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Abnormal spontaneous neural activity of brain regions in patients with primary blepharospasm at rest

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ABSTRACT

Background: Primary blepharospasm (BSP) is characterized by excessive involuntary eyelid spasms without significant morphological brain abnormalities. Its neural bases remain unclear. Resting-state functional magnetic resonance imaging (rs-fMRI) is a powerful tool for exploring cerebral function mechanisms in BSP.

Methods: Two subject groups (24 patients with BSP and 24 healthy controls) underwent rs-fMRI scans. The rs-fMRI images were analyzed using the regional homogeneity (ReHo) method to assess the local features of spontaneous brain activity. Correlation analysis was carried out to explore the relationship between the ReHo values of abnormal brain areas and clinical variables including illness duration, symptom severity, and depression/anxiety symptoms.

Results: Relative to healthy controls, patients with BSP showed significantly decreased ReHo in the left superior temporal pole/left insula, left calcarine cortex, and bilateral superior medial frontal gyrus (mSFG), and increased ReHo in the bilateral supplementary motor area (SMA). There were no significant correlations between ReHo values in these brain regions and clinical variables in the patients.

Conclusions: Our results suggest that abnormal spontaneous brain activity in multiple brain regions not limited to the basal ganglia may be trait alterations in the patients, which provides more insights into the pathogenesis of BSP.

1. Introduction

Primary blepharospasm (BSP) is a common focal dystonia characterized by excessive involuntary eyelid spasms and blinking, which results in disabling effects on work and daily living activities, and even functional blindness in the wake of disease progression [1,2]. In addition to movement disorder, several non-motor manifestations have been reported, including sensory abnormalities (such as dryness sensation and photophobia), mood disorders (such as depression and anxiety), sleep disorders, and cognitive disturbances [3,4]. Despite the well-defined clinical symptoms that enhance the diagnosis of BSP, its exact pathogenesis remains poorly understood. Thus, treatment is often limited to symptomatic therapy that has no prolonged curative effects. Further advancement in therapy requires better understanding of the pathophysiological mechanism of BSP.

Basal ganglia dysfunction was traditionally viewed as the sole cause of BSP [5]. Conventional clinical imaging examinations have failed to identify overt brain structural deficits in primary BSP [6,7]. With the development of neuroimaging imaging techniques, especially advanced MRI technology, microstructural and functional changes in multiple brain regions have been visualized, improving the understanding of neurological pathophysiology of BSP and extending the traditional focus. Voxel-based morphometry and diffusion tensor imaging studies have found gray matter volume and white-matter changes within several cortical areas outside the basal ganglia [2,6,8]. However, some studies have reported no significant changes in the basal ganglia microstructure [9,10]. These works report neuronal morphological changes in BSP, but direct evidence for changes in the neural mechanism is lacking. Functional MRI (fMRI) is an effective tool for investigating functional brain reorganization and has identified multiple

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cortical and subcortical brain areas with altered activity in patients with BSP [7,11–14]. An activation paradigm evoked by simple motor tasks was used in most fMRI procedures of BSP conducted. Different abnormalities have been shown in task-based fMRI studies during different task performances [11,12,14]. Supporting each other across the existing task-based studies may be difficult on account of the lack of a unified stimulus paradigm.

In contrast to task-based fMRI, resting-state fMRI (rs-fMRI) has received increasing attention. The rs-fMRI is a promising neuroimaging technique that can measure spontaneous neural activity based on fluctuation in the blood-oxygen-level dependent (BOLD) signal [15,16]. This technique could serve as a powerful tool to observe endogenous neurophysiological processes in the brain without requiring task performance, thereby avoiding the potential limitation of task-based fMRI. As a widely used rs-fMRI measurement, regional homogeneity (ReHo) reflects the local synchronicity of spontaneous brain activity of various brain areas by calculating the Kendall's coefficient concordance (KCC) of the voxel similarity of the time series of a given voxel with the nearest neighboring voxels [17]. This method has been successfully used to investigate regional neural activity alterations in various neurological and psychiatric diseases [18–24]. Furthermore, this method does not require prior knowledge for target brain regions and is thus highly suitable for studying diseases with unclear pathological mechanisms, such as BSP.

ReHo method was applied to explore alterations of spontaneous regional brain activity across the whole brain in patients with BSP to characterize the neural bases of the disease. Correlation analysis was used to examine the possible relationship of such alterations to clinical features of BSP. We hypothesized that abnormal ReHo would be discovered in certain regions not limited to the basal ganglia in patients with BSP.

2. Materials and methods

2.1. Ethics statement

The study was approved by the ethics committee of the First Affiliated Hospital, Guangxi Medical University. All participants were informed about the procedures and signed a written consent according to the Declaration of Helsinki.

2.2. Participants

Twenty-four patients with BSP were consecutively recruited from the outpatient clinic of the Department of Neurology, the First Affiliated Hospital of Guangxi Medical University. The patients were diagnosed according to the published criteria by a movement disorder specialist [25]. The inclusion criteria were as follows: 1) primary BSP diagnosis, 2) no history of severe neurological and psychiatric disorders, 3) no structural lesions with conventional MRI examination, and 4) no treatment of botulism toxin or related neuro-psychiatric drugs within 6 months, 5) right-handed. The exclusion criteria were as follows: 1) secondary BSP, 2) family history of neurological or psychiatric disorders, and 3) contraindications of the MRI scan. The severity of the disease was assessed using the Jankovic Rating Scale [26]. In addition, participants with BSP were inspected by two qualified psychiatrists. The self-rating anxiety scale (SAS) and the self-rating depression scale (SDS) were used to evaluate anxiety and depression symptoms in patients with BSP, respectively.

Twenty-four healthy subjects were also recruited from the community and were all right-handed and matched with patients with respect to age, gender, and educational experience. They had no history of serious medical or neuropsychiatric illness and brain structural abnormity.

2.3. Data acquisition

MRI scanning was performed using a Siemens 3 T magnetic resonance scanner (Erlangen, Germany). All participants were laid supine with their head held in position by foam pads to minimize movement. The participants were then instructed to hold as still as possible with their eyes closed, and remain awake. High-resolution structural MRI images (T1 W1 and T2 W1) were obtained to exclude anatomical lesions. The rs-fMRI data were acquired from a gradient-echo-planar imaging sequence with the following parameters: repetition time/echo time = 2000/30 ms, 30 slices, 64 × 64 matrix, 90° flip angle, 24 cm field of view, 4 mm section thickness, 0.4 mm gap, and 250 volume (500 s).

2.4. Data preprocessing

Data preprocessing was conducted in MATLAB (http://www.mathworks.com) by using data-processing assistant software (DPARSF) [27]. The first 10 time points of each participant were removed for signal equilibrium and adaptation of patients to the scanning environment. The remaining 240 volumes underwent slice timing and head motion. The head motion of the participants should not exceed the 2 mm maximum displacement in the x-, y-, or z-axis and the 2° angular motion in any direction. The resulting fMRI images were spatially normalized to the standard Montreal Neurological Institute space by using the echo-planar imaging template and resampled to 3 mm × 3 mm × 3 mm. Finally, time-course linear detrending and band-pass filtering (0.01–0.08 Hz) were conducted to reduce the effects of low-frequency drift and the physiological high-frequency respiratory and cardiac noise for subsequent ReHo analysis.

2.5. ReHo calculation

ReHo analysis was performed using the REST software (http://resting-fmri.sourceforge.net). Individual ReHo mappings were generated by calculating KCC to synchronize the time series of a given voxel with those of its nearest 26 neighbors. To reduce the influence of individual variations, the ReHo mapping was normalized by dividing the KCC among each voxel by the average KCC of the whole brain for each subject. Afterward, the ReHo maps were smoothened with a 4 mm full width at half-maximum Gaussian kernel to reduce noise and residual differences [17].

2.6. Statistical analysis

Clinical and demographic information between the two groups was compared using SPSS 23.0 (SPSS Inc. Chicago, IL, USA). Two-sample *t*-test was performed to assess differences in age and educational experience. Chi-square test was used to estimate the difference in sex between the two groups. A two-tailed $p < 0.05$ indicates statistical difference.

Two sample *t*-tests were performed using Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) to explore the group differences in ReHo. Age was used as a covariate of no interest. Results were corrected for multiple comparisons at $p < 0.05$ by Gaussian random field (GRF) theory (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$).

To minimize the potential effects of depressive and anxiety symptoms on brain activity, the data were reanalyzed using age and SAS and SDS scores as covariates of no interest. The significance was set at $p < 0.05$ (GRF corrected).

Moreover, correlation analyses were conducted to assess the possible relationship of spontaneous brain activity in the brain regions with abnormal ReHo in patients with BSP to the clinical features including illness duration, symptom severity, and total SAS and SDS scores. The threshold of statistical significance was Bonferroni corrected at

Table 1
Demographic information and disease severity for the patients and controls.

	Patients (n = 24)	Controls (n = 24)	p value
Sex (male/female)	8/16	6/18	0.53[a]
Age (years)	49.58 ± 8.58	50.88 ± 8.13	0.59[b]
Education (years)	10.38 ± 2.34	10.63 ± 2.16	0.70[b]
Illness duration (months)	10.00 ± 3.82		
Symptom severity	2.63 ± 0.82		
SAS	43.79 ± 8.11		
SDS	47.95 ± 8.58		

SAS = Self-rating anxiety scale.
SDS = Self-rating depression scale.
[a] The p value for sex distribution was obtained by chi-square test.
[b] The p values were obtained by two-sample t-tests.

$p < 0.05/5 = 0.01$ (for five clusters with abnormal ReHo in the present study).

3. Results

3.1. Clinical characteristics of participants

Clinical characteristics of the participants are summarized in Table 1. No significant differences were found in age, gender, and years of education between the patients with BSP and controls. A total of 3 (12.5%) patients with BSP had comorbidity of depression. Moreover, 19 patients with BSP (79.16%) had sensory tricks, which temporarily improved eyelid spasms by wearing glasses, or touching the cheeks, or forehead. Furthermore, a total of 12 patients (50.00%) experienced worsened eyelid spasms when talking.

3.2. ReHo changes between two groups

Compared with healthy controls, patients with BSP showed significantly decreased ReHo in the left superior temporal pole/left insula, left calcarine cortex and bilateral superior medial frontal gyrus (mSFG) using age as a covariate of no interest (details shown in Fig. 1 [blue] and Table 2). Moreover, increased significantly ReHo was found in the bilateral supplementary motor area (SMA) (Fig. 1 [red] and Table 2).

When age and SAS and SDS scores were used as covariates of no interest, similar results were observed in the patients (Fig. 2 and Table 3) ($p < 0.05$, GRF corrected).

3.3. Correlation between ReHo values and the clinical factors

No correlations were observed between the ReHo values in any abnormal brain region and illness duration, symptom severity, SAS scores or SDS scores in the patients at Bonferroni corrected $p < 0.05/5 = 0.01$ (for five clusters with abnormal ReHo in the present study).

4. Discussion

In this study, the ReHo method for rs-fMRI analysis was utilized to reveal regional functional abnormality across the whole brain in patients with BSP. Compared with healthy controls, the BSP group exhibited significantly decreased ReHo in the left superior temporal pole/left insula, left calcarine cortex, and bilateral mSFG and increased ReHo in the bilateral SMA. No correlations were found between the ReHo values in any abnormal brain region and illness duration, symptom severity, SAS scores, and SDS scores in the patients.

Despite the fact that dystonia have traditionally been considered as a pure motor disorder derived prominently from basal ganglia, the focus for understanding the pathophysiological mechanism of dystonia has progressively switched to the sensory–motor integration. This concept is supported by alterations in the motor and sensory cortices, and the presence of associated sensory symptoms and sensory tricks [5,28,29]. Sensory tricks are a characteristic and diagnostic feature of primary dystonia, and were observed in approximately 70% of the patients [30]. In this study, 19 patients with BSP (79.16%) had sensory tricks, which temporarily improved eyelid spasms by wearing glasses, or touching the cheeks, or forehead. This phenomenon has been implicated in various sensorimotor processes [31], suggesting the dysfunction of sensory–motor integration in patients with BSP. According to the models of sensory-motor integration, which implicate the coordination of high- and low-level nodes, SMA acts in sensory–motor integration loop at high level [32,33]. SMA modulates the signals from low-level nodes, such as the basal ganglia, thalamus, and cerebellum, and then projects them back to the primary motor cortex to calibrate motor execution commands with other high-level nodes, such as primary somatosensory cortex. Hence, increased ReHo in SMA in patients with BSP may correlate with sensorimotor integration dysfunction in the development of dystonia. Analysis of a dystonia model in primates showed that the SMA of dystonic monkeys was over excitable, and the proprioceptive inputs to SMA dramatically increased with wide sensory receptive fields; this finding suggested that the disruption in the sensory–motor integration within the SMA may act in the pathophysiology of dystonia [34]. Moreover, recent evidence indicates that SMA can considerably be an alternative target for intervention in studies for the development of clinical and treatment actions [35]. Taken together, SMA serves as a pivotal role in the pathophysiology underlying BSP.

Interestingly, this study demonstrated decreased ReHo in the left superior temporal pole/left insula in patients with BSP. The human insula has emerged frequently from numerous neuroimaging studies as a core region affected by many psychiatric disorders including but not limited to schizophrenia, anxiety and depression disorders, autism, addiction, and chronic pain [36,37]. The cortex has been involved in various functions, including autonomic functions, language, pain, motor control, and sensory processing apart from emotional and cognitive functions [37,38]. This finding is consistent with the anatomical structure of the cortex, which has a wide array of connections to an extensive network of cortical and subcortical brain regions [36,39]. Common cortical connections include those connecting to motor cortices, such as orbitofrontal cortices, SMA, and primary motor cortex, which are engaged in motor control. From this perspective, the non-motor cortex could also be the correlates of motor control. Some studies have revealed the insula cortex was associated with motor function because of its anatomical connections to superior frontal sulcus, which has been identified to be involved motor commands via neuroimaging techniques [40,41]. In addition, the insula receives sensory afferents (auditory, somatosensory, olfactory, gustatory and visual information) from the thalamus and some horizontal cortices [36,42]. Hence, the insula might be involved in multisensory integration as a critical structure of the sensory system. On the basis of the involvement in motor and sensory functions, this region might act as a hub in sensorimotor integration. Therefore, functional abnormity in the insula, at least in part, might be involved in the impaired sensory–motor integration in patients with BSP. However, this issue needs further confirmation.

Sensory abnormalities, mood disorders and cognitive disturbances have been thought as important components of non-motor symptoms related to primary dystonia [3,4]. Many studies have reported a high comorbid incidence of depression and anxiety in patients with dystonia [43,44]. In the present study, 3 of 24 patients with BSP were diagnosed with depression, the morbidity (12.5%) of depression in patients with BSP was higher than in the Chinese population (approximately 4.2%) [45]. Conflicting evidence exists on whether depressive and anxiety symptoms are associated with disease severity. Some studies have showed correlations, whereas others have found no correlations, suggesting that this may be an independent manifestation of dystonia [4]. Here, we observed decreased ReHo values in the bilateral mSFG in patients with BSP. The mSFG is located at the superior part of the

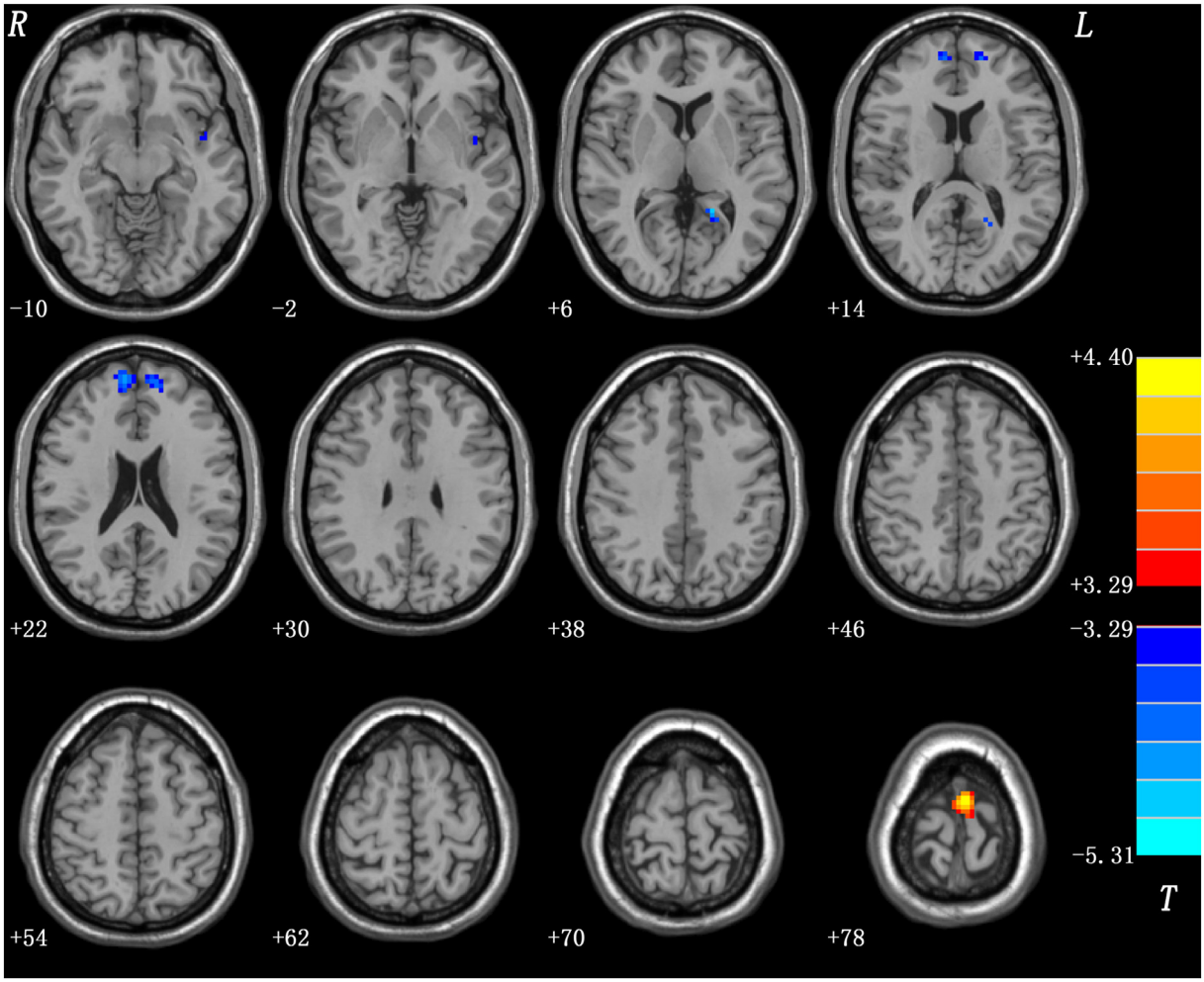

Fig. 1. Brain regions showing significant ReHo differences between patients with BSP and controls using age as a covariate of no interest. Red and blue denote higher and lower ReHo values respectively in the patients compared to the controls. The color bars indicate the T values of the group analysis. ReHo = regional homogeneity; BSP = blepharospasm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Brain regions with abnormal ReHo in the patients using age as a covariate of no interest.

Brain regions	x	y	z	*T*	Voxels size
Bilateral supplementary motor area	−6	−6	78	4.4027	36
Left superior temporal pole/Left insula	−48	3	−15	−4.5456	33
Left calcarine cortex	−21	−54	12	−5.3099	24
Right superior medial frontal gyrus	9	57	21	−4.4369	59
Left superior medial frontal gyrus	−9	57	24	−4.3083	41

$p < 0.05$, corrected for multiple comparisons using Gaussian Random Field (GRF) theory (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$). ReHo = regional homogeneity.

medial prefrontal cortex. Based on wide connections to emotional processing areas and limbic areas, the medial prefrontal cortex is implicated in attending to one's own emotional state [46]. Despite that abnormal functional activity of the mSFG has been commonly emphasized in the pathophysiology of psychiatric disorders, such as major depressive disorder [47], its function integrity and distinct modulation mechanism have no definite consensus. In fact, mSFG also is also links associated with the precentral gyrus, caudate and thalamus, which are the critical nodes of the motor control network [48]. Through these links, the mSFG could partly contribute to motor functions. Therefore, the reduced ReHo in mSFG may indicate the disrupted local connectivity of motor-related network of patients with BSP. In this study, no correlations were found between SAS or SDS scores and altered ReHo (including the ReHo values in the mSFG) in the patients. Moreover, similar results were obtained when age and SAS and SDS scores were used as covariates of no interest for the group comparisons, indicating that anxiety and depression symptoms have exerted limited effects on the present results. Taken together, these findings suggest that abnormal neural activity of this brain region might be the inherent characteristics of BSP independent of depression and anxiety severity. Our study extends previous findings by reflecting the possible role of the mSFG in the motor disorders of BSP.

Cognitive impairment investigations in patients with BSP conducted using neuropsychological testing indicated that the patients have a broad range of cognitive deficits, where the visuospatial function is the most frequently affected domain [49]. The visual cortex is a critical structure of the proper performance of the primary visual network, a well-defined resting-state network concerned with visual spatial information processing [50]. Therefore, decreased ReHo values in the calcarine cortex, where the primary visual cortex is located, provided evidence that patients with BSP might have abnormal visual–spatial deficit. Moreover, the visual areas are heavily connected with the basal ganglia and motor areas [51]. Therefore, the alteration in the cortex might suggest visual–motor integration dysfunction, a modality of sensory motor integration. These findings suggest the important role of functional changes in the visual cortices in the pathophysiology of BSP.

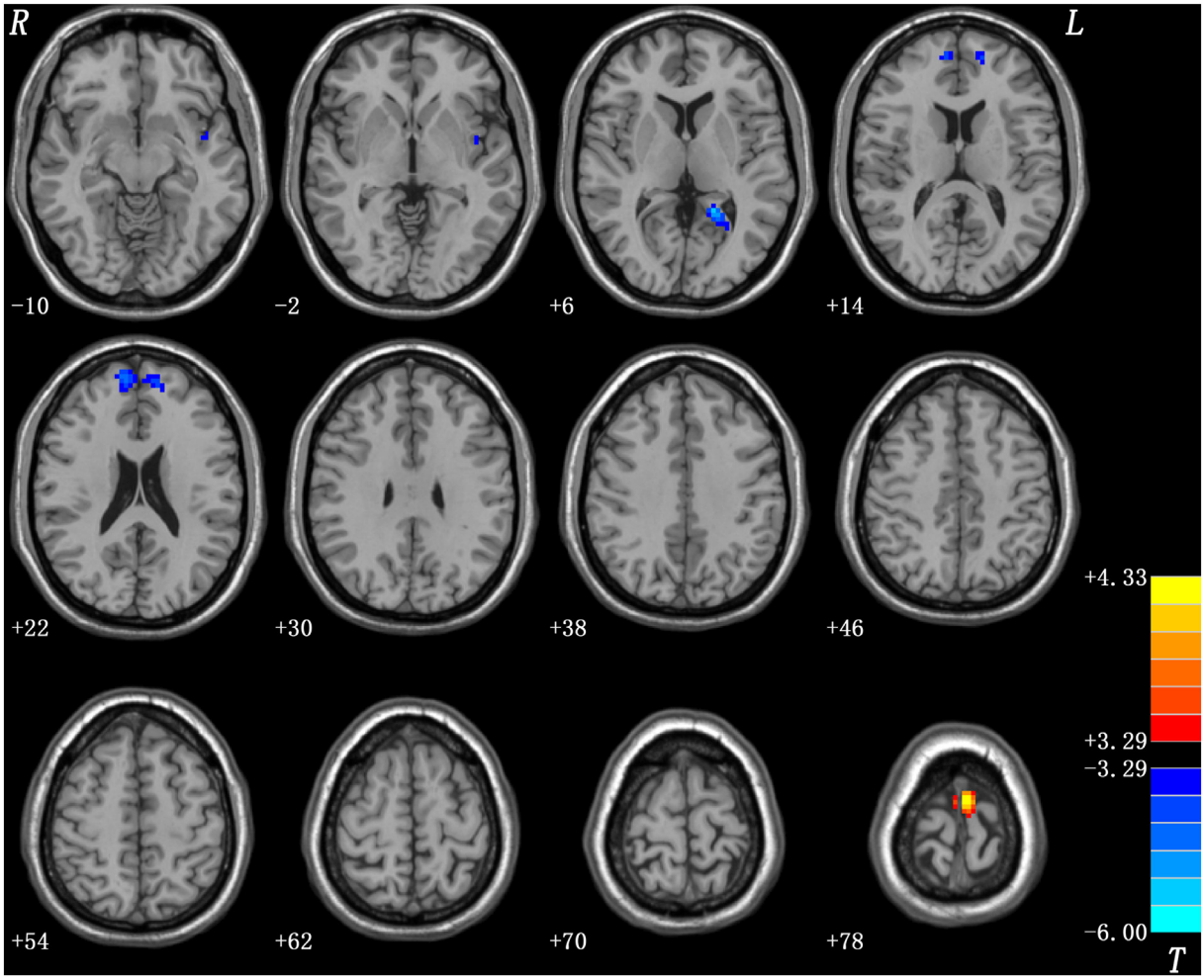

Fig. 2. Similar brain regions showing significant ReHo differences between the patients and controls for repeated statistical analysis using age and SAS and SDS scores as covariates of no interest. Red and blue denote higher and lower ReHo values respectively in the patients compared to the controls. The threshold was set at $p < .05$ corrected by GRF. The color bars indicate the T values of the group analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Brain regions with abnormal ReHo in the patients using age and SAS and SDS scores as covariates of no interest.

Brain regions	x	y	z	*T*	Voxels size
Bilateral supplementary motor area	−6	−6	78	4.3311	30
Left superior temporal pole/Left insula	−48	3	−15	−4.4511	31
Left calcarine cortex	−21	−51	9	−6.0007	53
Right superior medial frontal gyrus	9	60	21	−4.4578	62
Left superior medial frontal gyrus	−9	57	24	−4.2223	40

$p < 0.05$, corrected for multiple comparisons using Gaussian Random Field (GRF) theory (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$). ReHo = regional homogeneity; SAS = self-rating anxiety scale; SDS = self-rating depression scale.

Such an association is supported by the presence of photophobia and the finding that exposure to sunlight or eye diseases might be risk factors for BSP [52,53]. This result is in line with multiple neurophysiological and MRI studies, which revealed alterations in the visual cortices in patients with dystonia [51,54,55]. Our study provides a basis for supporting the involvement of the visual system in the pathogenesis of BSP.

In this study, we found no correlations between the abnormal ReHo values and illness duration or symptom severity apart from the SAS and SDS scores in patients using a relatively restricted corrected method. The possibility of this result is high that abnormal spontaneous neural activity in these brain regions may be inherent trait alteration for patients with BSP independent of disease severity, illness duration, and symptoms of anxiety and depression, rather than secondary manifestations.

Some limitations of this study should be acknowledged. First, the sample size was relatively small, which might have limited the statistical power and generalization of the results. Second, the assessment of other possible non–motor manifestation of patients with BSP, such as cognitive and visual–spatial deficit, could be further conducted for comprehensive illustration. Third, conventional structural MRI scans (T1W1 and T2W1) could be insufficient to identify subtle structural changes in the brain (e.g., infarction). Thus, potential interference of some small structural abnormalities in this disease, such as those in the basal ganglia, could not be eliminated. Lastly, similar to most rs-fMRI studies, this cross-sectional study is limited to discriminating causes from effects. Future longitudinal assessments in terms of pre-treatment to post-treatment changes or illness duration may contribute to elucidate this issue.

5. Conclusions

In summary, this study demonstrates that spontaneous brain activity is altered in patients with BSP. Statistically significant cores including

the left superior temporal pole/left insula, left calcarine cortex, bilateral mSFG and bilateral SMA, which might be associated with the pathogenesis of BSP. Functionally, these brain regions extending beyond the basal ganglia may reflect widespread impairment in neural networks, especially in the sensorimotor integration. The present findings provide more experience and implication for the further studies regarding the underlying mechanisms of BSP.

Authors contribution

SL and WG conceived and designed the study. WJ, YL (Yu Lan), and YL (Yiwu Lei) collected the original data. WG performed the data analysis. CC, YL (Yang Liu), CF assisted in the literature review. WJ and YL (Yu Lan) wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interests

The authors declare that there is no conflict of interests to disclose.

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Data availability

The data that support the findings of this study are available from the corresponding authors upon request.

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