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Original Article

Dysfunction of thalamocortical circuits in early-onset schizophrenia

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Previous studies have demonstrated that the thalamus is involved in multiple functional circuits in participants with schizophrenia. However, less is known about the thalamocortical circuit in the rare subtype of early-onset schizophrenia. A total of 110 participants with early-onset schizophrenia (47 antipsychotic–naive patients) and 70 matched healthy controls were recruited and underwent resting-state functional and diffusion-weighted magnetic resonance imaging scans. A data-driven parcellation method that combined the high spatial resolution of diffusion magnetic resonance imaging and the high sensitivity of functional magnetic resonance imaging was used to divide the thalamus. Next, the functional connectivity between each thalamic subdivision and the cortex/cerebellum was investigated. Compared to healthy controls, individuals with early-onset schizophrenia exhibited hypoconnectivity between subdivisions of the thalamus and the frontoparietal network, visual network, ventral attention network, somatomotor network and cerebellum, and hyperconnectivity between subdivisions of thalamus and the parahippocampal and temporal gyrus, which were included in limbic network. The functional connectivity between the right posterior cingulate cortex and 1 subdivision of the thalamus (region of interest 1) was positively correlated with the general psychopathology scale score. This study showed that the specific thalamocortical dysconnection in individuals with early-onset schizophrenia involves the prefrontal, auditory and visual cortices, and cerebellum. This study identified thalamocortical connectivity as a potential biomarker and treatment target for early-onset schizophrenia.

Key words: early-onset schizophrenia; thalamocortical functional connectivity.

Introduction

Schizophrenia is a neurodevelopmental disorder, in which the abnormal developmental trajectory of the brain appears to be established during gestation, long before clinical symptoms of the disease appear in early adult life (Stachowiak et al. 2013; Rund 2018). Individuals with early-onset schizophrenia (EOS), those who are diagnosed with schizophrenia before age 18, are an ideal group for studying the neurodevelopmental mechanism of schizophrenia, as they are less affected by long-term exposure to the environment and drugs and develop symptoms during a critical period for major changes in the brain (Paus et al. 2008).

Considerable evidence has shown abnormalities in the thalamus in individuals with schizophrenia. Studies have consistently reported that the cerebello–thalamo–cortical circuits and cortico–thalamocortical circuits are disconnected in individuals with schizophrenia (Cao et al. 2022). Thalamic hypoconnectivity with the prefrontal cortex and hyperconnectivity with sensory and motor areas have been identified in chronic individuals, early-stage individuals, and high-risk individuals with schizophrenia (Welsh et al. 2010; Woodward et al. 2012; Anticevic et al. 2014, 2015; Wang et al. 2015). Furthermore, it was demonstrated that functional connectivity (FC) between the thalamus and the rest of the brain was primarily increased after treatment with second-generation antipsychotic drugs in individuals with first-episode psychosis (Chopra et al. 2021). These studies suggest that the thalamus is potentially a core brain region in large-scale neural system disruptions in individuals with schizophrenia. However, few studies have focused on thalamocortical FC in individuals with EOS. Zhang et al. (2021) reported sensorimotor-thalamic hyperconnectivity and prefrontal–cerebello–thalamic hypoconnectivity in participants with EOS. Adolescence is considered a sensitive window for thalamocortical circuit maturation, which may be related to the symptoms and cognitive deficits of individuals with schizophrenia (Benoit et al. 2022b). Specially, executive function (EF) defects in individuals with schizophrenia may be related to abnormalities in thalamocortical circuits (Benoit et al. 2022a), and further exploration of thalamocortical FC in individuals with EOS and its relationship with EF deficits is necessary.

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Earlier functional magnetic resonance imaging (fMRI) studies investigated thalamic functional features in schizophrenia patients using the whole thalamus as the region of interest (ROI). However, because the composition of the thalamus is complex, not defining the specific thalamic subdivisions means that we cannot identify whether the alterations in thalamocortical FC in individuals with schizophrenia are due to the entire thalamus or a specific region. A few studies have used new methods to subdivide the thalamus, such as functional subdivision by fMRI (Woodward and Heckers 2016) and anatomical subdivision by diffusion tensor imaging (DTI). Recently, O'Muircheartaigh et al. (2015) proposed a method that used a combination of resting-state FC and white matter connectivity to subdivide the thalamus. Combining the relatively high spatial resolution of diffusion MRI (dMRI) and the high sensitivity of fMRI to long-range connectivity, this method can provide a flexible approach to subdivision of the thalamus by efficiently integrating information from functional and structural connectivity within a participant group. Using this method, Gong et al. (2019) reported a loss of connectivity between several thalamic subdivisions and the sensorimotor system, anterior cingulate cortex, and cerebellum in participants with adult-onset schizophrenia (AOS). This method is believed to be particularly suitable for the division of thalamic subdivisions in children and adolescents, as it does not depend on a cortical atlas or require a priori information.

In this study, we recruited 110 individuals with EOS and 70 age- and sex-matched healthy controls (HCs). We used an approach that combined dMRI and fMRI data to parcellate the thalamus of the participants. Next, differences in the FC maps of the subthalamic divisions between individuals with EOS and HCs were obtained. To better reveal the pattern of thalamocortical connectivity in individuals with EOS, we also evaluated the relationships between functional alterations and EF and clinical features in individuals with EOS. We hypothesized that compared with HCs, individuals with EOS may show abnormalities in thalamocortical FC and that some of these abnormalities might be related to EF dysfunction.

Materials and methods

Participants

Participants with EOS were recruited from inpatient and outpatient psychiatric units at West China Hospital, Sichuan University. Participants with EOS were defined as those who were diagnosed with schizophrenia before the age of 18 yr. The diagnosis was made according to the diagnositic and statistical manual of mental disorder-IV (DSM-IV) criteria. All participants were interviewed using the Structured Clinical Interview for the DSM-IV. Subjects underwent further clinical evaluation by completing the Positive and Negative Syndrome Scale (PANSS). All participants were followed up for at least 6 mo to confirm the diagnosis. The psychiatric history of participants was reviewed to exclude those with a previous history of any major psychiatric disorder, including psychotic, affective, and schizoaffective disorders; head trauma; substance use disorder; or neurological disorders. Participants who received electroconvulsive therapy were also excluded. In this study, 13 subjects were excluded due to poor-quality MR images. Of the 97 individuals with EOS, 43 were antipsychotic naive at the time of MRI scanning, and the remaining 54 had been treated with first-generation antipsychotics at a low dosage (average equal effective dose of olanzapine = 3.616 mg). Of the 54 treated participants, 37 took drugs for less than a week, 10 for a week to a month, and 7 for 1 to 3 mo. HCs were recruited from ordinary primary/secondary schools in Chengdu. HCs were screened by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid) to exclude psychiatric disorders. Subjects were excluded if a first/second/third-degree relative suffered from any mental disorders. Seven HCs were excluded due to poor-quality MR images.

Written informed consent was obtained from the parents of the participants and from the adolescents with consenting capacity. All participants were right-handed. This study complied with the content and requirements of the Helsinki Declaration and was reviewed by the ethics committee of West China Hospital, Sichuan University.

EF

The Cambridge Neuropsychological Test Automated Battery is a set of cognitive tests developed by The University of Cambridge. Three dimensions were used to measure EF, including stockings of Cambridge (SOC), spatial working memory (SWM), and intra-extra dimension (IED) set shift. The response time was automatically recorded by a computer to millisecond accuracy. To ensure that the results were highly consistent and minimally affected by human factors, the testers were trained and tested for consistency before the study. The tests were administered on a computer by 2 experienced testers (more details about the tests are provided in the Supplementary Material).

MRI scans

All participants were scanned using a 3.0 T Verio MRI system (Achieva, Philips, The Netherlands) at the Department of Radiology at West China Hospital, Sichuan University. Foam padding and earplugs were used to reduce head movement and scanner noise. Resting-state functional images were obtained using a gradient echo T2*-weighted sequence (repetition time (TR)/echo time (TE) = 2,000/30 ms, matrix size = 64 × 64, and voxel resolution = 3.75 × 3.75 × 4 mm^3). The scanning time was 8 min 6 s, and 240 image volumes were obtained. All the subjects were instructed to keep their eyes closed, think of nothing in particular, and remain awake. The parameters of the T1-weighted and T2-weighted sequences were described in detail in our previously published study (the parameters are also available in the Supplementary Material; Cai et al. 2022).

After obtaining 3 unweighted images, diffusion-weighted images were acquired in 32 directions using a diffusion-weighted spin–echo echo planar imaging (EPI) sequence with the following parameters: b = 1,000 s/mm^2, TR = 10,295 ms, frequency direction = right to left, acquisition matrix = 128 × 128, field of view = 128 × 128 mm, slice thickness = 2 mm and slices = 75. The voxel size of the DTI scans was 2 × 2 × 2 mm^3. All scans were reviewed by an experienced neuroradiologist to exclude obvious gross abnormalities.

Data preprocessing

The SPM12 toolbox (www.fil.ion.ucl.ac.uk/spm) was used to preprocess the fMRI data. The dMRI data were preprocessed by FMRIB Software Library (FSL version 5.0.9; detailed data preprocessing methods are described in the Supplementary Material).

Subdivision of the thalamus

Consistent with the approach used by Gong et al. (2019), we subdivided the thalamus by combining dMRI and fMRI data. First, voxels from the left (449 voxels, extracted from the Harvard–Oxford atlas with a resolution of 2 × 2 × 2 mm^3 in FSL) and right thalamus (444 voxels) were used as seeds to acquire white

matter tractograms. In the probabilistic tracking process (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide), the seed point, brain mask, termination mask, and weighting were set according to length, while the other parameters were set to the default values. Then, individual tractograms of all subjects were merged into 4D volumes for the left and right hemispheres individually. Then, the 2 4D-tractogram datasets (left and right) were subjected to group independent component analysis. The FC originating from the thalamus was used for the second step of thalamus parcellation. Finally, parcellation of the thalamus was carried out via the use of Pearson's correlation coefficients to construct a similarity matrix of resting-state FC *t*-maps of each thalamic origin. Details are shown in the Supplementary Material.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS 22.0 for Windows, IBM Corp, Armonk, NY, USA). Chi-square tests, Student's *t*-tests, and analysis of variance were used to compare the distribution and differences of categorical and continuous data, respectively.

Evaluation of FC of the thalamic subdivisions

The Morel atlas8 was used to identify which nuclei were included in each subdivision (see Supplementary Table 1). Subsequently, the composition of each subdivision of the thalamus was defined. The FC map of each thalamic subdivision was computed using Pearson's correlation coefficients between the time series of the thalamic subdivision and the whole brain for each participant. A second-level multiple regression was used to test the differences in FC maps between groups. Age and sex were used as covariates, and false discovery rate (FDR) correction ($P < 0.05$) was performed for multiple comparisons in the voxel-level analyses.

Correlations between EF/clinical features and neuroimaging findings

Spearman's rank correlation coefficients were used to quantify the correlation between EF and clinical features (i.e. PANSS) and neuroimaging metrics (the FC value of each voxel with a significant intergroup difference; $P < 0.05$, FDR-corrected).

Results

Demographic characteristics

The demographic characteristics of the participants are shown in Table 1. There were no significant differences in age (range = 10 to 18 yr; $t = 1.945$, df = 158, $P = 0.055$), sex ($x^2 = 0.986$, df = 1, $P = 0.321$), or education ($t = 0.815$, df = 158, $P = 0.417$) between the 2 groups. Table 1 shows that, compared with the controls, the EOS group exhibited worse performance on the SWM, IED, and SOC tasks ($P < 0.05$, FDR-corrected).

Parcellation of the thalamus

All voxel-based tractography maps were decomposed into 11 spatial components for the left thalamus and 12 for the right thalamus. According to the clustering process of FC maps for the 23 weighted thalamic origins, they were labeled into 5 ROIs (Supplementary Fig. 1). Subsequently, the bilateral thalamus was parcellated into 5 nearly symmetrical subdivisions.

As shown in Supplementary Table 1, ROI1 mainly include lateral posterior nucleus (LP), medial geniculate nucleus (MD), anterior pulvinar, ventral posterior inferior nucleus, ventral lateral nucleus (VL), ventral anterior nucleus (VA), and ventral posterior lateral nucleus (VPL). ROI2 include anterior medial nucleus, anterior ventral nucleus (AV), central medial nucleus, center median nucleus (CM), central lateral nucleus (CL), mediodorsal nucleus parvocellular part (MDmc), ventral lateral anterior nucleus (VLa), ventral lateral dorsal part (VLpd), and ventral lateral ventral part. ROI3 include AV, CM, lateral dorsal nucleus (LD), and VLpd. ROI4 include medial pulvinar, lateral pulvinar, LP, and medial pulvinar (MP). ROI5 include CL, CM, MDmc, VA parvocellular part, VLa, ventral LP (VLp), VLpd, and ventral medial nucleus.

Connectivity map of thalamocortical circuits

Figure 1 shows that, compared with the HC group, the EOS group showed hyperconnectivity and hypoconnectivity between 5 subdivisions of the thalamus and several cortical regions ($P < 0.001$, uncorrected; Fig. 1A, Supplementary Table 3). However, the differences in FC were still significant after correction in only 3 of the thalamic subdivisions (ROI1, ROI2, and ROI4; Supplementary Fig. 2A; $P < 0.05$, FDR-corrected). Compared with the HCs, the EOS patients showed hypoconnectivity between 5 subdivisions of the thalamus and the cerebellum (Fig. 1B and Supplementary Table 3). However, only the differences for ROI2 and ROI4 were still significant after correction (Supplementary Fig. 2B, $P < 0.05$, FDR-corrected).

Specifically, as shown in Fig. 1A, Supplementary Fig. 2A, and Supplementary Table 3, significant hypoconnectivity was found between subdivisions of the thalamus and regions in the frontoparietal networks (i.e. the middle and superior frontal gyrus) and the ventral attention network (i.e. temporal pole and right middle cingulum), visual network (i.e. left lingual gyrus, right calcarine sulcus, and fusiform), and somatomotor networks (i.e. left precentral, right supplementary motor area [SMA], and right middle frontal gyrus). For ROI1, the EOS group exhibited hypoconnectivity mainly with the left lingual gyrus, bilateral anterior cingulate cortex (ACC), and left superior frontal gyrus. For ROI2, the EOS group exhibited hypoconnectivity mainly with the somatomotor networks, including the cingulate cortex, SMA, and left precentral gyrus. For ROI4, the EOS group exhibited hypoconnectivity mainly with the ACC, middle temporal gyrus (MTG), and bilateral putamen.

For ROI1, individuals with EOS also exhibited hyperconnectivity with the left parahippocampal gyrus and the left inferior temporal gyrus. For ROI2 individuals with EOS exhibited hyperconnectivity with the left parahippocampal gyrus.

Correlations between EF/clinical features and neuroimaging findings

In the EOS group, we found that FC between the right posterior cingulate cortex (PCC) and ROI1 was positively correlated with the general psychopathology scale score ($r = 0.41$). After correcting for the number of clinical comparisons, the correlation was still significant ($P < 0.001$). FC between the right inferior frontal gyrus (IFG) and ROI4 was positively correlated with SOC score ($r = 0.27$; Fig. 2 and Table 2; $P < 0.05$, FDR-corrected). However, the result did not survive FDR correction ($P = 0.07$).

Discussion

The present study clarified the characteristic changes in the thalamocortical circuit in individuals with EOS via an updated method. In this study, individuals with EOS exhibited hypoconnectivity between subdivisions of the thalamus and the frontoparietal network, visual network, ventral attention network, somatomotor

Table 1. Demographic profiles of EOS patients and HCs and comparisons of EF between the 2 groups (mean [SD]).

	EOS($n = 97$)	HC($n = 63$)	T/χ2	P
Age, year	15.06 ± 1.584	14.29 ± 2.876	1.945	0.055[a]
Sex (male/female)	34/63	27/36	0.986	0.321[b]
Education, years	9.01 ± 1.468	8.70 ± 2.798	0.815	0.417[a]
Handless (left/right)	0/97	0/63	/	/
Age of onset, years	14.25 ± 1.671	/	/	/
Course, months	8.7 ± 13.22	/	/	/
Medication time, days	7.59 ± 17.224	/	/	/
Equal effective dose of olanzapine, mg	3.616 ± 5.411	/	/	/
Positive symptoms scale score	20.77 ± 6.823	/	/	/
Negative symptoms scale score	20.68 ± 8.429	/	/	/
General psychopathology scale score	37.05 ± 12.093	/	/	/
PANSS	78.51 ± 23.981	/	/	/
EF				
IED				
IED_PEDE	10.31 ± 9.28	7.03 ± 4.22	2.915	0.006
IED_EDSE	13.34 ± 10.75	10.74 ± 10.79	1.435	0.153
IED_TT	97.82 ± 25.57	86.0 ± 21.99	2.897	0.006
SOC				
SOC_MM2M	2.11 ± 0.38	2.03 ± 0.18	1.636	0.111
SOC_MM3M	3.72 ± 0.92	3.30 ± 0.50	3.59	<0.001
SOC_MM4M	5.89 ± 1.13	5.34 ± 1.11	2.906	0.006
SOC_MM5M	7.80 ± 1.69	7.16 ± 1.49	2.38	0.026
SWM				
SWM_BE	37.94 ± 23.87	20.86 ± 19.15	4.802	<0.001
SWM_Stra	35.94 ± 5.35	32.76 ± 4.81	3.68	<0.001

a) Two-sample *t*-test; b) chi-square test; $P < 0.05$. IED_PEDE: pre-ED errors; IED_EDSE: EDS errors; IED_TT: total trials; SOC_MM2/3/4/5 M: mean moves (2/3/4/5 moves); SWM_BE: SWM between errors; SWM_Stra: SWM strategy; $P < 0.05$, FDR-corrected. More detailed information about the indices of the IED, SOC, and SWM tasks is provided in the Supplementary Material.

network and cerebellum, and hyperconnectivity between subdivisions of thalamus and the parahippocampal and temporal gyri, which were included in limbic network. Notably, FC between the right PCC and ROI1 was positively correlated with the general psychopathology scale score. This study expands upon previous work that demonstrated thalamocortical disruption in individuals with AOS (Gong et al. 2019).

Previous studies that used the whole thalamus as the seed identified thalamo–prefrontal hypoconnectivity in individuals with schizophrenia. An increasing amount of evidence from FC studies supports a consistent pattern of reduced coordination of resting endogenous activity between the thalamus and prefrontal cortex in individuals with schizophrenia (Ramsay 2019), and anatomical connectivity studies also support this dysconnectivity pattern (Giraldo-Chica et al. 2018; Yao et al. 2020). Furthermore, a longitudinal study reported thalamo–prefrontal hypoconnectivity in clinically high-risk individuals, and this hypoconnectivity was greater in individuals who converted to psychosis than in those who did not (Anticevic et al. 2015). Interestingly, we found that FC between the right IFG and ROI4 was positively correlated with SOC, although after correction for the number of EF values, the correlation was no longer significant. These results suggested that thalamo–prefrontal hypoconnectivity may be associated with EF deficits, especially inhibition, in individuals with EOS. Consistent with our study, previous studies also reported an association between thalamo–prefrontal hypoconnectivity and impaired cognitive functions, such as working memory (Giraldo-Chica et al. 2018), cognitive flexibility, initiation, and inhibition (Niendam et al. 2012), in individuals with schizophrenia. A longitudinal study further demonstrated that thalamo–prefrontal hyperconnectivity was associated with improved global cognitive function in individuals with chronic schizophrenia (Ramsay et al. 2017). Thalamo–prefrontal hypoconnectivity has been reported in both individuals with chronic schizophrenia and early psychosis, and it has been hypothesized that this condition may result from a disturbance in brain development during the transition from adolescence to adulthood that prevents the thalamo–prefrontal circuitry from fully developing (Woodward and Heckers 2016). In this study, most individuals with EOS were in the early stage (with a disease course of less than 2 yr), which further supports this hypothesis. Thalamo–prefrontal hypoconnectivity in individuals with schizophrenia may not be affected by age at onset. Thalamo–prefrontal hypoconnectivity may be a promising neurobiological marker for the risk of both AOS and EOS which may be associated with cognitive function deficits.

In our study, we observed increased and decreased thalamic FC with the auditory and visual cortices, including the left lingual gyrus, right calcarine sulcus, left MTG, and left IFG, in individuals with EOS. The altered thalamic subdivisions were located at ROIs 1, 2, and 4; these ROIs cover the LP and the LD, which anatomically connect with the visual cortical areas. The lingual gyrus is part of the occipital lobe of the brain and is implicated in both basic and higher-order (HO) visual processing (Palejwala et al. 2021). The lingual gyrus affects the relationship between visual memory and visual imagery, possibly because the lingual gyrus is an important area for storing visual information. The calcarine cortex is next to the lingual gyrus and is the central part of the primary visual cortex and plays an important role in visual stimuli (Huff et al. 2023). Individuals with schizophrenia often experience auditory hallucinations (AHs) and visual hallucinations (VHs; Zhuo et al. 2020). Previous studies have demonstrated that FC between the thalamus and the MTG is positively correlated with hallucinations and delusions in schizophrenia patients (Ferri et al. 2018). These studies suggested that thalamic–auditory and visual cortex

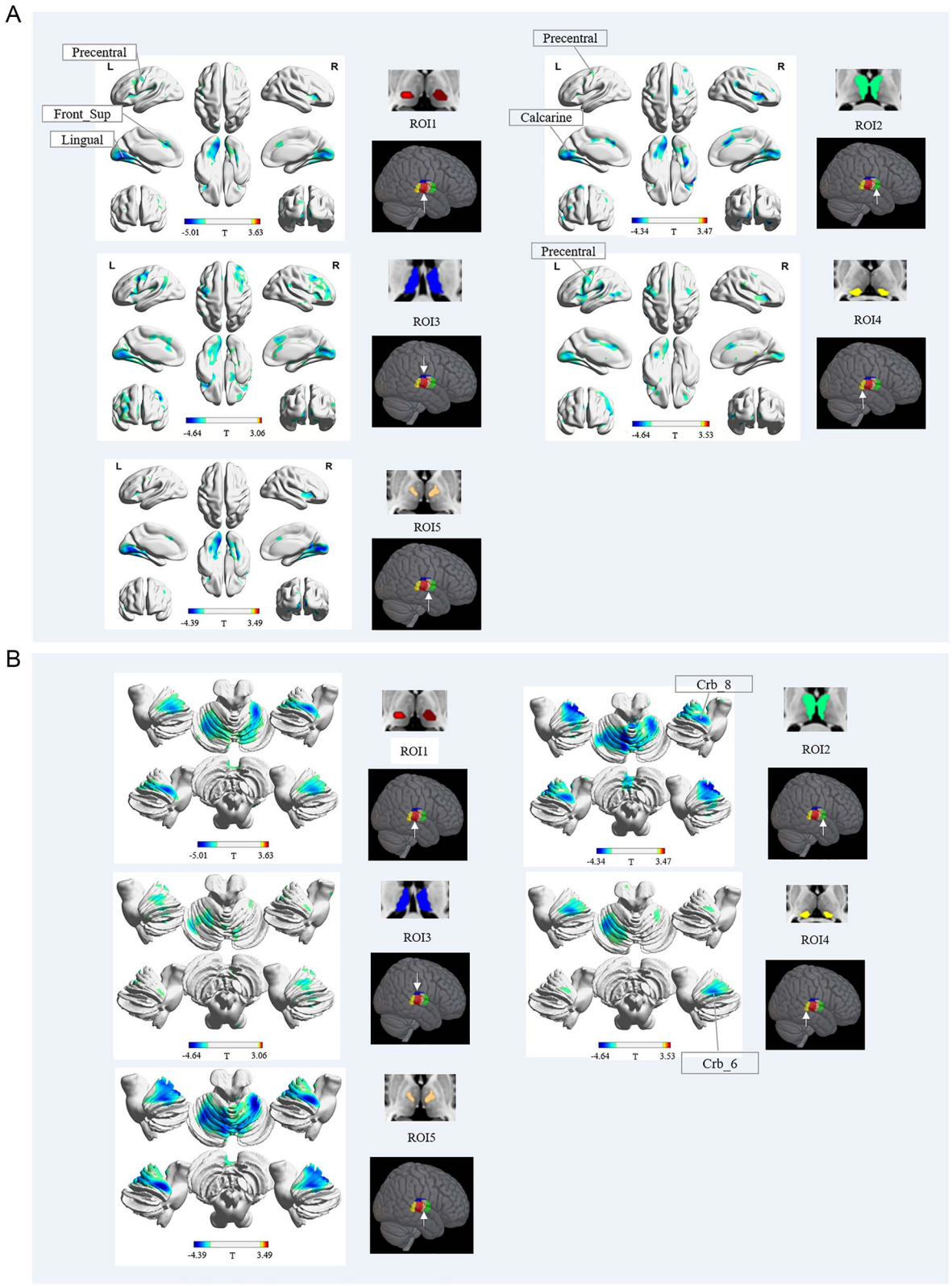

Fig. 1. Distribution of thalamocortical/thalamocerebellum function connectivity between the EOS group and HCs group. A) Compared with the HCs, the EOS group showed hyperconnectivity and hypoconnectivity between 5 subdivisions of thalamus and several cortical regions ($P < 0.001$, uncorrected; Fig. 1A, Supplementary Table 3). However, only 3 of the thalamic subdivisions (ROI1, ROI2, and ROI4) still showed significant differences in FC with the cortical regions after correction (Supplementary Fig. 2A; $P < 0.05$, FDR-corrected). B) Compared with the HCs group, the EOS group showed hypoconnectivity between 5 subdivisions of thalamus and cerebellum (Fig. 1B, Supplementary Table 3). However, only ROI2 and ROI4 still showed significant differences in FC after correction (Supplementary Fig. 2B; $P < 0.05$, FDR-corrected).

Table 2. Correlations between EF/clinical features and neuroimaging findings.

Seed	EF/clinical features	Region	MNI (x,y,z)	r
Set 1	General psychopathology scale	Right PCC	9 33 15	0.41
Set 4	SOC_MM3M	Right IFG	39 3 24	0.27

$P < 0.05$, FDR-corrected.

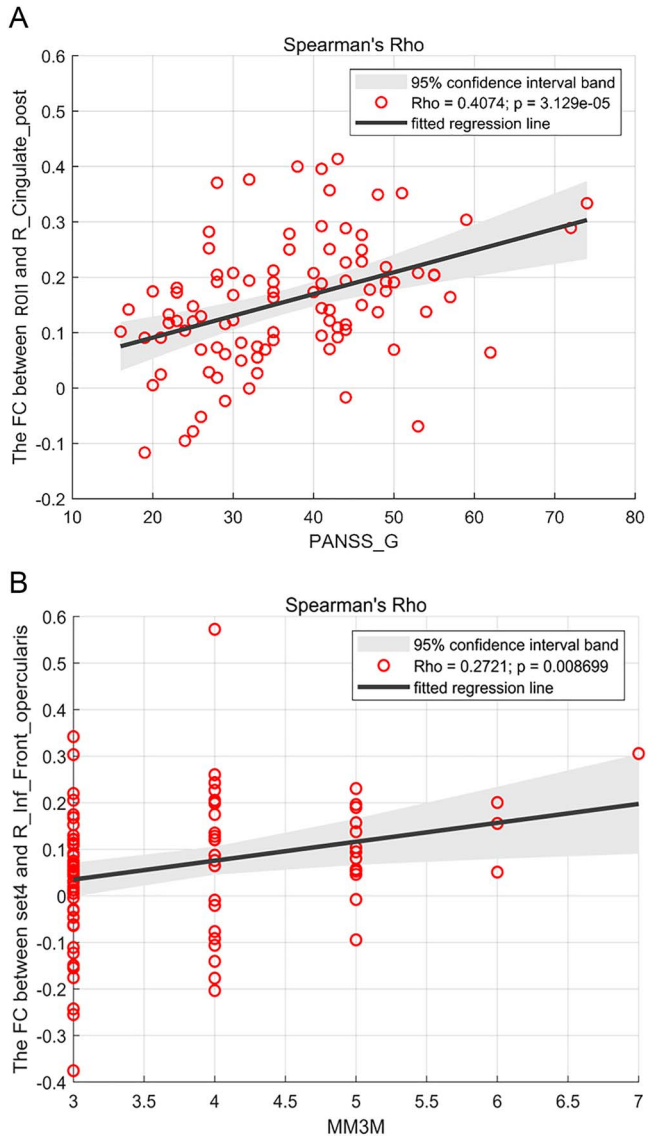

Fig. 2. Correlation of EF/clinical features and neuroimaging findings. A) FC between the right PCC and ROI1 was positively correlated with the score of general psychopathology scale. B) FC between right inferior frontal lobe and ROI 4 was positively correlated with SOC. PANSS-G: Positive and Negative Syndrome Scale (general psychopathology scale), MM3M: mean moves (3 moves).

dysconnectivity may be 1 of the core neurobiological features of schizophrenia that underpins positive symptoms such as VHs and AHs.

Dysfunction in thalamic FC with sensorimotor-related cortices, including the cingulate gyrus, precentral gyrus, postcentral gyrus, and right SMA, was found in the present study. Thalamo–sensorimotor dysconnectivity was consistently reported in individuals with schizophrenia and high-risk individuals in previous studies (Welsh et al. 2010; Woodward et al. 2012; Anticevic et al. 2014, 2015; Wang et al. 2015). Sensorimotor impairments are common in individuals with schizophrenia and in adolescents at familial high risk for schizophrenia, and an earlier age at first diagnosis is associated with more pronounced motor impairment (Manschreck et al. 2015; Carment et al. 2019). Additionally, according to the results of the data-driven parcellation, 2 thalamic first-order (FO) nuclei were included in ROIs 1 and 2: the VL and ventral posterior nucleus. The former receives cerebellar input from the dentate nucleus and projects it to the primary motor cortex; the latter is part of the somatosensory system. The alteration of sensorimotor-related connections between these 2 subdivisions in EOS patients may suggest that EOS affects the ventral lateral and ventral posterior nuclei. Thalamo–sensorimotor hypoconnectivity in EOS patients may indicate the neurobiological features of sensorimotor impairments in individuals with EOS.

Consistent with previous studies, individuals with EOS also exhibited thalamo–cerebellar hypoconnectivity (Gong et al. 2019; Zhang et al. 2021). Using the same method, Gong et al. (2019) demonstrated the same dysconnectivity in chronic AOS patients. The cerebellum has substantial anatomic connections with the prefrontal cortex, suggesting that it could perform cognitive and motor functions in humans (Yuan et al. 2022; Fuentes and Bastian 2007). The role of the cerebellum in schizophrenia has been highlighted by Andreasen's hypothesis of "cognitive dysmetria", which suggests that dysfunctions in the cortico–cerebellar–thalamo–cortical circuit could explain a variety of behavioral symptoms of the disease (Andreasen et al. 1999; Kim et al. 2023). For example, thalamus–cerebellar connectivity was negatively correlated with delusions and bizarre behavior (Ferri et al. 2018). The altered thalamic subdivisions were located at ROI2 and ROI4, which include HO nuclei, including the MD nucleus and pulvinar, and FO nuclei, including the lateral geniculate nucleus (LGN) and ventral posteromedial/VPL. Given that their inputs arise from associated cortical areas, HO nuclei are critical for cognitive functioning (Giraldo-Chica and Woodward 2017). The LGN is considered an early gatekeeper in the control of visual attention and awareness (mapping the human LGN and its cytoarchitectonic subdivisions using quantitative MRI). These studies suggest that thalamo–cerebellar hypoconnectivity may be a possible pathological mechanism of cognitive function deficits in individuals with EOS.

In this study, we found that FC between the right PCC and ROI1 was positively correlated with the general psychopathology scale score. The PCC receives major inputs from parietal cortical areas that receive from the somatosensory areas and dorsal visual stream, and is involved in action in space, spatial processing, and some types of memory (Rolls and Wirth 2018; Rolls 2018; Oane et.al 2023). Functional imaging studies have consistently shown that emotional stimuli activate the PCC, suggesting that the PCC may mediate the interaction between emotion and memory-related processes (Bubb et al. 2017). The finding that FC between the right PCC and ROI1 was positively correlated with the general psychopathology scale score might reflect an inability to engage

the DMN in EOS patients due to/as a result of psychopathology (i.e. hallucinations).

Consistent with previous research, our study revealed that the EOS group performed significantly worse than the HC group in the EF tests, including SWM, SOC, and IED (Zhang et al. 2020; Zhao et al. 2022). FC between the right IFG and ROI4 was positively correlated with the SOC result. This finding indicates that the greater the change in thalamic FC is, the more severe the EF deficit is. The SOC test mainly assesses behavioral inhibition related to planning ability. Previous studies have shown that the IFG is a brain region involved in cognitive control processes, especially those related to inhibition and switching (Functional Organization for Response Inhibition in the Right Inferior Frontal Cortex of Individual Human Brains; Cunillera et al. 2016). Neuroimaging studies have demonstrated a prominent role for the IFG in response inhibition tasks, particularly in the right hemisphere (Fuentes-Claramonte et al. 2016). Our results are consistent with those of previous studies. However, the correlation was not significant after correction for the number of EF comparisons. Our research indicated that the dysconnection of thalamo–prefrontal FC may be associated with EF deficits, especially inhibition behavior, in EOS patients.

There are several limitations to the present study. First, a percentage of EOS patients were treated with antipsychotic drugs, and we cannot exclude the possibility that these drugs may have an effect on thalamocortical FC. However, the medication dosage was relatively low, and the duration of administration was short. In addition, we have analyzed FC differences between the drug–naïve subgroup and the subgroup on antipsychotics. Compared to the medicated subgroup, the drug–naïve subgroup primarily showed different thalamic–cortical FC. However, these results did not survive FDR correction (shown in Supplementary Fig. 6). Therefore, the inclusion of these patients may reduce the effect size of this study, but the results are still credible. Second, although we found a significant relationship between general psychopathology scale scores and reduced connectivity between the right PCC and thalamus, we did not find a relationship between the core symptoms of schizophrenia and FC. Consistent with our results, Zhang et al. (2021) reported no significant behavioral correlations in the EOS group. Giraldo et al. suggested that complex clinical phenomena assessed via coarse, subjective rating scales may not directly map to specific brain circuits, and measures that capture core cognitive and perceptual processes underlying clinical phenomena may be more useful for revealing the behavioral and cognitive consequences of thalamocortical dysconnectivity (Giraldo-Chica and Woodward 2017). Third, our study reflected only thalamocortical changes at 1 time point, and it is not known whether thalamocortical network dysconnectivity worsens over time, which strongly suggests a need for longitudinal investigation.

Conclusion

This study showed that the specific thalamo–cortical dysconnection in individuals with EOS involves frontal–parietal network, visual network, ventral attention network, somatomotor network, limbic network, and cerebellum. This study identified thalamocortical connectivity as a potential biomarker and treatment target for EOS.

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Author contributions

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Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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