Impaired connectivity between the thalamus and the visual pathway in schizophrenia: a multimodal MRI study

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Abstract

Background

Schizophrenia is a severe psychiatric disorder characterized by cognitive deficits as well as positive and negative symptoms. It is considered a disorder of widespread network dysconnectivity, including aberrant connectivity between the thalamus and the visual pathway. However, the relationships between the thalamus and various regions of the dorsal and ventral visual pathways in schizophrenia, and how the thalamus affects interactions among these visual regions, remain unclear.

Methods

Resting-state functional magnetic resonance imaging, task-state functional magnetic resonance imaging, and diffusion tensor imaging data were acquired to examine the neural activity within the thalamus and the visual pathway, along with the relationships between them (i.e., functional connectivity, structural connectivity, and structure-function coupling). We also correlated the altered imaging parameters with clinical characteristics. Furthermore, based on previous molecular imaging in healthy controls, we explored the spatial associations between altered imaging parameters and receptors/transporters distributions.

Results

We found significantly decreased neural activity and widespread altered thalamo-visual pathway connectivity in both dorsal and ventral pathways in schizophrenia patients. Moreover, schizophrenia patients exhibited altered mediation effects within the thalamo–dorsal visual pathway, involving MT, V1, V2, and V3. Abnormal neural

activity and connectivity were related to disease duration and positive symptoms severity. Altered neural activity of MT was correlated with the density of multiple neurotransmitters.

Conclusions

Our findings further expand our understanding of thalamo-visual pathway dysconnectivity and primary information-processing deficits in schizophrenia, which may be related to clinical symptoms. Our findings may provide more potential insights for non-invasive intervention treatments.

Keywords: Schizophrenia, Thalamo-visual pathway dysconnectivity, Multimodal MRI

Introduction

Schizophrenia is a severe psychiatric disorder characterized by cognitive deficits, positive symptoms, and negative symptoms. It significantly impacts both patients and society (Owen *et al.*, 2016). Cognitive deficits, such as executive functions, attention, and working memory, are key features of schizophrenia and are associated with long-term disability (Schultz *et al.*, 2013). However, a growing body of evidence has suggested that schizophrenia involves bottom-up processing dysfunction (Dong *et al.*, 2019; Hou *et al.*, 2023). Patients with schizophrenia show abnormal sensory gating, which may result in sensory overload in the cortex and, in turn, the development of psychotic symptoms (Bak *et al.*, 2014; Judd *et al.*, 1992). The thalamus commonly acts as a gated relay for sensory information. It plays a crucial role in cortical-subcortical communication and is an important regulator of cortical activity (Giraldo-Chica and Woodward, 2017; Sherman, 2007, 2016). Numerous neuroimaging studies in patients

with schizophrenia have uncovered alterations of the thalamus, including decreased volume, altered spontaneous activity, and changes in activity during cognitive or sensory gating tasks (Csukly *et al.*, 2020).

Sensory processing deficits have been shown to be associated with the symptoms of schizophrenia. In addition, visual processing deficits may drive secondary impairments in higher cortical regions (Butler *et al.*, 2007; Li *et al.*, 2020). Numerous magnetic resonance imaging (MRI) studies have revealed abnormal spontaneous activity and dysconnectivity in the visual cortex of schizophrenia patients (Iwabuchi and Palaniyappan, 2017; Li *et al.*, 2023). Moreover, these abnormalities are associated with clinical symptoms, such as hallucinations and delusions (Li et al., 2020). Several resting-state functional connectivity (FC) studies have reported aberrant thalamocortical connectivity in schizophrenia, including altered connectivity between the thalamus and occipital cortex (Anticevic *et al.*, 2014a; Yamamoto *et al.*, 2018). Therefore, understanding the mechanism underlying the link between the thalamus and visual cortex in schizophrenia may be key to understanding the pathophysiology of schizophrenia and developing effective interventions.

Previous studies have shown that functional MRI (fMRI) has been widely used to investigate functional activity alterations in both gray and white matter across a range of neuropsychiatric disorders (Ji *et al.*, 2025; Ji *et al.*, 2017; Ji *et al.*, 2019). Therefore, we used fMRI to evaluate intrinsic brain activity within and between the thalamus and visual pathway to elucidate the pathophysiological mechanisms underlying schizophrenia. Intra-regional activity can be measured using the amplitude of low-

frequency fluctuations, which reflects the characteristics of spontaneous neural activity (Zang *et al.*, 2007). Previous studies have shown altered amplitude of low-frequency fluctuations in the bilateral inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, and left middle occipital gyrus of schizophrenia patients (Li et al., 2023; Wang *et al.*, 2019). Moreover, it has been found that there are frequency-specific alternations in the amplitude of low-frequency fluctuations of schizophrenia (Yu *et al.*, 2014). However, the specific changes in the amplitude of low-frequency fluctuations within various visual cortical regions and the thalamus across different frequency bands remain unclear. In addition, previous studies in schizophrenia have found that transcriptome/neurotransmitters (serotonergic, dopaminergic, gamma-aminobutyric, and glutaminergic pathways) are associated with abnormalities in the functional features based on fMRI (Chen *et al.*, 2021; Jiang *et al.*, 2023) and the white matter dysfunction (Ji *et al.*, 2023). We further explored whether the abnormal neural activity was related to the spatial topography of underlying molecular characteristics.

Inter-regional relationships can be measured by FC, which reflects relationships within and among different brain regions and networks. FC has been used to study various psychiatric and neurological disorders (Jiang *et al.*, 2024; van den Heuvel and Hulshoff Pol, 2010). Previous studies have revealed the reconfiguration of human brain networks during task and rest states, and emphasized the role of the thalamus in network configuration changes during these states (Di *et al.*, 2013). Task-state fMRI studies have shown that patients with schizophrenia exhibit differently altered thalamic activity during a range of tasks (Pergola *et al.*, 2015); moreover, their FC organization is

aberrant during task and resting states (Riedel *et al.*, 2022). Structural connectivity (SC) measured using diffusion tensor imaging (DTI) is a measure of the white matter pathways between regions (Jiang *et al.*, 2021). In general, SC and FC reflect the distinct profiles of the brain network, and the coupling between SC and FC would be an essential characteristic and is more sensitive than any single MRI modality to detect network dysconnectivity in disease (Liu *et al.*, 2022b; Wang *et al.*, 2023). Therefore, we used resting-state fMRI (rsfMRI), task-state fMRI, and DTI to study alterations in thalamo-visual pathway connectivity in schizophrenia.

In this study, we aimed to comprehensively investigate dysconnectivity within the visual pathway and between the visual pathway and the thalamus in schizophrenia using multimodal MRI. We hypothesized that patients with schizophrenia would exhibit abnormal neural activity within both dorsal and ventral visual pathways, accompanied by dysconnectivity within the visual pathway and between the visual pathway and the thalamus. To test these hypotheses, we first quantified intra-regional neural activity across multiple frequency bands. We then examined thalamo–visual functional connectivity during rest-state and visual task performance, and assessed structural connectivity using diffusion tensor imaging. Mediation analyses were conducted to evaluate the role of key visual regions in thalamo–visual pathway interactions. Finally, we explored the associations between altered imaging parameters and clinical characteristics. Through this multimodal, hypothesis-driven approach, we aimed to provide a multilevel characterization of thalamo–visual pathway dysfunction in schizophrenia, thereby advancing the understanding of thalamo–visual pathway

dysconnectivity and its relevance to symptom expression and potential intervention targets.

Methods

Participants

We recruited 112 schizophrenia patients (mean age: 41.76±11.67 years, range 16-70 years, 81 males) and 124 sex- and age-matched healthy controls (HCs) (mean age: 38.78±14.35 years, range 18-68 years, 77 males). Detailed demographic and clinical information are presented in Table 1. All patients were diagnosed according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-V Axis I Disorders-Clinical Version (SCID-I-CV). Patients with active substance use disorders or comorbid axis I diagnoses were excluded. All patients were treated with antipsychotic medications. We obtained written informed consent from patients and all HCs.

All patients participated in the resting-state fMRI experiment. However, due to study design and scanning protocol constraints, only a subset of participants completed the task-state fMRI and DTI acquisitions. In addition, task-state fMRI data were excluded for some participants because of limited task tolerance, excessive head motion, or incomplete task performance. Consequently, task-state fMRI data from 30 patients and 20 HCs, and DTI data from 83 patients and 119 HCs, were included in the final analyses. Detailed demographic and clinical characteristics of the subsamples are presented in Tables S1 and S2.

Task design

Alternating black and white images were used to simulate steady-state visual evoked potentials (SSVEP). The stimulation frequencies were 5, 10, and 20 Hz. Participants were required to keep their heads as still as possible and maintain fixation on the screen. The SSVEP task consisted of a 10-s baseline, nine task blocks, and 20 s of rest between blocks. Each frequency was repeated three times. Each task block lasted 20 s, and the entire task lasted 350 seconds.

Data acquisition

MRI data were acquired on a 3 Tesla GE Discovery MR 750 system with an eight-channel array head coil. MRI sessions comprised rsfMRI, task-state fMRI, and DTI scans. The rsfMRI data were acquired using a standard echo-planar imaging pulse sequence (repetition time [TR]/echo time [TE] = 2000/30 ms, flip angle = 90°, field of view = 24 × 24 cm^2, data matrix = 64 × 64, 35 interleaved slices, slice thickness = 4 mm, 0.4 mm slice gap, eyes closed, 510 seconds and 255 volumes). The parameters of task-state fMRI were consistent with those of rsfMRI, but it lasted for 350 seconds and generated 175 volumes. The DTI data were acquired using a single-shot, spin-echo, echo-planar sequence using the following parameters: voxel size = 2 × 2 × 2 mm^3, diffusion weighting isotropically distributed along 64 directions, 75 slices, 128 × 128 base resolution, and a b-value of 1000 s/mm^2.

Preprocessing

Functional images were preprocessed using an independently developed software package, Neuroscience Information Toolbox (Dong *et al.*, 2018). The first 10 volumes

were discarded, and the data were then slice-timing corrected, realigned, spatially normalized to standard Montreal Neurological Institute space, resampled to 3 × 3 × 3 mm^3 voxel size, spatially smoothed using an 8-mm full-width half-maximum Gaussian filter, and linearly detrended. We removed subjects with motion > 2 mm and/or 2°, and we regressed out 24 head motion parameters, white matter signal, cerebrospinal fluid signal, and global signal. Finally, the data were filtered using a bandpass filter (0.01–0.1 Hz). For the neural activity analysis, the functional images were not subjected to global signal regression or filtering.

DTI data were preprocessed using the Diffusion Toolkit. Preprocessing involved removing non-brain tissue, head motion correction, eddy current correction, and estimation of diffusion tensor elements.

Neural activity analysis

Functional images were processed using the DPABI toolbox (Yan *et al.*, 2016) based on SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/). We first defined several visual regions of interest based on previous studies: bilateral V1, V2, V3, V4, middle temporal cortex (MT), inferior temporal cortex (IT), angular gyrus (ANG), supramarginal gyrus (SMG), and superior parietal lobule (SPL) (Choi *et al.*, 2020; Fan *et al.*, 2016). We also defined the bilateral thalamus using a brain atlas proposed by Jiang's group (Fan et al., 2016). The locations of the visual regions of interest were demonstrated in Figure S1 and Table S3 of the supplementary materials. We first examined frequency-specific neural activity to identify local abnormalities within the visual pathway. Fluctuation amplitude, which reflects the characteristics of spontaneous neural activity, was calculated from the

preprocessed data using the Fast Fourier Transform to transform the time series for each voxel into the frequency domain and obtain the power spectrum. We computed the average square root of the power spectrum in the conventional frequency band (CFB; 0.01–0.1 Hz), Slow3 (0.073–0.198 Hz), Slow4 (0.027–0.073 Hz), and Slow5 frequency bands (0.01–0.027 Hz) respectively and subsequently converted them into Z-scores across the brain. Finally, we extracted the mean amplitude of fluctuations for each visual region of interest for each subject. For each group, the mean regional neural activity was first examined using one-sample t-tests. Between-group differences in mean regional neural activity were then assessed using an analysis of covariance (ANCOVA) within the general linear model framework, with mean framewise displacement (mFD), sex, and age included as nuisance covariates (FDR corrected, $p < 0.05$).

FC and mediation analysis

We then assessed functional connectivity to characterize network-level thalamo–visual pathway dysconnectivity. First, the resting-state FC was calculated using rsfMRI data in the CFB. Average time series across all voxels in a region were extracted, and pairwise correlations between brain regions were computed using Pearson correlation analysis. All Pearson correlation coefficients were Fisher-Z-transformed. Then, task-state fMRI data were used to calculate task-state FC by correlating the whole time series between regions, thereby capturing overall task-state connectivity that occurs during task performance, analogous to resting-state FC analysis. Within each group, FC was first examined using one-sample t-tests. Between-group differences in FC were then

assessed using ANCOVA, with mFD, sex, and age included as nuisance covariates (FDR corrected, $p < 0.05$).

Based on the FC results, we further examined whether the association between two regions was statistically accounted for by activity in a third region using mediation analyses, with regional time courses entered as variables. The mediation model portrayed a three-region mediation clique (Jiang et al., 2024). Within each group, c and c' values were first examined using one-sample t-tests. Between-group differences in c and c' values were then assessed using ANCOVA, with mFD, sex, and age included as nuisance covariates.

Structural connectivity analysis

The Fiber Assignment by Continuous Tracking algorithm within the Diffusion Toolkit (www.trackvis.org/dtk/) was used to perform deterministic tractography of the DTI images in native diffusion space to construct the structural connectivity. During the tracking process, if the fractional anisotropy of the encountered voxel was less than 0.15 and/or the turning angle was greater than 35°, fiber tracking was terminated. For each subject, the total number of streamlines between two regions was used to index the strength of SC. Within each group, SC was first examined using one-sample t-tests. Between-group differences in SC were then assessed using ANCOVA, with sex and age included as nuisance covariates (FDR corrected, $p < 0.05$).

Evaluation of structure-function coupling

To evaluate the association between functional representation and structural foundation for each connection, Pearson correlation was measured between resting-state FC and

SC in two groups, respectively. In detail, for a given pair of brain regions i and j, we extracted the corresponding structural connectivity value (SC_{ij}) and functional connectivity (FC_{ij}) across all subjects in one group (Patients or HCs). We then calculated the Pearson correlation coefficient (r) to quantify the relationship between structural and functional connectivity: r=corr ($\mathbf{SC}_{ij}$, $\mathbf{FC}_{ij}$), where $\mathbf{SC}_{ij}$ and $\mathbf{FC}_{ij}$ are vectors containing the SC and FC values for all subjects. Thus, a 20 × 20 correlation coefficient matrix was generated for each group. Group significances in structure-function coupling were assessed using permutation testing, in which group labels were randomly reassigned 10,000 times to evaluate statistical significance.

Spatial association between neural activity and molecular architecture, and correlation between altered brain imaging features and clinical characteristics

Finally, we evaluated spatial associations between regions with abnormal neural activity (i.e., case-control t-value) and the density of certain receptors/transporters to check whether our findings reveal molecular architecture in patients. According to previous studies(Chen et al., 2021; Luo *et al.*, 2023), we examined serotoninergic receptors (5-HT1A, 5-HT1B, 5-HT2A, and 5-HT4 receptors), dopaminergic receptors (D1 and D2 receptors), mu-opioid receptors (MOR), gamma-aminobutyric acidergic receptors (GABAa receptor), metabotropic glutamate receptor 5 (mGluR5), several transporters (serotonin reuptake transporter [5-HTT], dopamine transporter [DAT], and norepinephrine transporter [NET]), and F-DOPA (reflects presynaptic dopamine synthesis capacity). Density estimates were obtained from average group maps of healthy volunteers scanned in previous multi-tracer molecular imaging studies(Dukart

et al., 2021). Detailed methods are shown in the supplementary materials. We used a permutation test to evaluate the significance of a spatial correlation compared with chance, and the null distribution was estimated to be random 10000 times. We also calculated partial correlations between clinical characteristics (PANSS scores and disease duration) and the altered brain imaging features, with mFD, sex, and age as nuisance covariates.

Results

Decreased neural activity in the dorsal and ventral visual pathways

Compared with healthy controls, patients with schizophrenia exhibited broadly reduced fluctuation amplitude within the bilateral visual pathway, including V1, V2, V3, V4, MT, SPL, and IT, across the conventional frequency band and the Slow3–Slow5 frequency bands. These reductions indicate a general decrease in neural activity within visual-related regions. In addition, lower fluctuation amplitude was observed in the bilateral SMG and thalamus in specific frequency bands, predominantly in the Slow3 band. Notably, the left ANG showed increased fluctuation amplitude in the Slow5 band in patients with schizophrenia compared with healthy controls (Figure 1; FDR corrected, $p < 0.05$).

Altered FC between the thalamus and the visual pathway

To explore the relationship between the visual pathway and thalamus in schizophrenia, we investigated thalamo-visual pathway FC at resting-state. The FC pattern in HCs and patients with schizophrenia at resting-state was shown in Figure S2. In the left hemisphere, schizophrenia patients exhibited higher FC between the thalamus and V1,

V4, and MT compared with HCs, reflecting less negative correlation coefficients. The FC between IT and V4 was lower in patients than in HCs. The FC between IT was higher in patients than in HCs (Figure 2A).

In the right hemisphere, patients with schizophrenia showed significantly higher FC between the thalamus and V1, V3, V4, and MT compared with healthy controls. The lower FC between MT and V4 was found in the visual cortex in schizophrenia patients (Figure 2B).

A feature of interhemispheric FC was that the largest group differences in FC were observed between homotopic brain regions (i.e., significantly lower FC between the bilateral thalamus, V1, V2, V3, V4, MT, and ANG in patients than in controls). Moreover, differences in interhemispheric FC between different brain regions were similar to differences in intrahemispheric FC (Figure 2C).

The FC patterns in HCs and schizophrenia patients at the task-state were demonstrated in Figure S3, respectively. When performing the SSVEP task, only the FC between the bilateral thalamus was lower in the schizophrenia group than in the HCs (Figure 2D-F). Reported FC results were corrected using FDR ($p < 0.05$). It should be noted that the task-state FC was conducted in a smaller subset of participants, and the number of significant task-state FC alterations after multiple comparisons was relatively limited compared with the resting-state findings.

Altered relationships among the thalamus, MT, and V1/V2/V3

The FC results revealed that the relationship between the thalamus and MT was most significantly altered in the patient group. Given that V1, V2, and V3 are key regions

within the dorsal visual pathway along with MT, and play crucial roles in visual information processing and relay, we further used a mediation model to analyze the role of V1, V2, and V3 in the thalamic-MT pathway, as well as changes in schizophrenia. The selection of V1, V2, and V3 as mediator regions was based on their anatomical and functional connectivity with MT within the dorsal visual pathway. In the HCs, when V1 acted as a mediator, the direct and indirect effects were significant in both hemispheres. Nevertheless, in schizophrenia patients, the direct effect of the left hemisphere was not significant , whereas the indirect effect was significant (ab=-0.0276, p<0.05); in the right hemisphere, neither the direct nor the indirect effect was significant. The direct and indirect effects of V2 and V3 as mediators were significant in both hemispheres of HCs. However, the direct effect was not significant in the mediation model of schizophrenia patients. There were significant differences in c' and c values between the two groups (p < 0.05, uncorrected, Figure 3).

During the SSVEP task, indirect effects mediated by V1 and V2 were not significant in both hemispheres of HCs. However, indirect effects were significant in both hemispheres in patients with schizophrenia, while direct effects were not. When the V3 was a mediator, results were the same as those for the rsfMRI data in both hemispheres (p < 0.05, uncorrected, Figure 4).

Alterations in SC

We observed altered SC between patients with schizophrenia and HCs. In both hemispheres, SC was lower between the thalamus and V1, V2, and ANG in the schizophrenia group than in the HCs. Interhemispheric SC of homotopic visual regions

(V1, V2, and ANG) was lower, and the SC between bilateral thalamus was higher in patients than in HCs (FDR corrected, $p < 0.05$, Figure 5).

Altered structure-function coupling

The structure-function coupling pattern in HCs and patients with schizophrenia was shown in Figure S4. For the structure-function coupling on each pair of connections, we found weaker coupling in these connections, including left SMG–right IT (lSMG–rIT, *l* as a prefix represents for left hemisphere, *r* for the right hemisphere in the following text), lV2–lIT, rSPL–rIT, and rSMG–rIT, and stronger coupling of lMT–lANG, lSMG–lANG, lV3–rV3, and rSMG–rV1 connections in schizophrenia patients ($p_{perm} < 0.05$, uncorrected, Figure S5).

Association between altered neural activity/FC/SC and clinical variables

In schizophrenia patients, the neural activity of rV2, rV3, and lV4 in the CFB was negatively correlated with disease duration. Disease duration was positively correlated with altered lV1–rThalamus, rThalamus–rV1, and rThalamus–rV3 FC. There was a positive correlation between positive symptom scores and lV1–rV1, lV3–rV3, and lV4–rV4 FC. There was a negative correlation between disease duration and lV2–rV2 SC. Positive symptom scores were negatively correlated with lThalamus–lV1, lThalamus–rThalamus, lV1–rThalamus, lV2–lANG, and lV3–lANG SC. lThalamus–lV2 and lV1–rThalamus SC were negatively correlated with negative symptom scores. Additionally, total symptom scores were negatively correlated with lV1–rThalamus SC ($p < 0.05$, uncorrected, Figure 6A).

Relationship between neural activity and molecular architecture

We found that the case-control t-value of bilateral MT neural activity in the CFB was negatively correlated with the densities of 5-HT1a, 5-HT1b, 5-HT2a, 5-HTT, D1, D2, DAT, F-DOPA, GABA, MOR, NAT, and mGluR5 ($p_{perm} < 0.05$, uncorrected, Figure 6B).

Discussion

The present study investigated the dysconnectivity within the visual pathway and between the visual pathway and thalamus in patients with schizophrenia using a multimodal imaging approach that combined rsfMRI, task-state fMRI, and DTI. Consistent with our hypotheses, we found significantly altered neural activity and thalamo–visual pathway connectivity in both the dorsal and ventral visual pathways. Notably, altered mediation effects were prominent within the dorsal visual pathway. In addition, aberrant neural activity and connectivity were associated with disease duration and clinical symptoms, and altered neural activity in MT was correlated with the density of multiple neurotransmitters. Together, these findings provide convergent multimodal evidence for thalamo–visual pathway dysconnectivity and impaired early information processing in schizophrenia, with potential relevance to clinical symptom expression.

Dysconnectivity within the visual pathway

Schizophrenia patients exhibited significantly lower neural activity than HCs in the dorsal and ventral visual pathways across all frequency bands. This is consistent with previous findings that the amplitude of low-frequency fluctuations is decreased in schizophrenia patients in several visual regions, such as the bilateral lingual gyrus,

calcarine sulcus, temporal pole, and cuneus (Gao *et al.*, 2022; Li et al., 2023; Wang et al., 2019). Jin et al. reported that early-onset schizophrenia patients show hypoactivity in the left ventral visual stream and bilateral primary and early visual cortices (Jin *et al.*, 2023). Stephanie et al. reported reduced low-frequency fluctuations in the lingual gyrus, precuneus, cuneus, and other occipital regions in both the Slow4 and Slow5 frequency bands; moreover, these effects were stronger in the Slow4 frequency band (Hare *et al.*, 2017). Abnormalities in visual perception and processing are common in schizophrenia patients and may be related to alterations in the visual pathway (Adhan *et al.*, 2020). Poorer visual perception and processing are strongly associated with greater severity of positive and/or negative symptoms and an earlier age of onset (Keane *et al.*, 2018; Turkozer *et al.*, 2019). We also observed that the neural activity in the CFB in the left V4, right V2, and right V3 was negatively correlated with disease duration. These results provide additional data to support abnormal neural variability in the visual pathway of patients with schizophrenia.

The interhemispheric FC and SC of the thalamus and the visual pathway were significantly lower in patients than in HCs, which is consistent with previous studies that reported decreased effective connectivity from the right thalamus to the left thalamus (Csukly et al., 2020). Wang and colleagues used voxel-mirrored homotopic connectivity (VMHC) to investigate interhemispheric information exchange, work collaboration, and integration capabilities in schizophrenia patients and revealed decreased VMHC in the bilateral middle occipital gyrus (Wang *et al.*, 2024). Guo et al. also observed reduced VMHC in schizophrenia patients in several brain regions, such

as the superior temporal gyrus, fusiform gyrus, and middle occipital gyrus (Guo *et al.*, 2014). Moreover, we found that left V3–right V3 structure-function coupling was higher in patients than in HCs, and lV1–rV1, lV3–rV3, and lV4–rV4 FC were related to positive symptom scores. These findings may reflect abnormal interhemispheric visual information transfer and explain the development of schizophrenia symptoms, such as hallucinations and delusions.

Dysconnectivity between the visual pathway and the thalamus

There is growing evidence that the thalamus functions as a gated relay for information flow. Schizophrenia patients have thalamocortical dysconnectivity, which is characterized by hypoconnectivity between the prefrontal-striatal-cerebellar circuits and the thalamus and hyperconnectivity between the sensorimotor cortex and the thalamus (Anticevic *et al.*, 2014b; Woodward *et al.*, 2012). Indeed, a previous study found that the connectivity of the thalamus with the superior temporal gyrus and occipital lobe is increased in patients with schizophrenia (Anticevic et al., 2014a). Yamamoto et al. reported that FC between the left thalamus and occipital cortices is significantly increased in patients and that the strength of FC is associated with attentional deficits (Yamamoto et al., 2018). Another study found increased dynamic FC between the thalamus and the visual-related cortex (Yang *et al.*, 2023). Although these studies reported visual deficits in patients with schizophrenia, few have specifically investigated abnormalities in the thalamo-visual pathway. Here, we investigated the FC between the thalamus and both dorsal and ventral visual pathways during rest and found higher negative FC in patients than in HCs between the thalamus

and both pathways. This lack of negative connectivity is consistent with previous studies (Iwabuchi and Palaniyappan, 2017; Klingner *et al.*, 2014). It has been shown that schizophrenia patients have sensory gating deficits in the thalamus, which could lead to an overload of sensory information passing via the thalamus to the cerebral cortex (Bak et al., 2014; Pergola et al., 2015). We also revealed that altered FC was associated with disease duration. Previous reports have emphasized the role the thalamus and left inferior temporal cortex play in the reconfiguration of brain networks during task and resting states (Di et al., 2013). Although network topography remains largely the same, FC is reconfigured systematically to suit the requirements of different tasks (Gonzalez-Castillo and Bandettini, 2018). Therefore, these results suggest that the etiology of schizophrenia may disrupt sensory gating in the thalamus, thereby disrupting the information flow between the visual pathway and the thalamus during the resting-state.

In addition to the thalamo-visual pathway FC, we investigated SC using DTI. We found that SC between the thalamus and the dorsal and ventral visual pathways was reduced in schizophrenia in bilateral hemispheres. Altered FC is often accompanied by corresponding alterations in SC. In terms of thalamo-frontal SC, reduced SC in schizophrenia patients has been consistently reported (Sheffield *et al.*, 2020). However, there is limited research on the SC between the thalamus and other cortical regions, and the existing evidence is inconsistent. Sheffield et al. and Chica et al. observed increased SC between the thalamus and somatosensory cortex in schizophrenia patients, whereas other researchers have found increased SC between the thalamus and motor, occipital,

or parietal cortices. They also did not find altered SC between the thalamus and temporal cortex (Cho *et al.*, 2016; Giraldo-Chica *et al.*, 2018; Yao *et al.*, 2020). We also observed the structure-function decoupling of the dorsal and ventral visual pathways in schizophrenia patients. Studies have shown that significant structure-function decoupling within the occipital and subcortical modules in patients with schizophrenia correlated with early visual processing impairments, and this structural-functional decoupling is associated with more severe clinical symptoms and longer disease duration (Fotiadis *et al.*, 2024). Furthermore, we found that altered SC was correlated with disease duration and positive symptom scores in schizophrenia. Taken together, we suggest that our finding of abnormal thalamo-visual pathway SC offers important insight into thalamocortical dysconnectivity and primary information processing deficits in schizophrenia.

Altered relationships within the dorsal visual pathway

We found abnormal mediation patterns among brain regions in the dorsal visual pathway in patients with schizophrenia during both resting-state and task-state. The MT, located at the upper end of the visual hierarchy, is a core region for processing visual motion and has been implicated in various psychiatric disorders (Liu *et al.*, 2022a; Song *et al.*, 2021). Previous studies have also demonstrated abnormalities in the MT in patients with schizophrenia(Schultz et al., 2013; Turkozer *et al.*, 2022). Notably, a prior study applied low-frequency transcranial magnetic stimulation to the MT region and found enhanced motion perception accompanied by impaired spatial suppression. The authors further reported that this pattern is consistent with spatial suppression deficits

observed across multiple patient populations, suggesting that MT dysfunction may constitute a neural correlate of the perceptual abnormalities reported in older adults, patients with schizophrenia, and individuals with a history of depression (Tadin *et al.*, 2011). In addition to the main dorsal visual pathway, visual motion information has been shown to travel directly from the thalamus to the MT (bypassing V1) to process slow and fast movements, which may explain why the MT continues to respond in individuals with severe V1 damage (Gaglianese *et al.*, 2012; Gaglianese *et al.*, 2015). The altered relationship within the dorsal visual pathway was further validated using a passive visual task that requires minimal involvement of higher-order cortical areas. Thus, the altered associations among the thalamus, MT, and V1/V2/V3 may suggest disrupted functional relationships between the thalamus and the dorsal visual pathway in schizophrenia. Collectively, these findings further demonstrate thalamo-visual cortical dysconnectivity in schizophrenia. Furthermore, given the key role that the MT plays in the dorsal visual pathway, this region may serve as a novel target for non-invasive interventions, pending validation from longitudinal and causal designs.

We also revealed that abnormal MT activity correlated with dopamine, serotonin, glutamate systems, and MOR. In line with these results, the classic dopamine theory, the glutamate hypothesis, the serotonin hypothesis, and the endogenous opioid theory have all been implicated in the pathophysiology of schizophrenia (Blokhin *et al.*, 2020; Stahl, 2018). Moreover, previous studies have shown that the spatial pattern of white matter dysfunction in major psychiatric disorders is associated with multiple neurotransmitter systems, particularly dopaminergic, serotonergic, and GABAergic

systems (Ji et al., 2023). Therefore, we speculate that altered visual cortex activity in schizophrenia is related to multiple neurotransmitter systems.

Conclusions

Using multimodal MRI data, we comprehensively examined the connectivity between the thalamus and both the dorsal and ventral visual pathways in patients with schizophrenia. Schizophrenia patients demonstrated significant dysfunction in both dorsal and ventral visual pathways. In the dorsal visual pathway, patients with schizophrenia demonstrated abnormal relationships among brain regions at resting-state and task-state. Additionally, altered imaging parameters correlated with the clinical and molecular characteristics of the schizophrenia group. Taken together, our study further expands our understanding of thalamo-visual pathway dysconnectivity in schizophrenia and opens a novel therapeutic option that MT could be an effective stimulation target.

Limitations

There are several limitations in this study. First, all patients with schizophrenia in this study were receiving long-term antipsychotic treatment and were clinically stable at the time of scanning, with no acute symptom exacerbation. Although this reduces variability related to acute illness effects, it may limit the generalizability of the findings to patients in acute, first-episode, or unmedicated stages of the disorder. Second, the task-state FC analyses were conducted in a relatively small sample, resulting in fewer significant findings compared with the resting-state analyses. This limited sample size may reduce the robustness and generalizability of the task-related conclusions. Third,

the receptor/transporter maps were obtained from a previous molecular imaging study in HCs and not from the schizophrenia patients in the current study. Fourth, while we applied some motion correction procedures and included head motion as a covariate in our analyses, some residual effects of head motion may still influence the results, particularly in regions sensitive to small motion shifts. Future studies could benefit from more advanced motion correction techniques or stricter motion exclusion criteria to further mitigate these effects.

Author contributions

Changyue Hou (Formal analysis, Methodology, Software, Visualization, Writing—original draft, Writing—review & editing), Meihua Yan (Data curation, Investigation, Resources), Sisi Jiang (Formal analysis, Validation), Yuting Deng (Data curation), Lang Zhang (Investigation, Resources), Hechun Li (Methodology, Software), Mingjun Duan (Methodology, Resources), Yafeng Wang (Methodology), Gang Yao (Investigation, Resources), Hui He (Investigation), Roberto Rodríguez-Labrada (Investigation), Dezhong Yao (Project administration), Cheng Luo (Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing).

Competing interest

The authors declare that they have no competing interests.

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Availability of data and materials

The data of this study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data associated with this article can be found in the online version.

References

Adhan, I., Lizano, P., Bannai, D. et al. (2020) Visual Cortical Alterations and their Association with Negative Symptoms in Antipsychotic-Naive First Episode Psychosis. Psychiatry Research. 288.

Anticevic, A., Cole, M.W., Repovs, G. et al. (2014a) Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. Cerebral cortex. 24:3116-3130.

Anticevic, A., Yang, G., Savic, A. et al. (2014b) Mediodorsal and visual thalamic connectivity differ in schizophrenia and bipolar disorder with and without psychosis history. Schizophr Bull. 40:1227-1243.

Bak, N., Rostrup, E., Larsson, H.B.W. et al. (2014) Concurrent Functional Magnetic Resonance Imaging and Electroencephalography Assessment of Sensory Gating in Schizophrenia. Hum Brain Mapp. 35:3578-3587.

Blokhin, I.O., Khorkova, O., Saveanu, R.V. et al. (2020) Molecular mechanisms of psychiatric diseases. Neurobiol Dis. 146:105136.

Butler, P.D., Martinez, A., Foxe, J.J. et al. (2007) Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. Brain : a journal of neurology. 130:417-430.

Chen, J., Muller, V.I., Dukart, J. et al. (2021) Intrinsic Connectivity Patterns of Task-Defined Brain Networks Allow Individual Prediction of Cognitive Symptom Dimension of Schizophrenia and Are Linked to Molecular Architecture. Biol Psychiatry. 89:308-319.

Cho, K.I., Shenton, M.E., Kubicki, M. et al. (2016) Altered Thalamo-Cortical White Matter Connectivity: Probabilistic Tractography Study in Clinical-High Risk for Psychosis and First-Episode Psychosis. Schizophr Bull. 42:723-731.

Choi, S.H., Jeong, G., Kim, Y.B. et al. (2020) Proposal for human visual pathway in the extrastriate cortex by fiber tracking method using diffusion-weighted MRI. NeuroImage. 220:117145.

Csukly, G., Szabó, Á., Polgár, P. et al. (2020) Fronto-thalamic structural and effective connectivity and delusions in schizophrenia: a combined DTI/DCM study. Psychol Med. 51:1-11.

Di, X., Gohel, S., Kim, E.H. et al. (2013) Task vs. rest-different network configurations between the coactivation and the resting-state brain networks. Frontiers in Human Neuroscience. 7.

Dong, D., Duan, M., Wang, Y. et al. (2019) Reconfiguration of Dynamic Functional Connectivity in Sensory and Perceptual System in Schizophrenia. Cerebral cortex. 29:3577-3589.

Dong, L., Luo, C., Liu, X.B. et al. (2018) Neuroscience Information Toolbox: An Open Source Toolbox for EEG-fMRI Multimodal Fusion Analysis. Front Neuroinform. 12.

Dukart, J., Holiga, S., Rullmann, M. et al. (2021) JuSpace: A tool for spatial correlation analyses of magnetic resonance imaging data with nuclear imaging derived neurotransmitter maps. Hum Brain Mapp. 42:555-566.

Fan, L., Li, H., Zhuo, J. et al. (2016) The Human Brainnetome Atlas: A New Brain Atlas Based on

Connectional Architecture. Cerebral cortex. 26:3508-3526.
Fotiadis, P., Parkes, L., Davis, K.A. et al. (2024) Structure-function coupling in macroscale human brain networks. Nat Rev Neurosci. 25:688-704.
Gaglianese, A., Costagli, M., Bernardi, G. et al. (2012) Evidence of a direct influence between the thalamus and hMT plus independent of V1 in the human brain as measured by fMRI. NeuroImage. 60:1440-1447.
Gaglianese, A., Costagli, M., Ueno, K. et al. (2015) The direct, not V1-mediated, functional influence between the thalamus and middle temporal complex in the human brain is modulated by the speed of visual motion. Neuroscience. 284:833-844.
Gao, Y.J., Tong, X., Hu, J.X. et al. (2022) Decreased resting-state neural signal in the left angular gyrus as a potential neuroimaging biomarker of schizophrenia: An amplitude of low-frequency fluctuation and support vector machine analysis. Frontiers in Psychiatry. 13.
Giraldo-Chica, M., Rogers, B.P., Damon, S.M. et al. (2018) Prefrontal-Thalamic Anatomical Connectivity and Executive Cognitive Function in Schizophrenia. Biol Psychiatry. 83:509-517.
Giraldo-Chica, M., Woodward, N.D. (2017) Review of thalamocortical resting-state fMRI studies in schizophrenia. Schizophr Res. 180:58-63.
Gonzalez-Castillo, J., Bandettini, P.A. (2018) Task-based dynamic functional connectivity: Recent findings and open questions. NeuroImage. 180:526-533.
Guo, W., Xiao, C., Liu, G. et al. (2014) Decreased resting-state interhemispheric coordination in first-episode, drug-naive paranoid schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 48:14-19.
Hare, S.M., Ford, J.M., Ahmadi, A. et al. (2017) Modality-Dependent Impact of Hallucinations on Low-Frequency Fluctuations in Schizophrenia. Schizophrenia Bulletin. 43:389-396.
Hou, C., Jiang, S., Liu, M. et al. (2023) Spatiotemporal dynamics of functional connectivity and association with molecular architecture in schizophrenia. Cerebral cortex. 33:9095-9104.
Iwabuchi, S.J., Palaniyappan, L. (2017) Abnormalities in the effective connectivity of visuothalamic circuitry in schizophrenia. Psychological Medicine. 47:1300-1310.
Ji, G.-J., Sun, J., Hua, Q. et al. (2023) White matter dysfunction in psychiatric disorders is associated with neurotransmitter and genetic profiles. Nature Mental Health. 1:655-666.
Ji, G.J., Cui, Z., D'Arcy, R.C.N. et al. (2025) Imaging brain white matter function using resting-state functional MRI. Sci Bull (Beijing). 70:1384-1388.
Ji, G.J., Liao, W., Chen, F.F. et al. (2017) Low-frequency blood oxygen level-dependent fluctuations in the brain white matter: more than just noise. Sci Bull (Beijing). 62:656-657.
Ji, G.J., Ren, C., Li, Y. et al. (2019) Regional and network properties of white matter function in Parkinson's disease. Hum Brain Mapp. 40:1253-1263.
Jiang, S., Huang, H., Zhou, J. et al. (2023) Progressive trajectories of schizophrenia across symptoms, genes, and the brain. BMC Med. 21:237.
Jiang, S., Li, H., Pei, H. et al. (2021) Connective profiles and antagonism between dynamic and static connectivity underlying generalized epilepsy. Brain structure & function. 226:1423-1435.
Jiang, S., Pei, H., Chen, J. et al. (2024) Striatum- and Cerebellum-Modulated Epileptic Networks Varying Across States with and without Interictal Epileptic Discharges. Int J Neural Syst. 34:2450017.
Jin, X., Zhang, K., Lu, B. et al. (2023) Shared atypical spontaneous brain activity pattern in early onset schizophrenia and autism spectrum disorders: evidence from cortical surface-based analysis. Eur Child Adolesc Psychiatry.

Judd, L.L., Mcadams, L., Budnick, B. et al. (1992) Sensory Gating Deficits in Schizophrenia - New Results. American Journal of Psychiatry. 149:488-493.
Keane, B.P., Cruz, L.N., Paterno, D. et al. (2018) Self-Reported Visual Perceptual Abnormalities Are Strongly Associated with Core Clinical Features in Psychotic Disorders. Front Psychiatry. 9:69.
Klingner, C.M., Langbein, K., Dietzek, M. et al. (2014) Thalamocortical connectivity during resting state in schizophrenia. European archives of psychiatry and clinical neuroscience. 264:111-119.
Li, K., Sweeney, J.A., Hu, X.P. (2020) Context-dependent dynamic functional connectivity alteration of lateral occipital cortex in schizophrenia. Schizophr Res. 220:201-209.
Li, X., Liu, Q., Chen, Z. et al. (2023) Abnormalities of Regional Brain Activity in Patients With Schizophrenia: A Longitudinal Resting-State fMRI Study. Schizophr Bull. 49:1336-1344.
Liu, D.Y., Ju, X., Gao, Y. et al. (2022a) From Molecular to Behavior: Higher Order Occipital Cortex in Major Depressive Disorder. Cerebral cortex. 32:2129-2139.
Liu, Z.Q., Vazquez-Rodriguez, B., Spreng, R.N. et al. (2022b) Time-resolved structure-function coupling in brain networks. Communications biology. 5:532.
Luo, Y., Dong, D., Huang, H. et al. (2023) Associating Multimodal Neuroimaging Abnormalities With the Transcriptome and Neurotransmitter Signatures in Schizophrenia. Schizophr Bull. 49:1554-1567.
Owen, M.J., Sawa, A., Mortensen, P.B. (2016) Schizophrenia. Lancet. 388:86-97.
Pergola, G., Selvaggi, P., Trizio, S. et al. (2015) The role of the thalamus in schizophrenia from a neuroimaging perspective. Neurosci Biobehav R. 54:57-75.
Riedel, P., Lee, J.H., Watson, C.G. et al. (2022) Reorganization of the functional connectome from rest to a visual perception task in schizophrenia and bipolar disorder. Psychiatry Research-Neuroimaging. 327.
Schultz, C.C., Wagner, G., Koch, K. et al. (2013) The visual cortex in schizophrenia: alterations of gyrification rather than cortical thickness--a combined cortical shape analysis. Brain structure & function. 218:51-58.
Sheffield, J.M., Huang, A.S., Rogers, B.P. et al. (2020) Thalamocortical Anatomical Connectivity in Schizophrenia and Psychotic Bipolar Disorder. Schizophr Bull. 46:1062-1071.
Sherman, S.M. (2007) The thalamus is more than just a relay. Current Opinion in Neurobiology. 17:417-422.
Sherman, S.M. (2016) Thalamus plays a central role in ongoing cortical functioning. Nature neuroscience. 19:533-541.
Song, X.M., Hu, X.W., Li, Z. et al. (2021) Reduction of higher-order occipital GABA and impaired visual perception in acute major depressive disorder. Mol Psychiatr. 26:6747-6755.
Stahl, S.M. (2018) Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. CNS spectrums. 23:187-191.
Tadin, D., Silvanto, J., Pascual-Leone, A. et al. (2011) Improved motion perception and impaired spatial suppression following disruption of cortical area MT/V5. The Journal of neuroscience : the official journal of the Society for Neuroscience. 31:1279-1283.
Turkozer, H.B., Hasoglu, T., Chen, Y. et al. (2019) Integrated assessment of visual perception abnormalities in psychotic disorders and relationship with clinical characteristics. Psychol Med. 49:1740-1748.
Turkozer, H.B., Lizano, P., Adhan, I. et al. (2022) Regional and Sex-Specific Alterations in the Visual Cortex of Individuals With Psychosis Spectrum Disorders. Biol Psychiatry. 92:396-406.

van den Heuvel, M.P., Hulshoff Pol, H.E. (2010) Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol. 20:519-534.
Wang, N., Liang, C., Zhang, X. et al. (2023) Brain structure-function coupling associated with cognitive impairment in cerebral small vessel disease. Front Neurosci. 17:1163274.
Wang, P., Jiang, Y., Biswal, B.B. (2024) Aberrant interhemispheric structural and functional connectivity within whole brain in schizophrenia. Schizophrenia Research. 264:336-344.
Wang, P., Yang, J., Yin, Z. et al. (2019) Amplitude of low-frequency fluctuation (ALFF) may be associated with cognitive impairment in schizophrenia: a correlation study. BMC Psychiatry. 19:30.
Woodward, N.D., Karbasforoushan, H., Heckers, S. (2012) Thalamocortical dysconnectivity in schizophrenia. Am J Psychiatry. 169:1092-1099.
Yamamoto, M., Kushima, I., Suzuki, R. et al. (2018) Aberrant functional connectivity between the thalamus and visual cortex is related to attentional impairment in schizophrenia. Psychiatry Res Neuroimaging. 278:35-41.
Yan, C.G., Wang, X.D., Zuo, X.N. et al. (2016) DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. Neuroinformatics. 14:339-351.
Yang, W., Niu, H., Jin, Y. et al. (2023) Altered dynamic functional connectivity of the thalamus subregions in patients with schizophrenia. J Psychiatr Res. 167:86-92.
Yao, B., Neggers, S.F.W., Kahn, R.S. et al. (2020) Altered thalamocortical structural connectivity in persons with schizophrenia and healthy siblings. Neuroimage Clin. 28:102370.
Yu, R.J., Chien, Y.L., Wang, H.L.S. et al. (2014) Frequency-Specific Alternations in the Amplitude of Low-Frequency Fluctuations in Schizophrenia. Hum Brain Mapp. 35:627-637.
Zang, Y.F., He, Y., Zhu, C.Z. et al. (2007) Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev. 29:83-91.

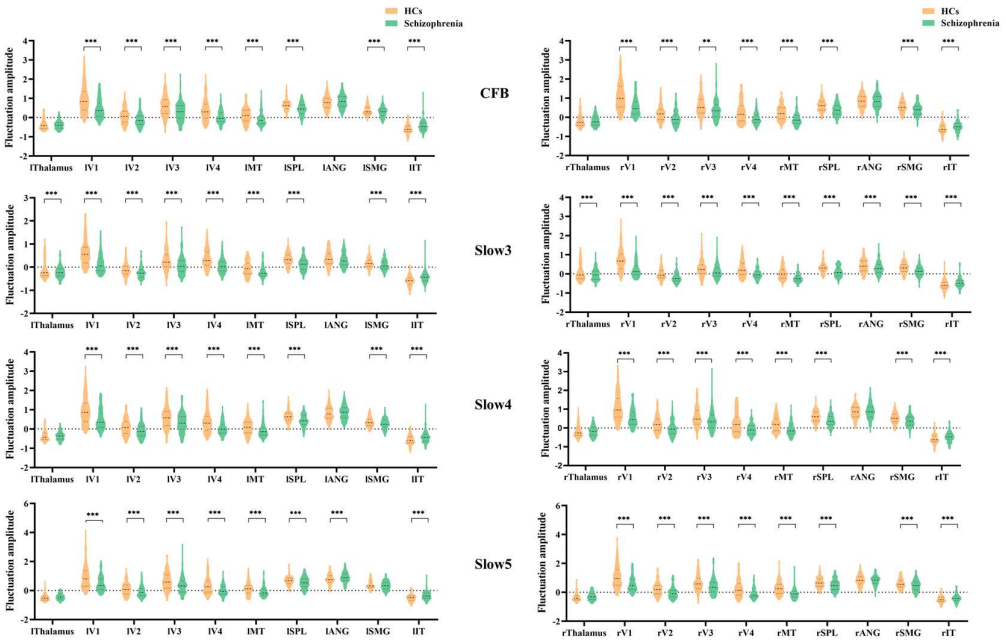

Figure 1: The significantly altered fluctuation amplitude across frequency bands in patients with schizophrenia. Asterisks denote statistical significance (FDR-corrected p<0.05). l, left; r, right.1: The significantly altered fluctuation amplitude across frequency bands in patients with schizophrenia. Asterisks denote statistical significance (FDR-corrected p<0.05). l, left; r, right.

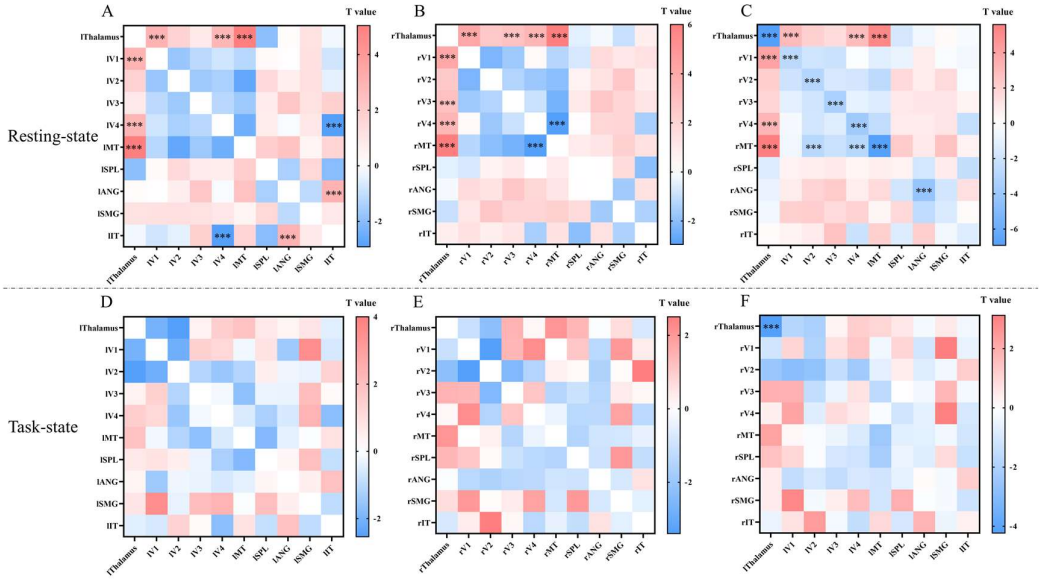

Figure 2: The significantly altered FC in patients with schizophrenia at resting-state (A-C) and task-state (D-F). Red indicates FC values higher in schizophrenia patients compared to healthy controls, while blue indicates FC values lower in schizophrenia patients compared to healthy controls. Asterisks denote statistical significance (FDR-corrected p<0.05). l, left; r, right.

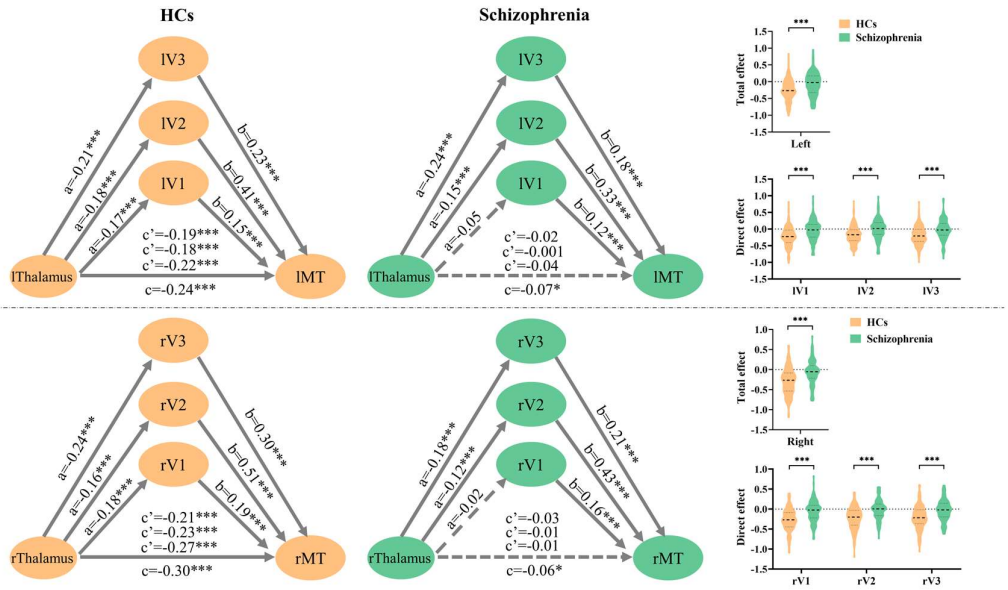

Figure 3: Mediation analysis of the thalamus–MT pathway at resting-state in HCs and patients with schizophrenia. The diagram illustrates mediation models examining whether activity in early visual regions (V1, V2, and V3) mediates the association between the thalamus (independent variable) and MT (dependent variable). Each visual region was tested as a mediator in a separate model. Path a denotes the effect of the thalamus on the mediator, path b denotes the effect of the mediator on MT while controlling for thalamic activity, c represents the total effect of the thalamus on MT, and c' represents the direct effect after accounting for the mediator. Numbers indicate standardized regression coefficients. Asterisks denote statistical significance ($p < 0.05$, $p < 0.005$, $p < 0.001$). l, left; r, right.

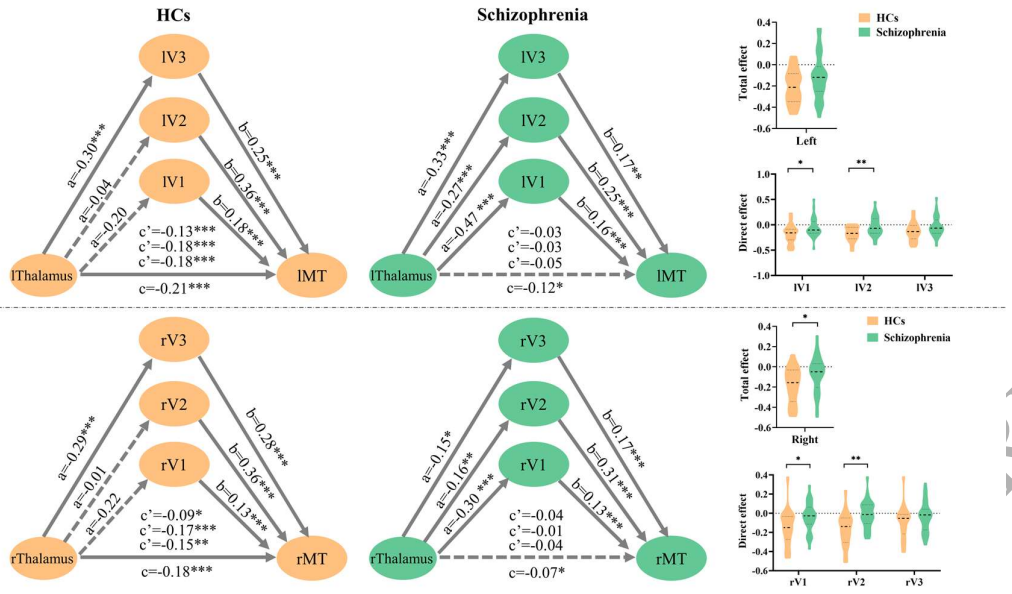

Figure 4: Mediation analysis of the thalamus–MT pathway during the task state. Mediation models with the same structure as those at resting-state were applied to task-state data to examine whether V1, V2, or V3 mediates the association between the thalamus and MT. Asterisks denote statistical significance ($p < 0.05$, $p < 0.005$, $p < 0.001$). l, left; r, right.

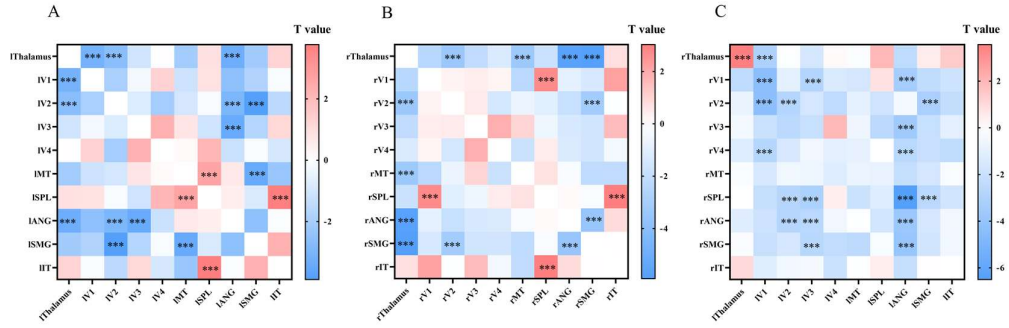

Figure 5: The significantly altered SC in schizophrenia. Red indicates SC values higher in schizophrenia patients compared to healthy controls, while blue indicates SC values lower in schizophrenia patients compared to healthy controls. Asterisks denote statistical significance (FDR-corrected $p<0.05$). l, left; r, right.

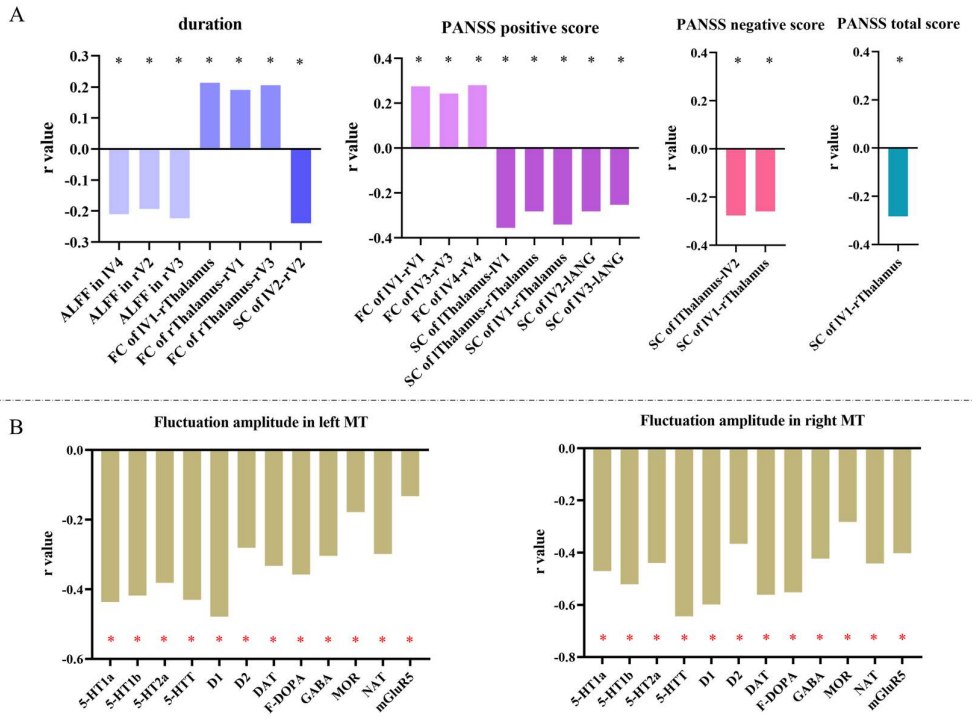

Figure 6: Relationships between neural activity, FC, SC, and disease duration and PANSS scores in schizophrenia (A). Spearman correlations between neural activity alterations in the conventional frequency band and regional receptor/transporter density estimates, assessed using permutation testing with 10,000 repetitions (B). The black asterisk demonstrates a significance of $p < 0.05$ without correction and the red asterisk demonstrates a significance of pperm <0.001.

Table 1 Demographic characteristics and clinical data of patients with schizophrenia and healthy controls (mean ± SD）

	Patients (N=112)	Healthy controls (N=124)	P value
Age (year)	41.76 ± 11.67	38.78 ± 14.35	0.083[a]
Gender (male/female)	81:31	77:47	0.095[b]
Education (years)[c]	11.28 ± 3.03	11.54 ± 3.61	0.581[a]
Duration (years)	15.69 ± 9.95		
Chlorpromazine equivalents (mg/d)[d]	338.05 ± 160.89		
PANSS-positive[e]	13.15 ± 5.69		
PANSS-negative[e]	21.42 ± 6.62		
PANSS-general[e]	29.09 ± 6.23		
PANSS-total[e]	63.66 ± 13.72		

[a]Two-sample t-test.

[b]χ^2 test.

[c]Data of 89 patients and 112 healthy controls available.

[d]Data of 73 patients available.

[e]Data of 80 patients available.

PANSS, positive and negative syndrome scale.