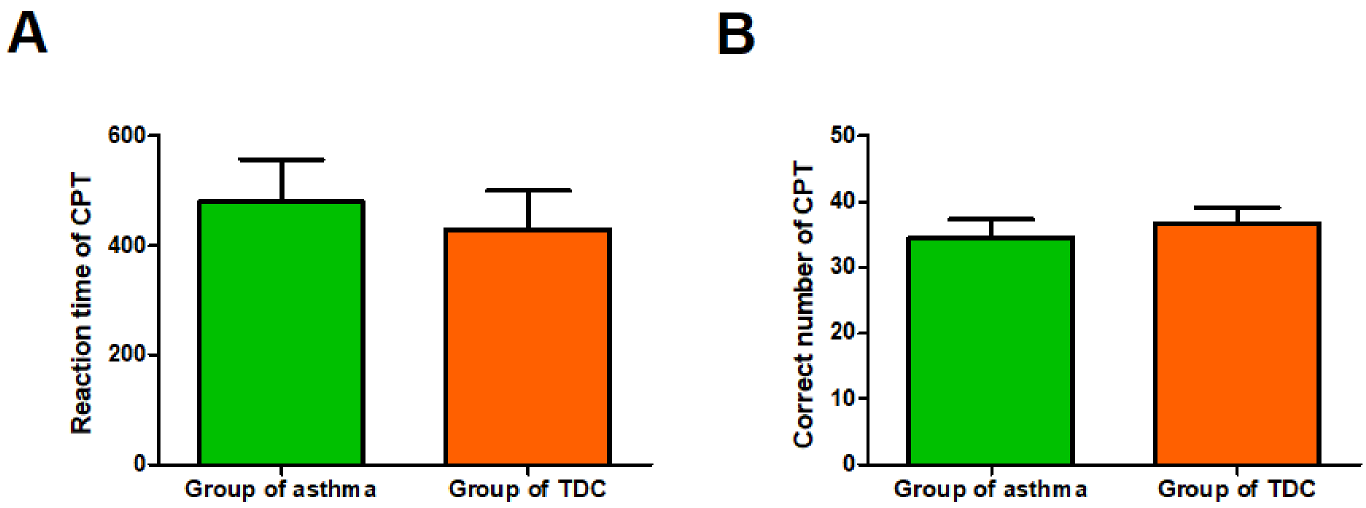

Figure 1

Comparison of CPT behavior between asthma and TDC group Note: “A” stands for the comparison of the reaction time of CPT between asthma and TDC group while “B” stands for the comparison of the correct number

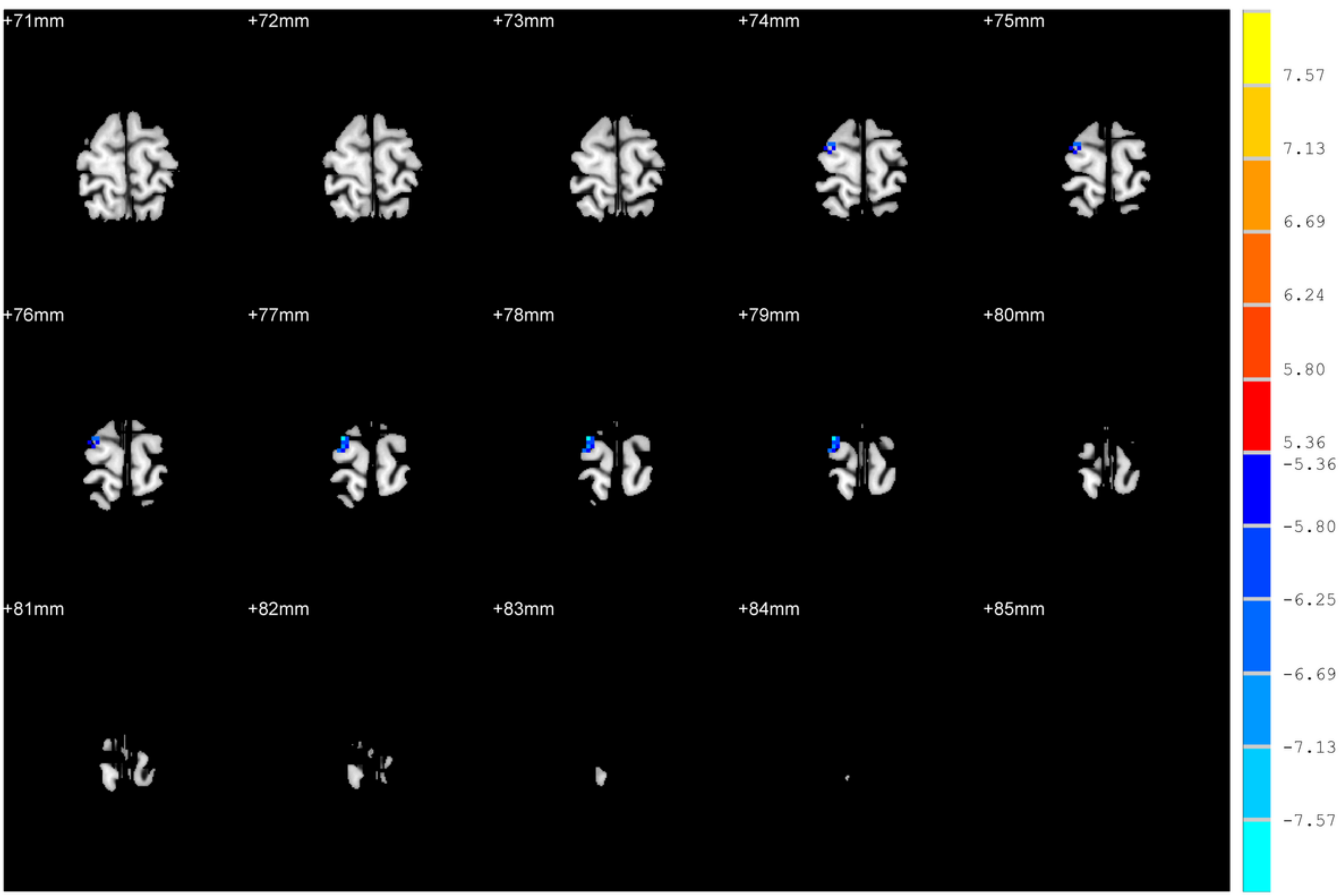

Figure 2

Comparison of DC values between asthma and TDC group Note: The blue areas showed the brain region which the DC value of asthma group was lower than that of the TDC group

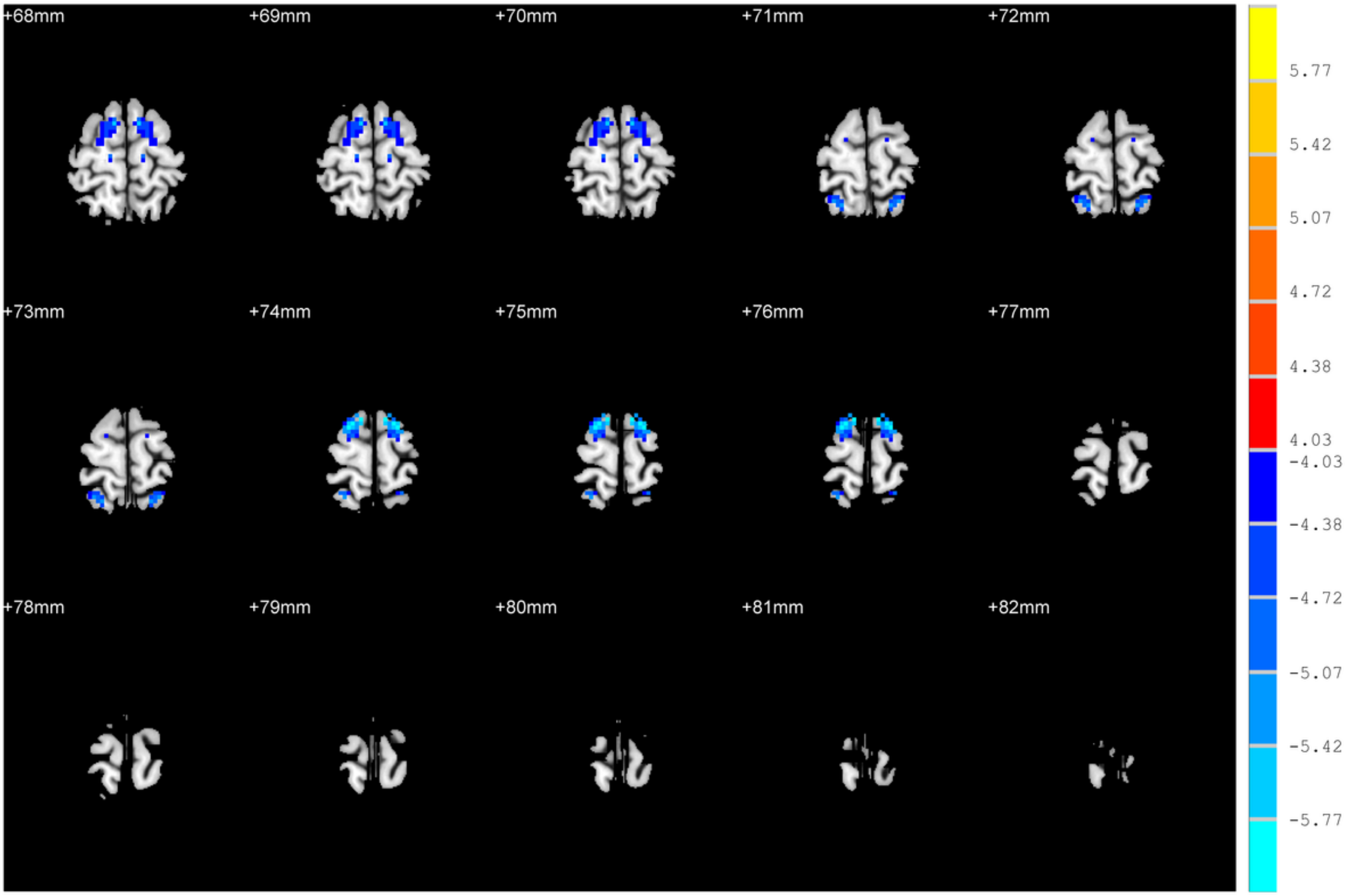

Figure 3

Comparison of VMHC values between asthma and normal group Note: The blue areas showed the brain regions which the VMHC values of asthma group were lower than those of TDC group