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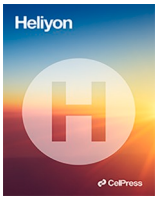

Research article

Association between homotopic connectivity and clinical symptoms in first-episode schizophrenia

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A B S T R A C T

Background: Abnormal functional connectivity (FC) in the brain has been observed in schizophrenia patients. However, studies on FC between homotopic brain regions are limited, and the results of these studies are inconsistent. The aim of this study was to compare homotopic connectivity between first-episode schizophrenia (FES) patients and healthy subjects and assess its correlation with clinical symptoms.

Methods: Thirty-one FES patients and thirty-three healthy controls (HC) were included in the study. The voxel-mirrored homotopic connectivity (VMHC) method of resting-state functional magnetic resonance imaging (rs-fMRI) was used to analyse the changes in homotopic connectivity between the two groups. The 5-factor PANSS model was used to quantitatively evaluate the severity of symptoms in FES patients. Partial correlation analysis was used to assess the correlation between homotopic connectivity changes and clinical symptoms.

Results: Compared to those in the HC group, VMHC values were decreased in the paracentral lobule (PL), thalamus, and superior temporal gyrus (STG) in the FES group ($P < 0.05$, FDR correction). No significant differences in white matter volume (WMV) within the subregion of the corpus callosum or in brain regions associated with reduced VMHC were observed between the two groups. Partial correlation analyses revealed that VMHC in the bilateral STG of FES patients was positively correlated with negative symptoms ($r_{left} = 0.46$, $p < 0.05$; $r_{right} = 0.47$, $p < 0.05$), and VMHC in the right thalamus was negatively correlated with disorganized/concrete symptoms ($r_{right} = 0.45$, $p < 0.05$).

Conclusion: Our study revealed that homotopic connectivity is altered in the resting-state brain of FES patients and correlates with the severity of negative symptoms; this change may be independent of structural changes in white matter. These findings may contribute to the development of the abnormal connectivity hypothesis in schizophrenia patients.

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1. Introduction

Schizophrenia is the most severe of all mental diseases, with a global prevalence of approximately 1 % [1]. The symptomatology of schizophrenia typically includes positive symptoms, such as hallucinations and delusions; negative symptoms, such as decreased motivation and diminished expressiveness; and cognitive deficits such as impaired executive functioning, memory, and mental processing speed [2]. This disease has a serious impact on quality of life and social functioning.

The brains of patients with schizophrenia exhibit structural and functional connectivity(FC) abnormalities that are significantly related to the underlying pathophysiological processes [3]: [4]. Studies have shown that this dysfunctional connectivity of the brain is present not only within the cerebral hemispheres but also between them [5–7]. The two hemispheres of the human brain communicate via the brain's white matter fiber bundles, such as the corpus callosum, anterior connections, posterior connections, interthalamic adhesions, and cerebellar connections [8]. The corpus callosum and extracallosal anatomical connections play a role in maintaining interhemispheric FC [9]. However, compared to healthy individuals, patients with schizophrenia have a smaller corpus callosum [10]. In addition, several diffusion tensor imaging (DTI) studies of schizophrenia patients have shown partial anisotropy abnormalities in some areas of the corpus callosum [11,12]. The term "bilateral dominance" refers to the fact that the two brain hemispheres together are more efficient than a single hemisphere at processing all types of information. Schizophrenia patients lack the advantage of bilateral processing of information found in healthy subjects [13]. These results suggest that people with schizophrenia have impaired interhemispheric interactions.

The resting-state magnetic resonance imaging (rs-fMRI) technique has become one of the most widely used methods in clinical studies of brain function in recent years because of its advantages of being free of ionizing radiation, noninvasive nature, and better balance between temporal and spatial resolution [14]. Compared to other known techniques, this approach requires only minimal cooperation from the subject. Thus, for patients who have schizophrenia with significant psychiatric symptoms and cognitive impairment, clinical research trials can be implemented with relative ease. VMHC is an rs-fMRI analysis technique. VMHC measures the ability to exchange information between the two hemispheres of the brain and is an important indicator of the synergistic effect of brain signal activity in both hemispheres [15,16]. A recent systematic review by Yao et al. [17] reports that different psychiatric disorders exhibit commonalities and different differences in VMHC changes, suggesting that these changes may serve as a potential marker for broad or specific psychopathologies. There are few studies on VMHC in schizophrenia patients, and the findings are inconsistent. Hoptman et al. [18] found decreased VMHC in a wide range of brain areas in schizophrenia patients, especially in the occipital lobe, thalamus, and cerebellum, and did not identify any areas of the brain with increased VMHC. In contrast, Yang et al. [19] discovered increased VMHC in the nucleus accumbens and caudate nucleus of unmedicated teenage first-episode schizophrenia patients. Additionally, Shi et al. [20] discovered that the radiomics-based machine learning approach, utilizing VMHC metrics, demonstrated excellent performance in classifying patients with schizophrenia and healthy controls. VMHC alterations in schizophrenia patients may be associated with psychotic symptoms. However, studies in this area are equally heterogeneous. Recent studies have suggested that decreased interhemispheric coordination in the STG and insula may contribute to cognitive deficits in patients with schizophrenia [21]. Chang et al. and Chen et al. [22,23] found that regional abnormalities in interhemispheric synaesthesia may be critical for the development of auditory and verbal hallucinations. These investigations indicate that interhemispheric communication deficits play a crucial role in the pathophysiology of schizophrenia.

Previous studies on interhemispheric connectivity in FES patients are rare and have yielded mixed results. This study aimed to further explore the homotopic connectivity of FES patients using rs-fMRI data and VMHC. Patients with schizophrenia were evaluated with the more detailed 5-factor PANSS to determine the severity of their symptoms [24,25]. We aimed to identify brain areas with altered functional connectivity between the cerebral hemispheres in patients with FES and to explore brain areas with potentially stable changes. In addition, we investigated the correlation between cerebral homotopic connectivity changes and different dimensions of clinical symptoms, and further considered the differences in structural MRI between the two groups. We examined the differences in WMV of the corpus callosum and region of interest (ROI)-defined brain regions. WMV and VMHC values of the corpus callosum subregion were further correlated to explore the effect of WMV on interhemispheric FC. Additionally, to account for potential confounding factors, we performed a partial correlation analysis between the WMV of the ROI and various demographic characteristics.

2. Materials and methods

2.1. Participants

A total of 64 subjects, including 31 FES patients and 33 healthy subjects, were recruited to participate in the study from the Affiliated Brain Hospital of Guangzhou Medical University. Written informed consent was obtained from the subjects or their legal guardians. The inclusion criteria for patients were as follows: (1) aged between 18 and 50 years, (2) met the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-4), (3) were taking psychotropic drugs for no more than 6 months, (4) had no history of electroconvulsive therapy in the previous 2 years, (5) were experiencing the first episode of schizophrenia (duration not more than 2 years), (6) had a total score of 50 or more on the Positive and Negative Syndrome Scale (PANSS) [26], and (7) were of Han Chinese ethnicity. The exclusion criteria were as follows: (1) met the diagnostic criteria of other psychiatric disorders in the DSM-4, (2) had any history of organic brain diseases, (3) had contraindications to MRI, or (4) had a history of alcohol or substance abuse. The inclusion criteria for the HC group were as follows: (1) no personal or family history of psychiatric diagnosis, (2) aged 18–50 years, (3) no less than 6 years of formal education, and (4) no history of psychiatric drug use. The

exclusion criteria for the HC group were the same as those for the patient group.

2.2. Clinical evaluation instruments and assessment

The five-factor model of the PANSS was used to determine the intensity of symptoms in FES patients [25]. The dimensions assessed included the following factors: positive, negative, disorganized/concrete, excitement and depressed. The patients' clinical and demographic information is summarized in Table 1.

2.3. Neuroimaging acquisition and data preprocessing

MRI data were obtained on the same day as the clinical evaluation at the Affiliated Brain Hospital of Guangzhou Medical University. Each patient was scanned using a 3.0 T Philips MRI system with an eight-channel SENSE head coil. During the scans, all participants were asked to remain calm, relaxed, supine, and awake with their eyes closed. Each subject's head was immobilized with a supportive foam pad to limit head movement. First, anatomical scans and locator scans were completed. Next, functional images were obtained by scanning 240 echo planar imaging sequences with the following parameters: repetition time/echo time (TR/TE) = 2000/30 ms, flip angle = 90°, slices = 33, field of view (FOV) = 192 mm × 192 mm, matrix = 64 × 64, slice thickness = 4 mm, interslice gap = 4.6 mm, and voxel size = 3.44 mm × 3.44 mm × 4.60 mm.

The rs-fMRI data were preprocessed using RESTplus in MATLAB 2013b (MathWorks, Inc) [27]. The maximum displacement of each subject's head in the x, y, or z dimensions could not exceed 2 mm, and the angular motion could not exceed 2°. The first ten volumes of each functional time series were eliminated to prevent potential signal distortion and allow for scanning noise adaptation. Then, slice-timing correction and realignment were performed. Normalization was performed by using traditional EPI templates, and scans were resampled to 3 mm × 3 mm × 3 mm. Finally, to reduce the impact of low-frequency drifts and physiological high-frequency noise, the images were smoothed spatially with an 8-mm full width at half-maximum Gaussian kernel, linearly detrended, and temporally bandpass filtered (0.01–0.08 Hz).

For subsequent analyses, the VMHC method in REST software (version 1.8) was used to calculate the FC between voxels with mirror symmetry. VMHC was determined by correlating the time series of each voxel in one hemisphere with the time series of the congruent voxel in the contralateral hemisphere. The Pearson correlation coefficient was calculated for each pair of mirror voxels between the two hemispheres. Then, Fisher Z transformation was used to improve the normality of the data distribution, and the final value obtained was recorded as the VMHC value.

High-resolution 3D-T1 structural images were obtained using a planar imaging sequence of gradient echoes with the following parameters: TR/TE = 8.2/3.8 ms, flip angle = 7°, matrix = 256 × 256, scanning layers = 165, and thickness = 1.0 mm. Voxel-based morphometry was used to examine changes in WMV and brain structure in both groups. Preprocessing of structural state data using the SPM8 subtool included the following steps. First, the 3D-T1 MR images were divided into cerebrospinal fluid, white matter, and grey matter. Then, the grey matter images were normalized to the MNI space. Finally, smoothing was performed by a Gaussian kernel with a full width at half maximum of 6.0 mm. The WMV of the region of interest was extracted using the RESTplus toolbox.

2.4. Statistical analysis

Statistical analysis of demographic and clinical data was performed using SPSS version 25.0. Two-sample t tests were employed to examine the differences between the two groups in terms of age and years of education. The chi-square test was used to assess sex differences between the two groups. Brain regions with significant VMHC differences were defined as ROIs. To make the results more reliable, we calculated the corresponding ROI means for VMHC based on the left and right hemispheres separately. We further

Table 1
Demographics of case group and healthy control group.

Variables	Patients with FES (n = 31)	Healthy Controls (n = 33)	P
	Mean(SD)	Mean(SD)	
Sex(male/female)	17/14	16/17	0.611a
Age(years)	25.0 ± 6.8	24.2 ± 5.0	0.629b
Education(years)	11.1 ± 3.3	11.7 ± 3.1	0.477b
Duration of illness(months)	8.5 ± 7.0	NA	NA
Antipsychotics drug use(mg)[1]	222.1 ± 244.4	NA	NA
PANSS total	65.6 ± 15.0	NA	NA
PANSS positive	14.4 ± 4.0	NA	NA
PANSS negative	18.4 ± 4.8	NA	NA
PANSS disorganized/concrete	4.2 ± 1.7	NA	NA
PANSS excitement	7.3 ± 3.5	NA	NA
PANSS depressive	5.5 ± 2.4	NA	NA

Notes: FES: first-episode schizophrenia; HC: healthy controls; SD: Standard Deviation; NA: not applicable; PANSS: positive and negative syndrome scale.
"1" Chlorpromazine equivalent doses were calculated; "a" presents Student's *t*-test analysis; "b" presents chi-square analysis.

performed a two-sample *t*-test on brain WMV in ROIs. In addition, we calculated the WMV after partitioning the corpus callosum according to previous studies and performed two-sample t tests [28]. The corpus callosum is divided into seven sections: the prefrontal, premotor and supplementary motor, motor, sensory, parietal, occipital and temporal sections. Two-sample t tests on VMHC maps between patients and controls were performed to compare VMHC between the two groups. FDR correction was then performed. After FDR correction, the significance threshold was set at $P < 0.05$, two-sided, uncorrected, with a cluster size of 50 voxels. Subsequently, we correlated the WMV of each corpus callosum region with the VMHC values of the calculated ROIs to further understand the relationship between interhemispheric FC and corpus callosum structure. Using sex, age, years of education, age of onset of schizophrenia, duration of illness, chlorpromazine equivalent doses of patients and WMV values of ROIs, a partial correlation analysis of ROI-based VMHC values with PANSS scores was performed ($P < 0.05$, two-sided test). More stable results were defined only when a correlation was found between the VMHC values of the bilateral ROIs of the brain and the scores of one of the PANSS dimensions.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the patients are shown in Table 1. Sex ($\chi^2 = 0.26$, $P = 0.611$, Table 1), age, and years of education (age: $t = 0.49$, $P = 0.629$; years of education: $t = -0.72$, $P = 0.477$, Table 1) were not significantly different between the FES patients and HC. In addition, the differences in the mean WMV of the ROIs between the two groups was not statistically significant ($P > 0.05$, Supplementary Table 1). Furthermore, our statistical comparisons did not reveal any significant differences in the mean VMHC values between the ROIs of the two groups or in the WMVs of the various corpus callosum regions between the two groups ($P > 0.05$, Supplementary Table 1).

3.2. Group differences in VMHC

Comparisons of VMHC values between patients and healthy subjects and specific information on the areas of interest are shown in Fig. 1. After FDR correction ($P < 0.05$), the differences in VMHC values between the two groups were statistically significant. Patients had lower VMHC in the PL, thalamus, and STG than HC did (Fig. 1, Table 2). In subsequent correlation analyses, we explored the association between WMV in distinct regions of the corpus callosum and VMHC values of ROIs. However, our findings were not statistically significant ($P > 0.05$, Supplementary Table 2).

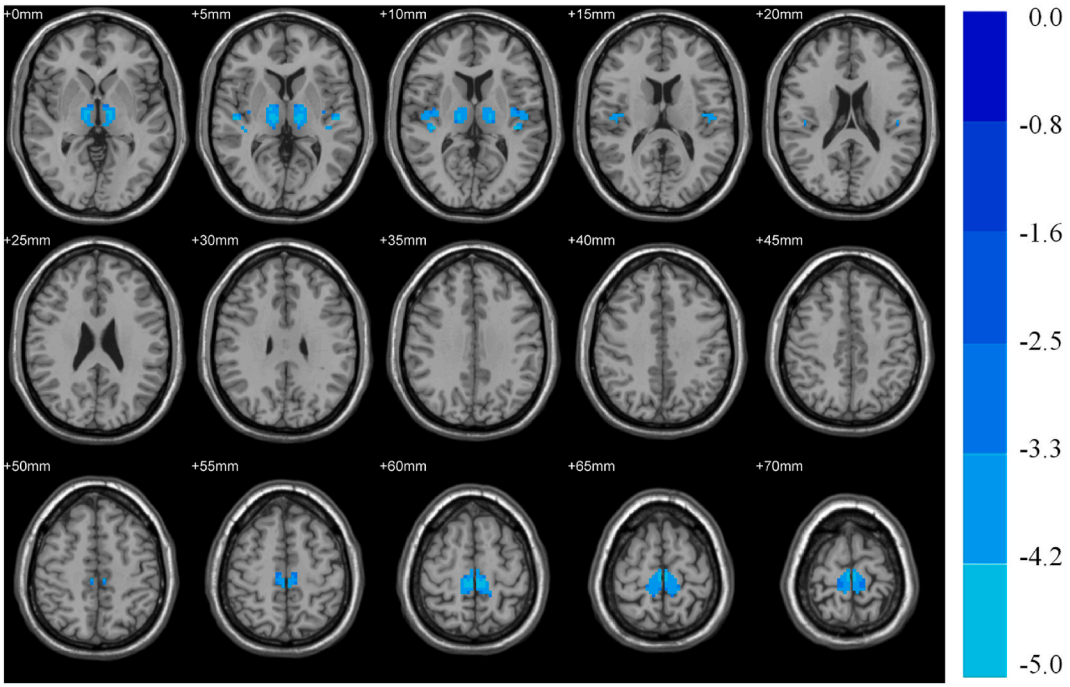

Fig. 1. Differences in voxel-based homotopic connectivity (VMHC) between patients with first episode schizophrenia (FES) and healthy controls (HCs).
Note: the color bar represents the *t* values of the VMHC group analysis.

Table 2
The different brain regions of mean of the VMHC value between two groups.

Brain region (AAL)	Cluster size voxels	Peak MNI coordintes		
		x	y	z
Paracentral lobule	145	±3	−33	60
Thalamus (ventral posterolateral nucleus/ventrolateral nucleus)	91	±12	−18	3
Superior Tempotal Gyrus	70	±51	−18	6

Note: VMHC: voxel-mirrored homotopic connectivity; AAL: anatomical automatic labeling; MNI: Montreal Neurological Institute.

3.3. Correlations between VMHC values and patient symptoms

After controlling for the variables sex, age, years of education, age at the first onset of schizophrenia, total duration of illness, chlorpromazine equivalents and WMV values of the ROIs, the partial correlation analysis between VMHC values and clinical symptoms showed a positive correlation between PANSS-negative scores and reduced VMHC in the bilateral STG ($r_{left} = 0.46$, $p < 0.05$; $r_{right} = 0.47$, $p < 0.05$). The VMHC values in the right thalamus, but not in the left thalamus, were negatively correlated with the PANSS-disorganized/concrete scores ($r_{left} = 0.36$, $p > 0.05$; $r_{right} = 0.45$, $p < 0.05$).

4. Discussion

This study aimed to explore the FC between symmetrical cerebral hemispheric areas in FES patients and its relationship with symptom severity. FES patients showed reduced homotopic connectivity, and the brain structures with reduced connectivity included the PL, thalamus, and STG. The difference in WMV between the FES and HC groups was not statistically significant. When comparing the WMV between the two groups after partitioning the corpus callosum, no statistically significant differences were found. Similarly, further correlation analyses between the WMV and VMHC of the ROIs also did not yield statistically significant results. This result suggested that the alterations in interhemispheric VMHC exhibited by FES patients may not be related to structural changes in white matter. Partial correlation analysis revealed a significant association between VMHC values of the STG and PANSS-NEG scores, indicating that this connectivity index may have important functional implications in psychopathology.

The PANSS is widely used to assess schizophrenia symptoms. In fact, the PANSS is considered the global gold standard for measuring schizophrenia symptoms [29]. The original PANSS assessed positive symptoms, negative symptoms, and overall psychopathology. However, numerous factor analyses and substantial clinical research evidence suggest that the five-factor model better captures the structure of the PANSS in schizophrenia patients [24,25]. The present study is the first to use this assessment method in a VMHC study, and we expect that future studies will find a closer association between schizophrenia pathogenesis and clinical symptoms.

In the present study, compared with HCs, FES patients exhibited attenuated homotopic connectivity, which is consistent with the findings of several previous studies. However, in terms of specific brain areas with VMHC changes, the findings of the present study are inconsistent with those of previous studies. Yao et al. [17] conducted a systematic review and further summarized the changes in VMHC in schizophrenic patients, again yielding many inconsistent results. They found that in patients with schizophrenia, the brain regions with reduced VMHC were mainly concentrated in the posterior regions of the brain. Hoptman et al. [18] reported reduced VMHC in the occipital, thalamic, and cerebellar areas in individuals with schizophrenia or schizoaffective disorder. A study by Li et al. [30] similarly found that, compared to HC, patients with early-onset unmedicated schizophrenia exhibited a reduction in VMHC in the STG and postcentral gyrus. Guo et al. [31] discovered decreased VMHC in the praecuneus, precentral gyrus, STG, middle occipital gyrus, and syrinx/cerebellar lobule VI in schizophrenia patients. Studies on interhemispheric connectivity have also involved areas such as the inferior frontal gyrus, parahippocampus, and striatum [32,33]. Different sample sizes, image acquisition parameters, data processing methods, and study populations could be responsible for these differences in results. Therefore, in studies on cerebral interhemispheric connectivity, it is important to pay attention to those involving repeated measures.

The PL is part of the sensorimotor area. Disorders of the connectivity of the sensorimotor pathway have been reported in patients with schizophrenia. One study reported a reduced amplitude of low-frequency fluctuations in the bilateral PL in schizophrenia patients [34]. Lang et al. reported lower VMHC values in the suboccipital gyrus, cingulate gyrus, and paracentral lobule in fully remitted and incompletely remitted schizophrenia patients, but there was no correlation between changes in the PL VMHC and PANSS scores [32]. The same results were found in our study, in which reduced VMHC in the PL was not correlated with scores in any PANSS dimension. An rs-fMRI study of healthy subjects showed that the PL is functionally linked to other frontal and parietal areas supporting motor function and spatial attention. Notably, patients with schizophrenia exhibit persistent attentional deficits [35]. Paracentral deficits may lead to attentional deficits [36,37]. Therefore, we hypothesize that reduced PL VMHC may be related to attention deficits in patients with schizophrenia and that the PANSS may not facilitate assessment of attention. Future research should examine specific VMHC alterations associated with attention problems.

Various thalamic nuclei have diffuse and specialized efferent projections to cortical, cerebellar, and subcortical areas. The thalamus is the gatekeeper and mediator of several cognitive, sensory, motor, and behavioural functions. Damage to the projection fibres of the thalamus can cause severe impairment of function [38]. Li et al. and Tomasino et al. [39,40] reported that lower thalamic volume in schizophrenia patients was associated with clinical symptoms. Research on the anatomy of the thalamus revealed aberrant and asymmetric changes in the morphology of the right and left thalamus in schizophrenia patients [41]. Thus, we speculate that patients

with schizophrenia may have abnormal homotopic connections in the thalamus. We found that FES patients had reduced VMHC in the thalamus. Guo et al. and Hoptman et al. [18,42] also reported lower VMHC of the thalamus in schizophrenia patients. Numerous studies have indicated that the intrinsic FC of the thalamus with the cerebellum and various cortical networks is disrupted and that this disruption correlates with symptoms such as cognitive impairment and positive symptoms in schizophrenia patients [43,44]. We found that the reduced VMHC values in the right thalamus were negatively associated with disorganized/concrete symptoms. It is important to emphasize that disorganized/concrete symptom scores are most strongly associated with cognitive function on the PANSS [25]. Liu et al. [21] reported a negative correlation between the presence of homonymous rsFC in the STG/insula and cognitive function test scores in adolescent schizophrenic patients. A functional characterization study of cognitive subgroups in schizophrenia patients revealed hyperconnectivity between the thalamus and large-scale brain regions in patients with moderate cognitive decline [45]. These findings suggest that VMHC changes in the thalamus may be related to neurophysiological mechanisms of cognitive impairment in schizophrenia patients. However, this result was unreliable in our study because symmetrical left thalamic VMHC changes did not correlate with disorganized/concrete symptoms. Some studies have shown that the thalamus can process information autonomously [46]. We speculate that the thalamus is involved in a more complex mechanism for the development of schizophrenia. In this study, we found decreased VMHC of the STG. Evidence from numerous studies suggests that the STG is one of the key brain areas involved in the pathophysiology of schizophrenia. A recent meta-analysis showed a reduction in STG volume in schizophrenia patients compared to healthy subjects [47]. An anatomical study of subjects at high risk of developing schizophrenia revealed a significant reduction in grey matter in the STG in patients who later developed schizophrenia [48]. In our study, FES patients exhibited the same decrease in VMHC of the STG. Chang et al. and Guo et al. [22,31] similarly reported lower VMHC of the STG in the brains of schizophrenia patients. This suggests that changes in VMHC of the STG in schizophrenia patients may be stable and can be used as a predictor of clinical features. The STG is believed to be involved in language and auditory processing. In this study, we identified a positive correlation between changes in the VMHC of the STG in FES patients and the negative symptom score on the 5-factor PANSS. A recent review noted that many studies reported stronger correlations between reductions in left STG volume and the severity of thought disorder than between this variable and changes in right STG volume [49]. Whether the different manifestations of changes in left and right STG volume and thought disorder are related to VMHC alterations is unclear. However, in our study, VMHC values calculated based on both the left and right hemisphere STG were positively correlated with negative symptom scores on the PANSS, suggesting that this result is reliable. In addition, Hovington et al. [50] found that frontotemporal white matter may be more closely related to persistent negative symptoms, and greater anhedonia may mediate this relationship. These results indirectly support a relationship between the homotopic connectivity of the STG and negative symptoms of schizophrenia, such as anhedonia and thought disorder. In a previous study, Kim et al. [51] similarly reported a positive correlation between the local grey matter volume of the right STG and the presence of negative symptoms. However, Guo et al. discovered associations of reduced VMHC in the interhemispheric STG with positive, negative, and total PANSS scores [31]. There are many possible explanations for these differences in the results. For example, we used the five-factor PANSS, which enables adequate assessment of the dimensions of schizophrenia symptoms. In addition, the sample size of our study was modest. Therefore, this result should be interpreted with caution.

5. Limitations

There are several limitations of the current study. First, the sample size was small, which may greatly exaggerate false-positive findings in the observed data. However, our study applied strict inclusion criteria. More independent samples will be needed to replicate (and verify) our findings in the future. Second, because the human brain is asymmetrical, we used a standard template for symmetry and smoothed functional images to improve functional coordination between mirror areas. Nevertheless, the effects of this brain asymmetry were not entirely eliminated. Finally, this study was exploratory. Although we have shown that the reduced VMHC of the STG was related to the severity of negative symptoms in FES patients, whether these symptoms could be interpreted more meaningfully in relation to more specific negative symptoms or as a biomarker of negative symptoms in FES patients remains unknown.

6. Conclusion

The current study showed that the VMHC of the PL, thalamus and STG was reduced in resting-state FES patients. The VMHC of the STG in FES patients was positively correlated with negative symptoms, and this relationship existed independently of white matter volume differences. Our results further support the abnormal FC hypothesis of schizophrenia.

Declarations

The Institutional Review Board of the Affiliated Brain Hospital of Guangzhou Medical University approved the study, and the ethics approval number for our study is (2018) No. (002). The patients/participants provided written informed consent to participate in this study.

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Data availability statement

Data is not included in any publicly available repository and will be made reasonably available on request.

CRediT authorship contribution statement

Hengyu Zhang: Writing – original draft, Methodology, Formal analysis. **Qijie Kuang:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Ruikeng Li:** Investigation, Funding acquisition. **Zhen Song:** Investigation. **Shenglin She:** Project administration, Conceptualization. **Yingjun Zheng:** Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30347.

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