

Altered Spontaneous Brain Activity in Somatic Symptom Disorder: A Resting-state fMRI Study

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Abstract

Background: Somatic symptom disorders (SSDs) are common medical disorders characterized by various biological, social, and psychological pathogenic factors. Little is known about the neural correlations of SSD.

Methods: In this study, we evaluated the dysfunction in 45 patients with SSD and in 43 controls by combining the regional homogeneity (ReHo) amplitudes of low-frequency fluctuation (ALFF) methods based on resting-state functional magnetic resonance imaging.

Results: Compared to the controls, the patients with SSD exhibited significantly greater ReHo in the right cingulate gyrus and smaller ReHo in the right precuneus, left inferior and temporal gyrus extending to the left middle temporal gyrus and left parahippocampal gyrus, and right pons. The SSD patients showed higher ALFF values in the cingulate gyrus extending to the left medial frontal gyrus, right insula extending to the right inferior frontal gyrus, and left medial frontal gyrus extending to the left anterior cingulate cortex.

Conclusions: These dysfunction areas seem to have a particular importance for the occurrence of SSD, which may result in dysfunction in self-relevant processes, emotional processing, multimodal integration, arousal, interoception, and body perception.

Background

Somatic symptom disorders (SSDs) are a heterogeneous group of psychiatric syndromes characterized by physical symptoms that suggest a medical condition but are not or not fully explained by any other medical condition and are related to psychological factors [1]. The symptoms are considered as somatoform disorders in the International Classification of Diseases, tenth edition (ICD-10) [2], and as somatic symptom disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1] or bodily distress disorder in ICD-11 [3]. The different scales are generally similar, but the emphasis is different. ICD-10 emphasizes the repeated presentation of physical symptoms in the absence of any physical basis due to repeated negative medical investigations. DSM-5 and ICD-11 emphasizes the distressing nature of somatic symptoms and excessive attention directed towards symptoms rather than the absence of a medical explanation for the somatic symptoms. SSD causes serious trouble to patients and causes impairment in occupational function, social function, or clinically relevant stress [1].

SSD is highly prevalent in many medical settings. A European prevalence study showed the 12-month prevalence rate for any somatoform disorder was found to be 3.8 among people aged 65–84 years from six different countries [4]. The prevalence of SSD for the strict diagnosis of a somatization disorder ranged from 0.8–5.9%, at least one type of somatoform disorder was present in the fraction of primary-care patients that ranged from 26.2–34.8%, and the percentage of patients complaining of at least one medically unexplained symptom ranged from 40.2–49% [5]. While the biologic nature of this disorder has

been widely accepted and many potential pathogenic factors have been discussed for SSD and related diagnoses, the neuroanatomical correlations characterizing SSD are still inconclusive.

Functional magnetic resonance imaging (fMRI) has been widely used in disease-related research. Resting-state fMRI, which requires no explicit task performance, is a useful tool for brain research. Amplitude low frequency fluctuation (ALFF) and regional homogeneity (ReHo) analyses are two common data analysis methods used to investigate the nature of local intrinsic activity in resting-state fMRI studies [6]. ALFF changes in signals are thought to be associated with local neuronal activity, and ALFF analysis is effective at detecting fluctuations in spontaneous low-frequency oscillations. The ReHo method tests for local correlations in blood oxygen level-dependent (BOLD) time series using Kendall's coefficient of concordance (KCC) to measure regional synchronizations of temporal changes in BOLD activity [7]. At present, research on the local features of spontaneous brain activity based on ReHo and Alff is very limited. Only a few studies have used the ReHo method to investigate the local features of spontaneous brain activity in somatoform disorders with a relatively small sample. Ou et al. reported that patients with first-episode, drug-naïve somatoform disorders showed an increased a coherence-based regional homogeneity in the left medial prefrontal cortex/anterior cingulate cortex compared with healthy controls [8]. Huang et al. found that compared with a healthy control group, patients with persistent somatoform pain disorder exhibited decreased ReHo in the bilateral primary somatosensory cortex, posterior cerebellum, and occipital lobe but increased ReHo in the prefrontal cortex and the default mode network [9]. Additionally, Song et al. observed that the somatoform disorders group had a significantly increased ReHo in the left angular gyrus compared to healthy controls [10]. Su et al. reported that patients with somatoform disorders showed increased fractional ALFF in the bilateral superior medial prefrontal cortex and decreased fractional ALFF in the left precuneus [11]. Although, previous studies have found abnormal spontaneous brain activity in SSD patients, previous studies have been limited, and their results have been inconsistent, thus requiring further exploration.

The aim of this study was to investigate dysfunction of spontaneous brain activity in the resting state by applying both ReHo and ALFF methods in a relatively large sample. We hypothesized that SSD presents functional alterations in spontaneous brain activity in specific brain regions (which are related to emotional processing, multimodal integration, and self-relevant processes) during the resting state.

Methods

Subjects

the outpatients of the Department of Neurology at Shanghai Ninth People's Hospital, China. These patients were diagnosed with SSD by a neurologist based on the Structured Clinical Interview from the DSM-5 [1]. Exclusion criteria for patients included: (1) those with other major psychiatric illness, including depression, anxiety, substance abuse, or dependence; (2) those with primary neurological illness, including dementia or stroke; and (3) those with any white matter changes, such as infarction or other

RI. During the interview, the neurologist also obtained SSD

demographic and clinical data, including age, sex, disease duration, Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder (GAD-7), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD) and Mini-mental State Examination (MMSE) scores. Of the SSD patients, 18 patients complained of headache (with and without dizziness), 8 patients complained of dizziness, 5 patients complained of peripheral pain, and 14 patients complained of other physical discomfort, such as local numbness. Half of the patients are drug-naive, and the rest were stopped on the day of the MRI scan. Forty-three age- and gender-matched healthy controls (19 males, 24 females) were recruited. All subjects were right-handed and had no substance abuse, and all neurological and psychiatric disorders were excluded based on clinical examination and structured interviews. The details are provided in Table 1.

Mri Acquisition

Functional and structural MRI data were acquired using a 3.0 T Siemens Prisma system that utilized a 64-channel head coil at the Shanghai Key Laboratory of Magnetic Resonance (East China Normal University, Shanghai, China). During scanning, custom-fit foam pads were used to minimize each subject's head movements. We obtained the whole-brain anatomical volume using a high-resolution T_1 -weighted 3-dimensional magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) pulse sequence with the parameters as follows: repetition time = 2530 ms, echo time = 2.34 ms, inversion time = 1100 ms, flip angle = 7° , number of slices = 192, sagittal orientation, field of view = $256 \times 256 \text{ mm}^2$, matrix size = 256×256 , and slice thickness = 1 mm with a 50% gap. The resting-state fMRI images were acquired using a T_2^* -weighted gradient-echo echo-planar imaging (EPI) pulse sequence with the following parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90° , field of view = $220 \times 220 \text{ mm}^2$, matrix size = 64×64 , number of slices = 32, transverse orientation, slice thickness = 3.5 mm, 25% distance factor, and total of 210 volumes. During the fMRI scan, the subjects were instructed to relax, remain still and close their eyes.

Resting-state Fmri Data Preprocessing

Resting-state fMRI data were analysed using MATLAB (The Math Works, Natick, MA) software and statistical parametric mapping software (SPM12; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12>). To avoid scanner instability and to adapt the participants to the noise of the scanner, the first 10 volumes were discarded for each participant. Next, slice timing was performed to correct for intra-volume differences in acquisition time and head motion correction using six-parameter rigid-body linear transformation conducted on the remaining volumes. Then, we set the anterior commissure as the origin on the high-resolution T_1 -weighted image to co-register the structural image to the mean functional image. The T_1 images were then segmented into grey matter, white matter and bias field-corrected structural images. Afterwards, the images were spatially normalized to the standard Montreal Neurological Institute (MNI) stereotaxic space and resampled to $3 \times 3 \times 3 \text{ mm}^3$. Then, spurious signals, parameters and the signal from the white matter and the

cerebrospinal fluid, were regressed out using a general linear model, and linear trends were removed from the fMRI data. Finally, spatial smoothing was performed on the functional images using a Gaussian filter (6 mm full-width half-maximum, FWHM).

The head motion parameters of all participants were calculated in the translational and rotational directions (i.e., x, y, z, roll, pitch, and yaw). The participants were excluded if their maximum translation was > 2 mm or if their rotation was $> 2^\circ$ in any direction. Head motion in all directions was compared between groups, and we found that the head motion parameters of the patients with SSD and control groups did not significantly differ (x , $p=0.57$; y , $p=0.29$; z , $p=0.47$; pitch, $p = 0.14$; roll, $p=0.11$; yaw, $p=0.30$).

Data analysis

ReHo analysis

We used DPABI (Data Processing & Analysis of Brain Imaging) v2.0 to conduct the ReHo based on unsmoothed data [12]. A temporal band-pass filter ($0.01 < f < 0.1$ Hz) was applied to reduce the influences of low-frequency drift and high-frequency respiratory and cardiac noise.

An individual ReHo map was generated by calculating the concordance of the KCC of the time series of a given voxel with those of its 26 nearest neighbours [7]. To eliminate the effect of individual diversification, the ReHo value of each voxel was converted into a z-score by subtracting the mean ReHo value and dividing the standard deviation of the whole-brain ReHo map. Finally, standardized ReHo maps were spatially smoothed with a 6-mm FWHM Gaussian kernel.

Alff Analysis

The ALFF analysis was the same as in previous studies and was based on preprocessed data. For a given voxel, the time series was transformed to the frequency domain using fast Fourier transforms, and the square root of the power spectrum was calculated and averaged for 0.01–0.1 Hz. This averaged square root was referred to as the ALFF. Finally, the ALFF value of each voxel was converted into a standardized z-score by subtracting the mean ALFF value and dividing the standard deviation of the whole-brain ALFF map so that the maps could be compared across subjects.

Statistical analysis

In this study, we focused only on the significant changes in the sensorimotor network in migraineurs without aura compared to the controls. The maps of the significant differences in ReHo and ALFF of the 45 patients and the 43 controls were compared using voxel-wise two-sample t -tests with age and gender as covariates. To address the issue of multiple comparisons, the ReHo and ALFF statistical maps were

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assigned thresholds at $p < 0.001$ (voxel level), and family-wise errors (FWE) were corrected to $p < 0.05$ at the cluster level. The surviving clusters were reported.

Results

Demographic and clinical data of the migraine and control groups

The demographic and clinical data of the migraine and control groups are presented in Table 1. The age and gender demographic factors did not significantly differ between the SSD and controls.

ReHo And Alff

Compared with the controls, the SSD patients exhibited significantly increased ReHo values in the right middle cingulate gyrus (MCG) and smaller ReHo in the right precuneus, left inferior and temporal gyrus extending to the left middle temporal gyrus and left parahippocampal gyrus, and right pons. The SSD patients showed higher ALFF values in the MCG extending to the left medial frontal gyrus, right insula extending to the right inferior frontal gyrus, and left medial frontal gyrus extending to the left anterior cingulate cortex (ACC).

There was no significant correlation between the values of ReHo and ALFF in these significant alteration areas and clinical indexes of the patients.

Discussion

In this study, we combined ReHo and ALFF analyses for evaluating the abnormalities of spontaneous brain activity in patients with SSD. Compared with the controls, the SSD patients exhibited abnormal ReHo values and ALFF values in the MCG, ACC, medial frontal gyrus, inferior frontal gyrus, insula, precuneus, inferior/middle temporal gyri, parahippocampal gyrus and pons. These findings are in line with previous neuroimaging studies [8, 13, 14]. A meta-analysis identified the middle frontal gyrus, the ACC, and the insula involved in SSD and consistently differed between patients and healthy controls, which seems to be of particular importance in SSD [15].

In our study, we found SSD exhibited spontaneous brain function alterations in frontal and subfrontal regions, including in the MCG, ACC, medial frontal gyrus, inferior frontal gyrus and insula. Previous structural and functional neuroimaging studies indicated alterations in the ACC and MCG play important roles in the neurobiology of functional neurologic disorder, and ACC dysfunction may be related to mood dysregulation and trauma symptoms, whereas MCG alterations may be related to impaired cognitive control, motor control, behavioural expression of mood states, nociception, and multimodal integration in patients with functional neurologic disorder [13]. The medial prefrontal cortex and ACC are involved in

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pression disorders [16, 17]. A systematic review of the

literature showed that the prefrontal cortex and ACC have decreased function and deficient top-down control during emotion regulation tasks in generalized anxiety disorder [18]. The insula has been implicated in interoceptive processes and in the integration of sensory, visceral, and affective information, thus contributing to subjective emotional experiences [19-21]. Furthermore, the insula is a key node of this salience network (SN). Specifically, the anterior insula is involved in the physical awareness as well as the affective aspects of pain perception [22, 23]. The cingulo-frontal cortex has been linked to the top-down control of pain transmission [24]. Our study further confirmed that the cingulo-frontal cortex and cingulo-insular are implicated in the pathophysiology of SSD and would be involved in emotional processing and control, interoceptive processes and physical awareness, pain perception and transmission, and multisensory perception and information integration.

The SSD patients exhibited decreased a ReHo value in the right precuneus. The precuneus, which is the strongest hub in the brain, has been functionally linked to regions that constitute the default mode network (DMN) and plays a pivotal role in the DMN [25, 26]. The precuneus has been proposed to participate in information transfer and multimodal integration, which may be essential for the processing of spontaneous thoughts and for internal awareness [26]. Specifically, its activity seems to correlate with self-reflection processes, possibly involving mental imagery and episodic/autobiographical memory retrieval [27]. The reduced ReHo values of the precuneus indicate a decrease in synchronization of local spontaneous brain activity, suggesting abnormal functional of the precuneus.

Our results showed that the areas of abnormal brain function in SSD patients were located in the DMN and SN. The DMN consists of the medial prefrontal cortex, ACC, the posterior cingulate cortex and the precuneus. The DMN deactivates during conscious attentional shift to environmental-related stimuli, reflecting introspective, self-relevant processes and affective decisions [28, 29]. The SN consists of the insular cortex, parietal ACC, striatum, and limbic structures [30, 31], which may be a transitional network that links cognition and emotion/interoception [32]. Previous neuroimaging studies indicated that DMN and SN activity are related to self-relevant processes and attention to internal and external stimuli, including nociceptive input [33-35]. In addition, the ACC, insula, and prefrontal cortex have been proposed to be involved in the intensity and spatial discriminative pain pathway of the pain processing system [36, 37]. Furthermore, an increased ReHo value in the right MCG, decreased ReHo in the right precuneus and increased ALFF value in the ACC and prefrontal cortex were observed, which suggested that the function of the DMN was out of balance. In our study, the abnormal spontaneous brain activity of the DMN and SN was probably related to aberrant self-relevant processes, emotional processing, multimodal integration, arousal, interoception, and nociceptive input.

The SSD patients exhibited decreased a ReHo value in the left Brodmann's area 20 (inferior/middle temporal gyri and parahippocampal gyrus) and right pone. The Brodmann's area 20 participates in language processes, and it could be regarded as a kind of language processing marginal area [38]. A previous study found that somatoform disorder patients showed extensive hypometabolism in the bilateral temporal gyrus, and the middle temporal gyrus was associated with somatic symptoms [39].

the anxiety subscale correlated positively with grey matter in the middle temporal gyrus [40]. The parahippocampal cortex has been associated with many cognitive processes, including visuospatial processing, emotion processing and episodic memory [41]. Our study found that there was regional brain dysfunction in the temporal lobe; however, the pathological role of the temporal lobe in the SSD is still unclear and needs further confirmation. The pons provides an important connection between the forebrain and the cerebellum related to motor function and is also involved with sleep and control of motor functions [26]. The pons contains the pontine and motor nuclei of the trigeminal nerve and the facial nerve, which are involved in the sensory processes related to touch and pain, facial sensation and expression, and the secretion of saliva and tears [42]. The abnormal function of pons may be directly or indirectly related to the discomfort of body sensation.

Limitations

Although our research revealed that SSD patients exhibit dysfunctions in local spontaneous brain activity, our study had several limitations. First, the samples contained different subtypes of SSDs. The results reflect the general characteristics of SSDs but do not reflect the characteristics of individual subtypes. In future studies, we should investigate the structural and functional changes that occur in different subtypes of SSD. Furthermore, in the current study, patients include those who have been treated with medication and those who were drug-naive and treatment may have an impact on the outcome. A longitudinal study would be able to observe changes in brain function before and after taking medication, which may be a better way to observe the effects of drugs on brain function.

Conclusions

In conclusion, SSD patients exhibited functional abnormalities in the MCG, ACC, prefrontal cortex, insula and precuneus, inferior/middle temporal gyri, parahippocampal gyrus and pons during the resting state. We proposed that DMN and SN key regions showed dysfunction; additionally, dysfunction in the temporal lobe and pons in SSD may result in dysfunction in self-relevant processes, emotional processing, multimodal integration, arousal, interoception, and body perception. The dysregulation of brain networks in SSD related to the processing of emotional information affects the integration of complex sensory inputs and may lead to somatic symptoms.

Abbreviations

SSD: Somatoform disorders; ICD: International Classification of Diseases; DSM: Diagnostic and Statistical Manual of Mental Disorders; fMRI: Functional magnetic resonance imaging; ALFF: Amplitude low frequency fluctuation; ReHo: regional homogeneity; BOLD: Blood oxygen level dependence; KCC: Kendall's coefficient of concordance; PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; MMSE: Mini-mental State Examination; MNI: Montreal Neurological Institute; FWHM: full-width half-maximum; MCG: middle temporal gyrus; SN: salience network; DMN: default mode network.

Declarations

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Author contributions

Xiaoxia Du and Jian-Ren Liu designed the study. Yangyang Cui, Huai-Bin Liang, Yue Hu, Yi-Sheng Liu, Rong Zhao, and Yuan Qiao performed the experiments. Yangyang Cui, Zhaoxia Qin, Qian Zhu, Wei Tang, and Tingting Gao analyzed the data, and Xiaoxia Du, Huai-Bin Liang, Yangyang Cui and Jian-Ren Liu prepared the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Independent Ethics Committee of Shanghai Ninth People's Hospital and the East China Normal University Committee on Human Research. All patients and healthy controls gave written informed consent using forms approved by the committee.

Consent for publication

Not applicable.

Competing interests

All authors have no competing interests.

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Tables

Table 1

Demographic and clinical characteristics of patients with somatic symptom disorder (SSD) and controls.

	SD group (Mean ± SD)	Control group (Mean ± SD)
Male/Female	20/25	19/24
Age (years)	49.67 ± 12.52	52.07 ± 11.48
Disease duration (years)	3.14 ± 3.0	-
PHQ-9	7.6 ± 5.1	-
GAD-7	7.5 ± 5.8	-
HAMA	8.4 ± 4.5	-
HAMD	6.6 ± 3.8	-
MMSE scores	27.3 ± 2.4	-
PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; MMSE: Mini-mental State Examination.		

Table 2

Significant differences observed between SSD patients and controls in the ReHo analysis.

Predominant regions in cluster	Cluster size	Peak T-value	MNI coordinates		
			x	y	z
SD > Controls					
Right middle cingulate gyrus	104	4.59	9	9	42
SD < Controls					
Right precuneus	83	5.04	18	-60	33
Left inferior temporal gyrus extending to	57(15)	4.37	-33	0	-42
left middle temporal gyrus	57(14)				
left parahippocampal gyrus	57(5)				
Right pons	52	4.24	21	-33	-36
The results were assigned thresholds at $p < 0.001$ (voxel level) and FWE-corrected to $p < 0.05$ at the cluster level.					

Table 3

Significant differences observed between SSD patients and controls in the ALFF analysis.

Predominant regions in cluster	Cluster size	Peak T-value	MNI coordinates		
			x	y	z
SD > Controls					
Middle cingulate gyrus	63(41)	4.93	-3	9	42
extending to left medial frontal gyrus	63(10)				
Right insula extending to	52(36)	4.78	36	15	9
right inferior frontal gyrus	52(11)	3.99	45	15	-6
Left medial frontal gyrus extending to	44(19)	4.74	-3	42	18
right anterior cingulate cortex	44(9)	3.83	3	36	27
The results were assigned thresholds at $p < 0.001$ (voxel level) and FWE-corrected to $p < 0.05$ at the cluster level.					

Figures

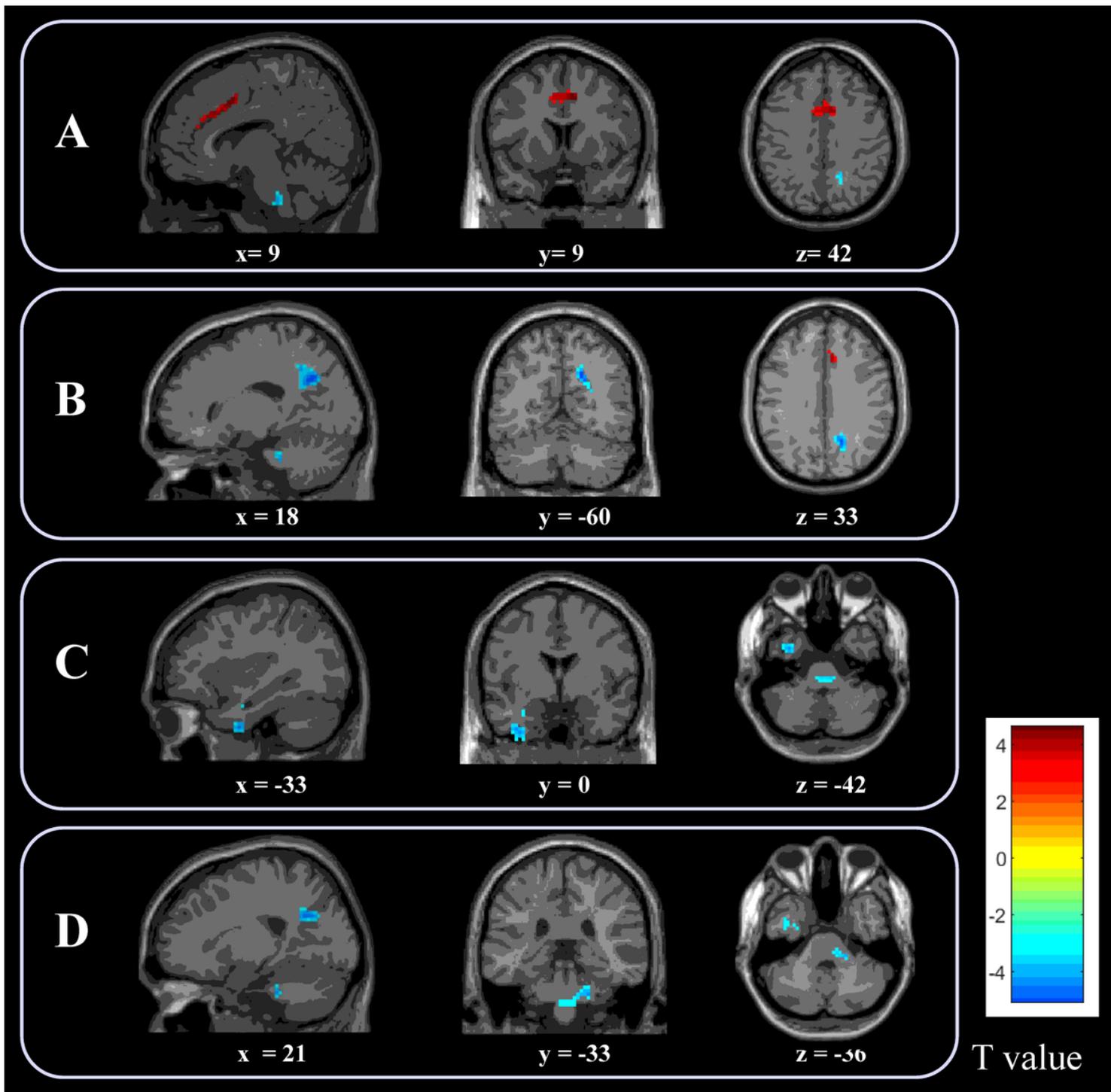


Figure 1

Significant differences in ReHo between SSD patients and healthy controls. Compared with the controls, SSD patients exhibited significantly increased ReHo values in the right middle cingulate gyrus (A, red colour) and smaller ReHo in the right precuneus (B, blue colour), left inferior and temporal gyrus extending to the left middle temporal gyrus and left parahippocampal gyrus (C, blue colour), and right pons (D, blue colour),

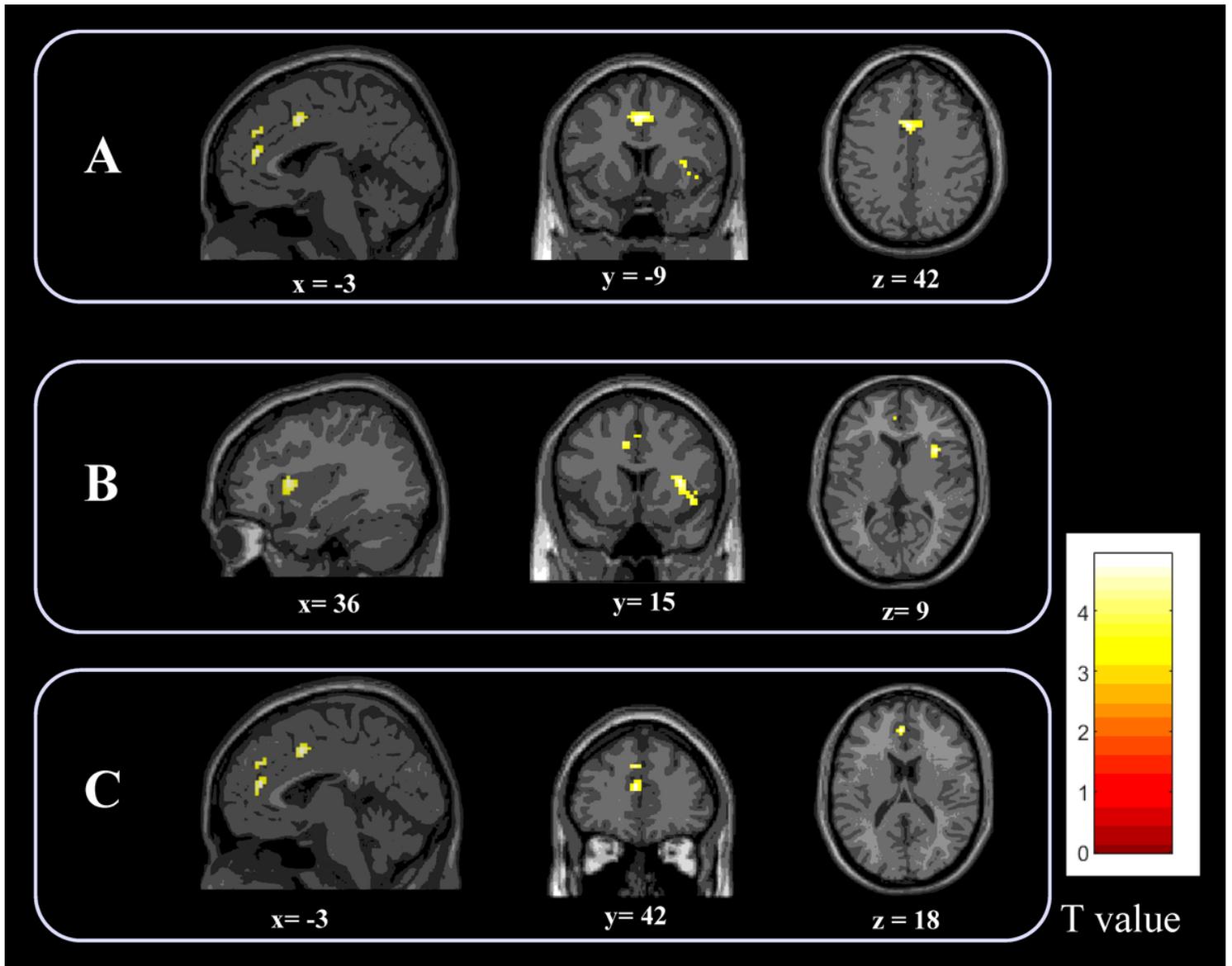


Figure 2

Compared with the controls, SSD patients showed significantly increased ALFF values in the middle cingulate cortex extending to the left medial frontal gyrus (A), right insula extending to the right inferior frontal gyrus (B), and left medial frontal gyrus extending to the left anterior cingulate cortex (C).