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Aberrant thalamocortical connectivity and shifts between the resting state and task state in patients with schizophrenia

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Abstract

Prominent pathological hypotheses for schizophrenia include auditory processing deficits and dysconnectivity within cerebral networks. However, most neuroimaging studies have focused on impairments in either resting-state or task-related functional connectivity in patients with schizophrenia. The aims of our study were to examine (1) blood oxygen level-dependent (BOLD) signals during auditory steady-state response (ASSR) tasks, (2) functional connectivity during the resting-state and ASSR tasks and (3) state shifts between the resting-state and ASSR tasks in patients with schizophrenia. To reduce the functional consequences of scanner noise, we employed resting-state and sparse sampling auditory fMRI paradigms in 25 schizophrenia patients and 25 healthy controls. Auditory stimuli were binaural click trains at frequencies of 20, 30, 40 and 80 Hz. Based on the detected ASSR-evoked BOLD signals, we examined the functional connectivity between the thalamus and bilateral auditory cortex during both the resting state and ASSR task state, as well as their alterations. The schizophrenia group exhibited significantly diminished BOLD signals in the bilateral auditory cortex and thalamus during the 80 Hz ASSR task (corrected $p < 0.05$). We observed a significant inverse relationship between the resting state and ASSR task state in altered functional connectivity within the thalamo-auditory network in schizophrenia patients. Specifically, our findings demonstrated stronger functional connectivity in the resting state ($p < 0.004$) and reduced functional connectivity during the ASSR task

Abbreviations: ASSR, auditory steady-state response; BOLD, blood oxygen level-dependent; DLPFC, dorsolateral prefrontal cortex; DMN, default-mode network; DSM, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; FA, flip angle; fMRI, functional magnetic resonance imaging; GLM, general linear model; HC, healthy control; MEG, magnetoencephalography; MPRAGE, magnetization-prepared rapid gradient echo; PANSS, Positive and Negative Syndrome Scale; rmANOVA, repeated-measures analysis of variance; ROI, region of interest; SES, socioeconomic status; STG, superior temporal gyrus; SZ, schizophrenia; TE, echo time; TR, repetition time.

Yoshifumi Takai and Shunsuke Tamura contributed equally to this work.

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($p = 0.048$), which was mediated by abnormal state shifts, within the schizophrenia group. These results highlight the presence of abnormal thalamocortical connectivity associated with deficits in the shift between resting and task states in patients with schizophrenia.

KEYWORDS

ASSR, resting-state, schizophrenia, state shift, thalamocortical connectivity

1 | INTRODUCTION

In 2002, schizophrenia (SZ) was officially renamed ‘integration disorder’ (‘Togo Shitcho Sho’) in Japan (Sato, 2006), a term that clearly captures the underlying pathophysiology of the disease. Recent functional imaging studies (e.g. Fornito et al., 2012; Minzenberg et al., 2009; Wheeler & Voineskos, 2014) have led to the hypothesis that SZ is a brain ‘dysconnection’ syndrome (Friston et al., 2016; Stephan et al., 2009). Therefore, there is an increasing need to investigate the pathophysiology of SZ from a network or connectome perspective (Damiani et al., 2022; Gao et al., 2023; Kitajima et al., 2023; Tagawa et al., 2022). Clinically, SZ is a debilitating psychotic disorder characterized by a heterogeneous array of symptoms, such as auditory hallucinations, delusions, disorganized thoughts, ego disturbances, passivity phenomena and cognitive deficits (Onitsuka, Hirano, Nakazawa, et al., 2022).

Among the various cognitive and sensory deficits, auditory dysfunction is considered one of the core features of SZ (Javitt & Sweet, 2015). Auditory-evoked paradigms such as the auditory steady-state response (ASSR) task have provided insight into the neural mechanisms underlying auditory dysfunction and associated symptoms (e.g. auditory hallucinations) in SZ patients (Hirano & Uhlhaas, 2021; Onitsuka, Hirano, Nemoto, et al., 2022; Onitsuka, Tsuchimoto et al., 2022). An essential question is the origin of the deficits observed during sensory processing, which may stem from modifications in intrinsic brain activity, deficiencies in stimulus-induced brain activity or a combination of the two. One method used to investigate this question is to collect combined intrinsic resting-state and stimulus-induced data in this population. Moreover, researchers have debated whether auditory processing abnormalities occur in the auditory cortex or are caused by abnormalities in subcortical sensory circuits.

The task-evoked paradigm has yielded numerous insights into the sensory processing or cognitive deficits observed in SZ patients. The majority of task-evoked functional magnetic resonance imaging (fMRI) studies have reported functional hypoconnectivity among several

brain regions, such as between the amygdala and prefrontal cortex, between the cerebellum and the primary motor cortex and between the prefrontal cortex and the parietal cortex (e.g. Anticevic et al., 2012; Deserno et al., 2012; Genzel et al., 2015; Moussa-Tooks et al., 2019). Abnormal functional network structures associated with SZ can be effectively examined with resting-state functional connectivity analysis. This approach is particularly valuable due to the importance of spontaneous networks, such as the default-mode network (DMN), which plays a fundamental role in the pathophysiology of SZ. Several studies (Bluhm et al., 2007; Garrity et al., 2007; Karbasforoushan & Woodward, 2012; Sheffield & Barch, 2016) have emphasized the simplicity of data acquisition with this method, further enhancing its suitability for research purposes (Satterthwaite & Baker, 2015).

Aberrations in subcortical sensory circuits, specifically deficits in thalamocortical connectivity, in individuals with SZ have garnered considerable attention from a network perspective. Notably, recent investigations have revealed thalamocortical white matter pathway deficits during the early stages of SZ (Hamoda et al., 2019). Furthermore, a resting-state fMRI study focusing on thalamocortical connections demonstrated a decrease in prefrontal-thalamic connectivity alongside an increase in motor and somatosensory connectivity with the thalamus among individuals with SZ (Giraldo-Chica & Woodward, 2017). More recently, a voxelwise resting-state functional connectivity study provided substantial evidence linking the thalamocortical circuitry to auditory hallucinations in drug-naïve first-episode SZ patients (Wei et al., 2022).

Combining resting-state fMRI data with task-related fMRI data could provide a better understanding of altered brain networks in SZ patients. A recent comprehensive review proposed that SZ patients exhibit a reduced shift in brain activity from the resting state to the task state, which reflects altered spontaneous activity in the resting state and reduced neural differentiation of task-related activity from resting-state activity, and that such abnormalities may be connected to psychopathological and cognitive symptoms of SZ (Northoff & Gomez-Pilar, 2021).

Although most fMRI studies on SZ have focused on brain activity in either the resting or task state, a limited number of studies have examined both resting-state and task-related functional connectivity using fMRI (Damme et al., 2019; Mwansisya et al., 2017). Notably, Mwansisya et al. (Mwansisya et al., 2017) conducted a systematic review of task-related and resting-state fMRI studies of first-episode SZ patients. This review revealed the convergence of task-related and resting-state brain abnormalities in the prefrontal-temporal pathway, including the dorsolateral prefrontal cortex (DLPFC), the orbital frontal cortex, and the superior temporal gyrus (STG). Taken together, these findings suggest that altered functional networks in SZ patients could interact differently in the resting state and in the task state.

Several electroencephalography (EEG) studies have also investigated the relationship between altered spontaneous and task-related activity, focusing on neural oscillations that play roles in the precise temporal coordination of neural activity across brain regions (Garakh et al., 2015; Goldstein et al., 2015; Hirano et al., 2015; Parker et al., 2019; Spencer, 2011). In particular, gamma-band neural oscillations have attracted increasing attention because they are known to be related to cognitive deficits and other symptoms of SZ (Uhlhaas & Singer, 2010). Several previous studies confirmed the inverse relationship between spontaneous and task-related gamma-band dysfunction in SZ patients using the ASSR task (Hirano et al., 2015; Parker et al., 2019; Spencer, 2011), which involves entraining a neural oscillation to the frequency of a repetitive auditory stimulus. Notably, Hirano et al. (Hirano et al., 2015) used ASSR stimuli at three stimulation frequencies (20, 30 and 40 Hz), which evoked beta-band and gamma-band oscillations. They observed reduced stimulus-phase locking of the 40 Hz ASSR in paranoid-hallucinatory SZ patients, while the induced power, which is a component not phase-locked to repetitive click sounds, was increased in the gamma band (30–100 Hz). This inverse relationship indicates that noisy spontaneous activity might interfere with stimulus-evoked activity in gamma-band oscillations. Notably, through the utilization of identical tasks in an fMRI investigation, Kuga et al. (2016) observed significantly increased blood oxygen level-dependent (BOLD) signals for 80-Hz stimuli in the left auditory cortex of patients with an acute episode of SZ. More importantly, Jacob et al. (2023) recorded simultaneous EEG–fMRI data at rest in patients with SZ and found that gamma coupling to the hemodynamic signal was reduced in the bilateral STG (a region implicated in auditory processing). This reduction was associated with deficits in sensory gating and increased symptom severity.

In the present study, our objective was to assess whether the abnormality in auditory processing is confined to the auditory cortex or arises from deficits in subcortical sensory circuits in patients with SZ from a network perspective. Additionally, we aimed to explore the state shifts in functional connectivity throughout auditory processing by evaluating the intrinsic resting state and stimulus-induced activity in patients with SZ.

2 | METHODS

2.1 | Participants

A total of 25 SZ patients and 25 healthy controls (HCs) were included. Twenty-two SZ patients and HCs participated in both the ASSR task and the resting-state recording. Resting-state fMRI data were not recorded for six participants (three SZ patients and three HCs). The mean age of the SZ group did not differ from that of the HC group in those participating in the ASSR task (SZ: 38.9 ± 9.4 years, HC: 37.7 ± 11.3 years) or those participating in the resting-state recording (SZ: 39.3 ± 8.7 years, HC: 39.3 ± 10.9 years). All HCs were recruited from the local community. All SZ patients were recruited through Hoaki Hospital in Oita City and diagnosed by the Structured Clinical Interview for the DSM-5 (SCID-5). The detailed exclusion criteria are described in Data S1. Psychiatric symptoms of the SZ patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The detailed demographic and clinical characteristics are summarized in Tables 1A and 1B. This study was approved by the Research Ethics Board of Hoaki Hospital (permission no. 12) and was carried out in accordance with the latest version of the Declaration of Helsinki. After a complete description of the study was provided, all participants signed an informed consent form.

2.2 | Stimuli and apparatus

We used four types of click-train sounds with different train frequencies for the ASSR task. The 20, 30, 40 and 80 Hz click-train stimuli with a 500 ms duration were created using a 1 ms rectangle-shaped click sound. These stimuli were presented binaurally through headphones at 80 dB. The fMRI and structural MRI data were acquired with a 3-Tesla MR scanner (MAGNETOM Spectra, Siemens, München, Germany) and a 16-channel head coil (Head/Neck 16 A 3T Tim Coil, Siemens, München, Germany) at the Psychiatry Neuroimaging Center of Hoaki Hospital.

TABLE 1A Demographic and clinical characteristics of the auditory steady-state response (ASSR) task study groups.

	HC (<i>n</i> = 25)	SZ (<i>n</i> = 25)	χ^2, t	<i>df</i>	<i>p</i> value
Age	37.68 (11.3)	38.88 (9.4)	0.40	48	0.691
Sex (male/female)	12/13	12/13	0.00	1	1.00
Handedness (right/left)	24/1	24/1	0.00	1	1.00
Handedness index	90.7 (35.1)	88.7 (38.2)	0.19	48	0.848
Education years (years)	14.4 (1.4)	12.6 (2.0)	3.62	48	<0.001
SES	3.04 (0.92)	4.44 (0.98)	5.11	48	<0.001
Parental SES	3.00 (0.80)	3.00 (0.98)	0.00	48	1.00
Duration of illness (years)		14.41 (10.78)			
PANSS positive		19.32 (4.9)			
PANSS negative		20.96 (6.6)			
PANSS general		41.28 (8.4)			
Antipsychotic drug dose (CPZ equiv), mean		634.3 (382.7)			

Note: The data are given as the mean (SD).

Abbreviations: HC, healthy control; PANSS, Positive and Negative Syndrome Scale; SES, socioeconomic status; SZ, schizophrenia.

TABLE 1B Demographic and clinical characteristics of the resting-state study groups.

	HC (<i>n</i> = 22)	SZ (<i>n</i> = 22)	χ^2, t	<i>df</i>	<i>p</i> value
Age	39.32 (10.9)	39.32 (8.7)	0.00	42	1.00
Sex (male/female)	9/13	10/12	0.093	1	0.761
Handedness (right/left)	21/1	21/1	0.00	1	1.00
Handedness index	90.55 (37.3)	87.09 (40.5)	0.288	42	0.778
Education years (years)	14.36 (1.4)	12.59 (2.1)	3.19	42	0.003
SES	3.14 (0.9)	4.41 (1.0)	4.23	42	<0.001
Parental SES	3.0 (0.8)	3.0 (1.0)	0.00	42	1.00
Duration of illness (years)		15.55 (10.7)			
PANSS positive		19.27 (5.0)			
PANSS negative		20.86 (6.1)			
PANSS general		41.50 (7.4)			
Antipsychotic drug dose (CPZ equiv), mean		675.4 (390.0)			

Note: The data are given as the mean (SD).

Abbreviations: HC, healthy control; PANSS, Positive and Negative Syndrome Scale; SES, socioeconomic status; SZ, schizophrenia.

2.3 | Study procedure

The fMRI data from the ASSR task and resting state were recorded on separate days to reduce fatigue due to the long recording procedure. Prior to the ASSR task, a structural MRI scan was also performed using magnetization-prepared rapid gradient echo (MPRAGE). The detailed procedures and parameter settings for the resting-state fMRI and structural MRI scans are described in Data S1. The average interval between the task-related fMRI scan and the resting-state fMRI scan was 27.9 days.

2.4 | ASSR task

A sparse sampling paradigm was used to collect fMRI data during the ASSR task to reduce the functional consequences of acoustic scan noise. The parameters were as follows: repetition time (TR) = 9000 ms (acquisition time = 2500 ms and TR delay = 6500 ms), echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FoV) = 192 mm, matrix size = 64 mm × 64 mm, slice thickness = 3 mm, voxel size = 3.0 × 3.0 × 3.0 and slice gap = 0.8 mm. The fMRI scans were conducted in four separate runs. The four stimuli were presented

separately in each run, and their order was counterbalanced across the participants.

There were a total of 33 blocks (1 block consisted of an MRI scan of 2.5 s and an ensuing scan gap of 6.5 s) in each run. The first four blocks were discarded to allow the MR signal to reach a state of equilibrium. Auditory stimulation was administered every two blocks from the 5th block to the 29th block (no stimulation was presented in the other blocks). In 10 out of the 13 blocks, the click-train stimulus was presented three times. Specifically, the click-train stimulus (20, 30, 40 or 80 Hz) was repeated three times with an intertrain interval of 800 ms from 3 s after the scan stopped in each block. In 3 out of the 13 blocks, only the first two click trains were presented as the target stimulus (i.e. the 2 click-train blocks). The 2 click-train blocks were allocated randomly. In total, we presented 36 click trains for each run (Figure 1). The participants were instructed to remain still with their eyes closed and pay attention to the click-train sounds presented through headphones. To validate the participants' level of arousal, we instructed them to provide responses through button presses after the presentation of the target stimulus. To mitigate any potential impact of button pressing on the cerebral activity of the left hemisphere, which is known to exhibit distinctive structural and functional impairments in SZ patients (Dierks et al., 1999; Hirano et al., 2015; Spencer, 2011; Tsuchimoto

et al., 2011), participants were specifically directed to use their left hand for this task.

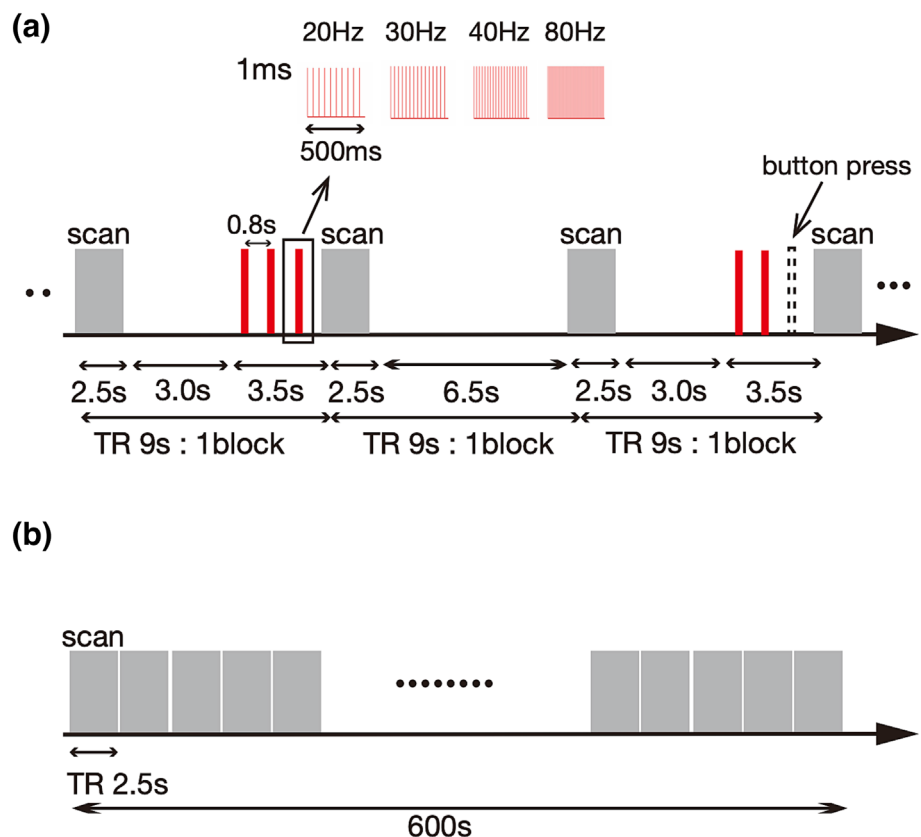
2.5 | Whole-brain BOLD signal analysis in the ASSR task

To analyse the preprocessed fMRI data recorded during the ASSR task, we first conducted whole-brain BOLD signal analysis (the detailed preprocessing procedures are summarized in Data S1). In the first-level analysis, individual contrast images between auditory stimulation and baseline were obtained for each stimulus condition (20, 30, 40 or 80 Hz) by applying a general linear model (GLM) to the preprocessed data. The GLM was used to identify the vertices in cortical and subcortical regions where the stimulation showed significant BOLD activation relative to baseline. In the GLM analysis, the task regressors were determined by convolving a canonical hemodynamic response function with a sequence of delta functions, representing stimulus timing, to generate the predicted time course of the BOLD signal for each two or three click-train block. In addition to the task regressors, the estimated motion correction parameters were included in the GLM as nuisance regressors.

Individual contrast images for each stimulus condition underwent the second-level analysis. The contrast of

FIGURE 1 Graphical summary of the functional magnetic resonance imaging (fMRI) experiment.

(a) Schematic illustration of the auditory-steady state response (ASSR) task. Stimulus waveforms of 20, 30, 40 and 80 Hz click trains and a part of one fMRI run are shown. In each run, auditory stimulation was conducted every two blocks (1 block consisted of an MRI scan of 2.5 s and an ensuing scan gap of 6.5 s). There were no stimulation blocks between the stimulation blocks. In the stimulation blocks, a click-train stimulus (20, 30, 40 or 80 Hz) was presented two or three times with an intertrain interval of 800 ms beginning at 3 s after the scan stopped. When the two click trains were presented, the participants were asked to press the button. (b) Schematic illustration of resting-state fMRI recording. A total of 240 scans with a repetition time of 2.5 s were conducted for 10 min.



interest in the second-level analysis was the group (HC vs. SZ). A cluster-based permutation simulation was used to conduct clusterwise correction for multiple comparisons. The clusterwise threshold was $p = 0.001$. We performed a total of 1000 permutation simulations and defined significant clusters with a clusterwise $p < 0.05$. We determined the specific locations of the significantly activated brain regions according to the Destrieux atlas (Destrieux et al., 2010). Regions activated during the 80 Hz condition (thalamus and bilateral auditory cortex) were used as regions of interest (ROIs) for functional connectivity analyses (see Section 3 for details).

2.6 | Functional connectivity analysis during the ASSR task and resting state

To identify the thalamo-auditory cortical networks involved in the ASSR task, we employed a GLM to compute individual seed-based functional connectivity under 20 or 80 Hz ASSR stimulation. In these stimulus conditions, there was a significant group difference in BOLD signal activation in the thalamus and bilateral auditory cortex (see Section 3 for details). The thalamus proper in each hemisphere was defined as a seed for functional connectivity analysis. The anatomical seed was defined using the subcortical automatic segmentation (aseg) function of FreeSurfer. In the GLM, the time course of the BOLD signal at the thalamus seed was included as a task regressor. In addition to the task regressor, the BOLD signal changes in the cerebrospinal fluid and white matter were included in the GLM as nuisance regressors. We also applied seed-based functional connectivity analysis to individual resting-state fMRI data in the same manner as the fMRI data during the ASSR task. Finally, we extracted individual thalamus-based functional connectivity values from the bilateral auditory ROIs that corresponded to the bilateral anterior transverse temporal gyrus (Heschl's gyrus) in the Destrieux atlas (Destrieux et al., 2010) for the ASSR task state and resting state separately.

2.7 | Statistical analysis

To examine the statistical significance of the demographic variables, we employed chi-square tests to assess group differences in sex and handedness. Additionally, unpaired t -tests were conducted for age, handedness index, years of education, socioeconomic status (SES) and paternal SES.

To analyse functional connectivity, we utilized a dataset comprising 22 HCs and 22 SZ patients who

participated in both the resting-state and ASSR tasks. We evaluated standardized resting-state functional connectivity because the degree of deviation in resting-state measures from the normal range is considered to be related to neural differentiation of task-related activity from resting-state activity (Northoff & Gomez-Pilar, 2021). The functional connectivity during the ASSR task was also standardized to enable evaluation on the same scale as resting-state functional connectivity. The standardized z score for functional connectivity was calculated separately for each state and each ROI (in the left and right hemisphere) by subtracting the mean of the HC group from the individual functional connectivity value and dividing it by the standard deviation of the HC group. We performed repeated-measures analysis of variance (rmANOVA) on z -transformed functional connectivity with the state (ASSR task state vs. resting state) and ROI hemisphere (left vs. right) as within-subject factors and group (SZ vs. HC) as a between-subject factor. Based on the results of the rmANOVA, we conducted an unpaired t -test with multiple comparison corrections using the Bonferroni method. Additionally, we calculated the effect size (Hedges' g) to examine the group differences in each state. To investigate state differences within each group, we conducted paired-sample t -tests with multiple comparison corrections using the Bonferroni method and calculated the effect size (Hedges' g) accordingly. For post hoc analyses, we multiplied the uncorrected p value by 4, the number of t -tests conducted, to obtain the corrected p value.

The relationships of functional connectivity between the resting state and ASSR task state were examined within and across groups for each ROI hemisphere using Spearman's rank correlation coefficients. We also examined the correlations of functional connectivity during the resting state and ASSR task state for each ROI hemisphere with PANSS positive, negative and general psychopathology scores. Bonferroni corrections were applied depending on combinations of states (resting state and ASSR task state) and symptom scales (positive, negative and general psychopathology).

3 | RESULTS

3.1 | Patient demographic characteristics

We found no significant group differences in demographic variables except for SES and years of education, consistent with reduced functioning due to SZ (Table 1A and Table 1B).

3.2 | ASSR-evoked BOLD signal

We first conducted whole-brain analyses to identify the brain areas activated by click-train stimuli during the ASSR task for the HC and SZ groups separately and then conducted group comparisons. The disparities in BOLD activity between groups were most prominent under the 80 Hz ASSR condition (Figure 2). Figure 2a and 2b show the activated regions (compared with the baseline) in the HC and SZ groups, respectively. During the 80 Hz ASSR condition, both groups exhibited clear activation in regions surrounding the bilateral auditory cortex. Activations in nonauditory cortical regions such as the frontal cortex and medial frontal cortex were also observed in the HC group but were less evident in the SZ group. In subcortical regions centred around the thalamus, significant BOLD signal activation was observed in the HC group. Notably, there were no significantly activated regions in the subcortical regions in the SZ group. In the group comparison (Figure 2c and Table 2), we found significant differences in activation in the left superior temporal cortex (clusterwise $p = 0.030$), rostral middle frontal cortex (clusterwise $p = 0.021$) and superior frontal cortex (clusterwise $p = 0.003$). In the right hemisphere, significant group differences were observed in the transverse temporal gyrus (clusterwise $p = 0.009$), rostral middle frontal cortex (clusterwise $p = 0.015$) and caudal

anterior cingulate cortex (clusterwise $p = 0.024$). We further examined these brain regions by dividing them according to the cortical parcellations of the Destrieux atlas (Destrieux et al., 2010) and identified specific locations within these regions where significant group differences were observed. The anterior transverse temporal gyrus, transverse temporal sulcus, planum temporale (or temporal plane) and lateral aspect of the STG were part of the superior temporal cluster of the left hemisphere. The rostral middle frontal cluster of the left hemisphere comprises the middle frontal sulcus, superior frontal sulcus and middle frontal gyrus. The middle-anterior part of the cingulate gyrus and sulcus and the anterior part of the cingulate gyrus and sulcus were part of the superior frontal cluster of the left hemisphere. The detailed brain regions comprising the transverse temporal cluster, the rostral middle frontal cluster and the caudal anterior cingulate cluster in the right hemisphere were almost the same as those in the clusters in the left hemisphere. In the subcortical regions, significant group differences were observed in broad areas centred around the bilateral thalamus (clusterwise $p = 0.003$). We also found significant group differences in the activation of several brain regions under the 20 Hz condition (Table 3), although these differences were not as clear as those under the 80 Hz condition (Figure 3a,b) (detailed results are described in Data S1). No significant group

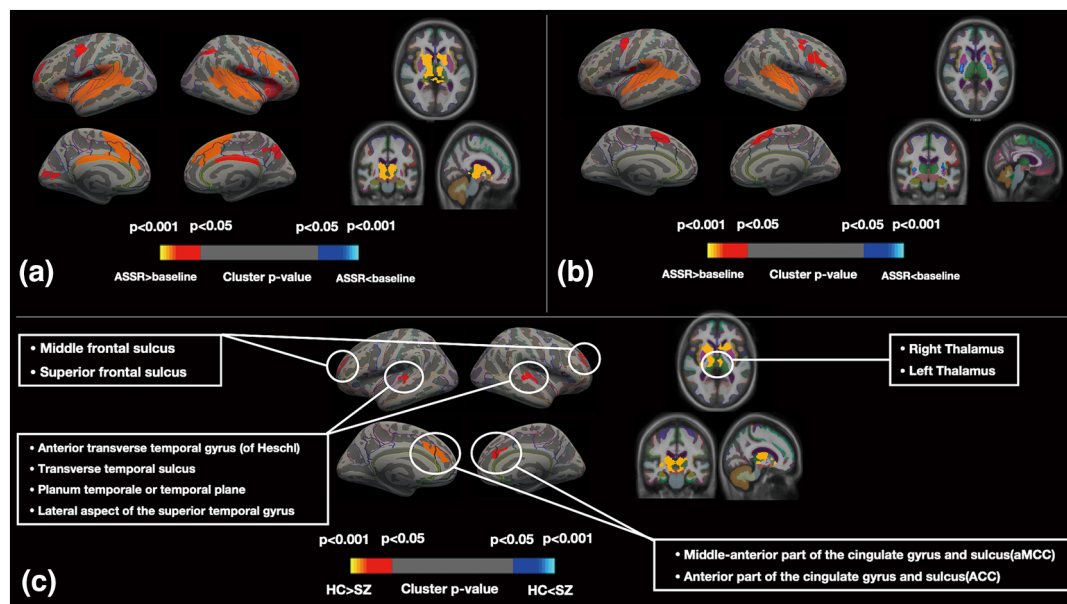


FIGURE 2 Results of blood oxygen level-dependent (BOLD) activations in cortical and subcortical spaces during 80 Hz auditory steady-state response (ASSR) stimulation. The regions activated by the 80 Hz click-train stimulus relative to baseline in the healthy control (HC) group (a) and schizophrenia (SZ) group (b). The hot and cool colours in the gradient colour bar of the cluster p value indicate ASSR > baseline and ASSR < baseline, respectively. (c) Group comparison of BOLD activations. The names of the activated regions are listed in the white line box. The activation and comparison maps are thresholded at a cluster p value < 0.05. The hot and cool colours in the gradient colour bar of the cluster p value indicate HC > SZ and HC < SZ, respectively.

TABLE 2 The functional magnetic resonance imaging (fMRI) results, including anatomical regions, seed voxel coordinates (MNI), cluster size and cluster *p* value, for each cluster with significant differences between healthy control (HC) and schizophrenia (SZ) in the auditory steady-state response (ASSR) 80 Hz task.

Left hemisphere		MNI coordinates			Cluster size	Cluster <i>p</i> value
Cluster no.	Annotation	x	y	z	mm ²	
1	Superior frontal	−12.8	28.9	28.5	537.45	0.00300
2	Rostral middle frontal	−24.4	34.1	25.8	322.26	0.02085
3	Superior temporal	−58.4	−28.0	4.9	272.88	0.02970
Right hemisphere		MNI coordinates			Cluster size	Cluster <i>p</i> value
Cluster no.	Annotation	x	y	z	mm ²	
1	Transverse temporal	49.3	−16.0	4.2	465.95	0.00897
2	Rostral middle frontal	24.3	42.8	31.9	351.09	0.01493
3	Caudal anterior cingulate	8.1	29.6	23.3	291.28	0.02381
Subcortical		MNI coordinates			Cluster size	Cluster <i>p</i> value
Cluster no.	Annotation	x	y	z	mm ³	
1	Brain-stem	6.00	−29.00	−19.00	33,928.0	0.00300

Abbreviation: MNI, Montreal Neurological Institute.

TABLE 3 Functional magnetic resonance imaging (fMRI) results, including anatomical regions, seed voxel coordinates (MNI), cluster size and cluster *p* value, for each cluster with significant differences between healthy control (HC) and schizophrenia (SZ) in the auditory steady-state response (ASSR) 20 Hz task.

Right hemisphere		MNI coordinates			Cluster size	Cluster <i>p</i> value
Cluster no.	Annotation	x	y	z	mm ²	
1	Lateral orbitofrontal	29.2	22.0	−3.3	319.57	0.00300
2	Transverse temporal	50.8	−20.6	3.8	231.55	0.02970
Subcortical		MNI coordinates			Cluster size	Cluster <i>p</i> value
Cluster no.	Annotation	x	y	Z	mm ³	
1	Right thalamus proper	22.00	−23.00	9.00	2608.0	0.01493

Abbreviation: MNI, Montreal Neurological Institute.

differences were found in any brain regions under the 30 or 40 Hz conditions (the brain regions activated in response to 30 and 40 Hz click-train stimuli are shown separately for each group in Figures S1 and S2, respectively).

3.3 | Thalamus-seed functional connectivity

As described above, we observed significant group differences in the bilateral auditory cortex and the thalamus under the 80 Hz condition. Subsequently, we investigated the functional connectivity between the thalamus and bilateral auditory cortex (specifically, the left and right Heschl's gyrus) during both the resting state and 80 Hz ASSR stimulation (Figure 4a). The z-transformed

functional connectivity was then compared between the HC and SZ groups under resting-state and 80 Hz ASSR stimulation for each auditory ROI hemisphere separately (Figure 4b). rmANOVA revealed a significant main effect of state ($F[1,42] = 12.85$, $p < 0.001$) and a group-by-state interaction ($F[1,42] = 12.85$, $p < 0.001$). However, no significant main effects were found for ROI hemisphere ($F[1, 42] = 0.484$, $p = 0.490$), group ($F[1, 42] = 3.331$, $p = 0.075$), group-by-ROI hemisphere interaction ($F[1, 42] = 0.484$, $p = 0.490$), ROI hemisphere-by-state interaction ($F[1, 42] = 0.464$, $p = 0.499$) or state-by-ROI hemisphere-by-group interaction ($F[1, 42] = 0.464$, $p = 0.499$). To analyse this group-by-state interaction, we conducted an unpaired *t*-test to investigate group differences in each state. The results showed stronger connectivity in the resting state ($p < 0.004$; Bonferroni corrected, Hedges' $g = 0.946$) and lower connectivity in

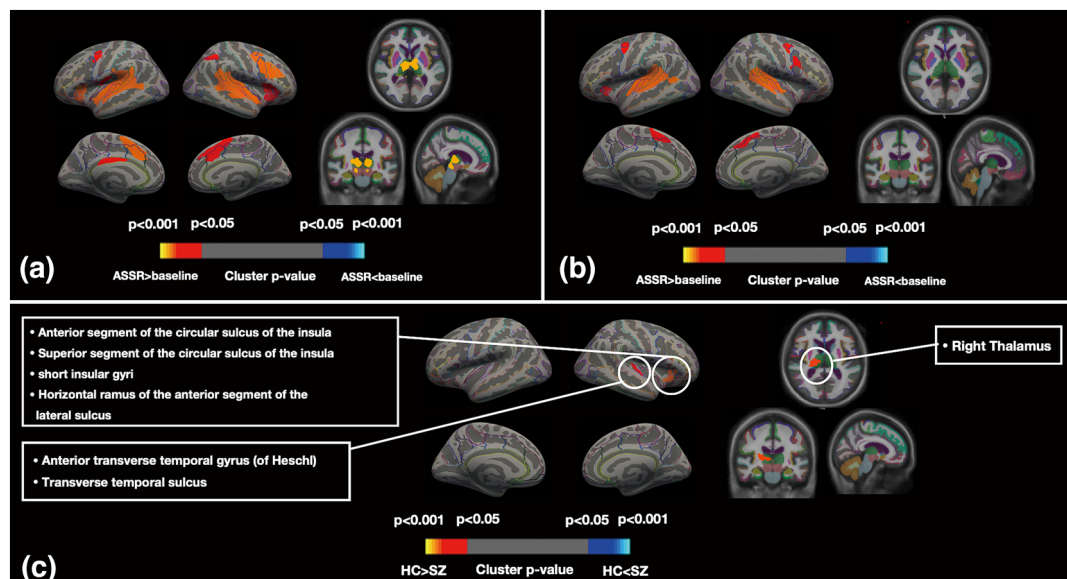


FIGURE 3 Results of blood oxygen level-dependent (BOLD) activations in the cortical and subcortical spaces during 20 Hz auditory steady-state response (ASSR) stimulation. The regions activated by the 20 Hz click-train stimulus relative to baseline in the healthy control (HC) group (a) and schizophrenia (SZ) group (b). The hot and cool colours in the gradient colour bar of the cluster p value indicate ASSR > baseline and ASSR < baseline, respectively. (c) Group comparison of BOLD activations in the 20 Hz condition. The names of the activated regions are listed in the white line box. The activation and comparison maps are thresholded at a cluster p value < 0.05. The hot and cool colours in the gradient colour bar of the cluster p value indicate HC > SZ and HC < SZ, respectively.

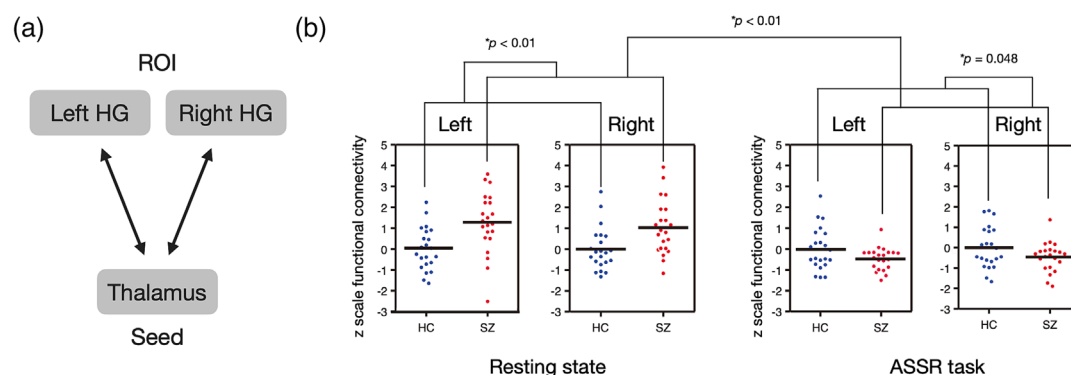


FIGURE 4 Results of seed-based functional connectivity analysis. (a) The bilateral thalamus is a seed, and the left and right Heschl's gyrus (HG) are the regions of interest for functional connectivity analysis. (b) Group comparisons (schizophrenia [SZ] vs. healthy controls [HCs]) of z-scale functional connectivity between the thalamus and the left HG and between the thalamus and the right HG separately for the resting-state (left panel) and auditory steady-state response (ASSR) task (right panel). The thick black lines in (b) show group-averaged z scored functional connectivity. The asterisk indicates a statistically significant difference between pairs after Bonferroni correction at the threshold of 0.05.

the ASSR task ($p = 0.048$; Bonferroni corrected, Hedges' $g = 0.547$) in the SZ group. Additionally, we conducted paired-sample t -tests to investigate state differences in each group. The results revealed a significant difference between the resting-state and ASSR task in the SZ group ($p < 0.004$; Bonferroni corrected, Hedges' $g = 1.036$), while no significant difference was observed in the HC group ($p = 1.00$; Bonferroni corrected, Hedges' $g = 0.00$).

Furthermore, we compared the z-transformed functional connectivity during the resting state and after 20 Hz ASSR stimulation separately between the HC and SZ groups for each auditory ROI hemisphere (Figure S3). The detailed results are summarized in Data S1.

Using the thalamus as a seed for functional connectivity analyses, we examined connectivity with the left Heschl's gyrus and found a significant negative

correlation between the resting state and the ASSR task state ($\rho = -0.298$, $p = 0.049$). Within each state, a significant negative correlation was observed in the HC group ($\rho = -0.429$, $p = 0.047$), while no significant correlation was found in the SZ group ($\rho = -0.010$, $p = 0.966$) (Figure 5a). No significant correlations were detected in connectivity between the thalamus and right Heschl's gyrus in the two states (all: $\rho = -0.253$, $p = 0.097$; HCs: $\rho = -0.251$, $p = 0.259$; SZ: $\rho = -0.056$, $p = 0.805$) (Figure 5b). With respect to the relationship between functional connectivity and clinical symptoms, we did not find any significant correlations of resting-state or task-related functional connectivity with

the PANSS score. The detailed results of the correlations between functional connectivity and clinical symptoms are summarized in Data S1.

4 | DISCUSSION

In the present study, we investigated abnormal functional connectivity patterns during both the resting state and ASSR task state in patients with SZ, specifically focusing on thalamo-auditory networks. The integration of resting-state and ASSR data enabled an exploration into whether SZ patients exhibit adaptive control over brain network activities contingent upon the state. The results revealed reduced BOLD activity in response to ASSR stimulation in the auditory cortex and thalamus in the SZ group compared with that in the HC group. In addition, we found increased functional connectivity during the resting state and reduced functional connectivity during the ASSR task state in the SZ group (Figure 6). To our knowledge, this study is the first to provide evidence of aberrant functional connectivity between the thalamus and auditory cortex in patients with SZ with an abnormal state shift between resting-state and task-related activities.

4.1 | Reduced BOLD activation associated with 80 Hz ASSR stimulation in SZ patients

The most pronounced difference in BOLD activity was observed in the bilateral auditory cortex and thalamus during 80 Hz stimulation, which is known to induce high gamma oscillations in the brain. The reductions in BOLD activity in the bilateral auditory cortex in the SZ group are consistent with previous magnetoencephalography (MEG) studies that showed reduced activity in the auditory cortex during the 80 Hz ASSR task in SZ patients (Hamm et al., 2011; Tsuchimoto et al., 2011). Notably, Tsuchimoto et al. showed that the power and phase locking of the 80 Hz ASSR task had greater sensitivity in SZ patients than those of the 20, 30 and 40 Hz ASSR tasks. The similarity between the previous MEG findings and our fMRI results indicates that the BOLD signals during 80 Hz stimulation might reflect high gamma-band oscillatory functions. Regarding the thalamus, Farahani et al. identified the left thalamus as a nonprimary source during 80 Hz ASSR stimulation, while thalamic activity was not observed during 20 or 40 Hz ASSR stimulation (Farahani et al., 2019). The utilization of an 80 Hz click-train stimulus appears to provide valuable insight into gamma-band oscillations and their associated BOLD

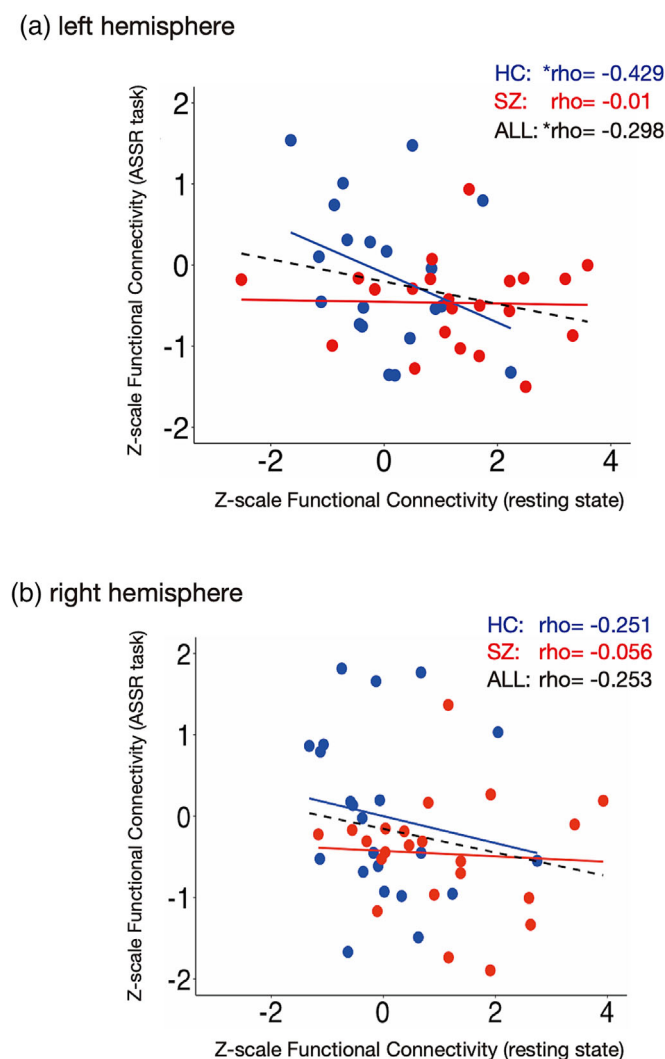


FIGURE 5 Scatter plots of z scored functional connectivity during the auditory steady-state response (ASSR) task as a function of z scored resting-state functional connectivity in the left hemisphere (a) and right hemisphere (b). The scatter plots and lines indicate individual data and regression lines, respectively, of the healthy control (HC) (blue) and schizophrenia (SZ) groups (red). The black line indicates the regression lines for all the data.

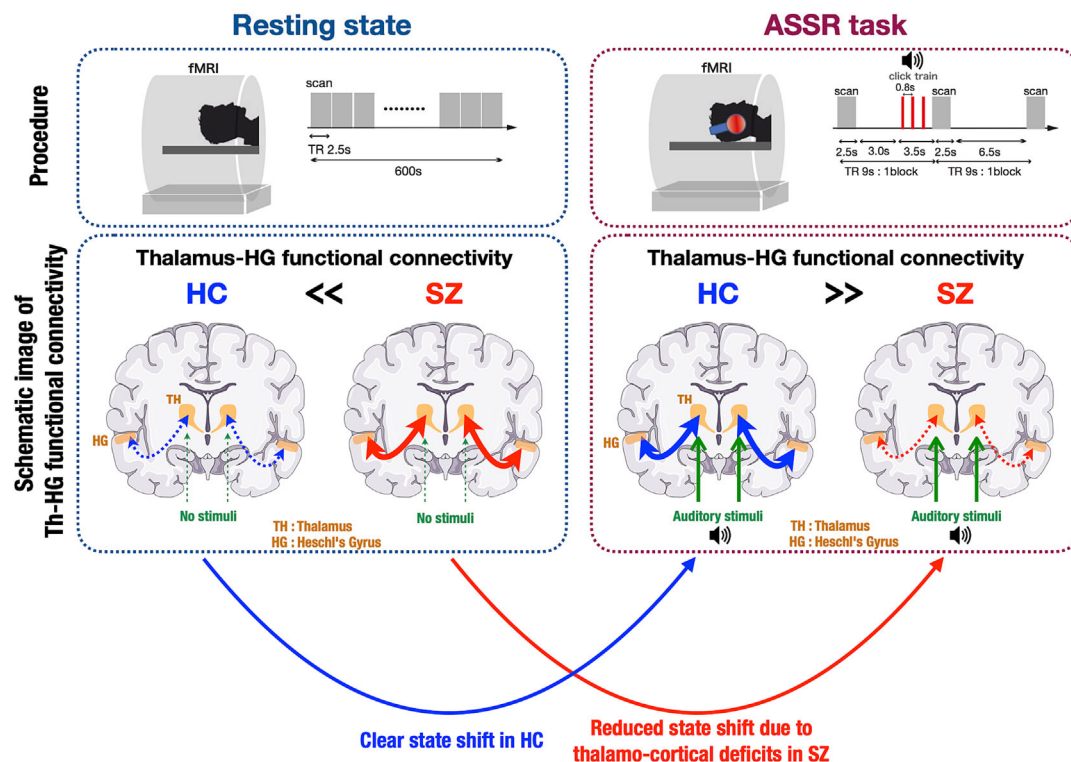


FIGURE 6 Summary of the main findings. Compared with those of healthy controls (HCs), the schizophrenia (SZ) patients demonstrated (1) stronger thalamus–Heschl’s gyrus (HG) functional connectivity in the resting state (left) and (2) reduced thalamus–HG functional connectivity in the auditory steady-state response (ASSR) task (right), which was mediated by state shift deficits. These results highlight the presence of abnormal thalamocortical connectivity associated with deficits in the shift between resting and task states in SZ patients.

responses in the thalamus. Consequently, we were able to detect distinctly reduced BOLD activity in patients with SZ under the 80 Hz condition.

We also observed diminished BOLD activation in various brain regions within the SZ group during 20 Hz ASSR stimulation, which elicits beta-band oscillations in the brain; however, these differences were not as prominent as those observed under the 80 Hz condition. Considering the negative correlation between beta-band neural oscillations and the BOLD signal (Hall et al., 2014), the reduced BOLD response in SZ patients may be attributed to increased beta-band oscillatory power during 20 Hz ASSR stimulation. In fact, several EEG and MEG studies have reported that the mean power of 20 Hz ASSR stimulation tends to be greater in SZ patients than in HCs (Kwon et al., 1999; Tsuchimoto et al., 2011). In addition, the 20 Hz stimulus is known to evoke not only beta-band oscillations but also gamma-band (40 Hz) subharmonic components (Metzner & Steuber, 2021), eliciting a lower 40 Hz subharmonic component in SZ patients (Spencer et al., 2008; Vierling-Claassen et al., 2008). Considering these subharmonic components, it is conceivable that the reduced BOLD signals observed in the SZ group might reflect both

increased beta-band and decreased gamma-band oscillatory power during the 20 Hz click-train stimulation.

4.2 | Thalamo-auditory dysconnectivity during the resting state and ASSR stimulation

In the present study, we identified enhanced functional connectivity between the thalamus and the bilateral auditory cortex in the resting state within the SZ group. Impairments in resting-state thalamocortical networks have been implicated in the pathophysiology of SZ (Anticevic et al., 2014; Avram et al., 2018, 2020; Woodward & Heckers, 2016). Notably, Avram et al. (2020) reported increased functional connectivity of the thalamus with auditory-sensorimotor cortical areas during the resting state in SZ patients, which aligns with our present findings.

In contrast to the resting-state functional connectivity findings, SZ patients exhibited lower functional connectivity during 80 Hz ASSR stimulation. Consistent with our findings, previous studies have also reported deficits in thalamocortical networks during cognitive tasks in SZ

patients (DeNicola et al., 2020; Minzenberg et al., 2009; Wagner et al., 2013). A meta-analysis of functional neuroimaging studies on executive function in SZ patients demonstrated reduced activation of the mediodorsal nucleus of the thalamus and prefrontal cortex (Minzenberg et al., 2009), regions known for their strong functional coupling during cognitive tasks (DeNicola et al., 2020). Furthermore, Wagner et al. (2013) utilized dynamic causal modelling to identify disrupted effective connectivity between the thalamus and prefrontal cortex during the Stroop task in SZ patients. Notably, our study is the first to reveal decreased functional connectivity between the thalamus and bilateral auditory cortex using the ASSR paradigm.

Taken together, these findings revealed that abnormal patterns of thalamo-auditory functional networks in SZ patients were state-dependent and characterized by both hypo- and hyperconnectivity. An inverse relationship between altered resting state and task-related thalamo-cortical connectivity was also reported by Damme et al. (2019), who identified abnormal functional connectivity during the resting state and self-referential task state in clinically high-risk subjects.

4.3 | Abnormal shifts in resting-state and task-state connectivity in the thalamo-auditory network

While most related studies have focused on either resting-state or task-related BOLD signal activation, our study evaluated activation in both states and revealed abnormal resting-state functional connectivity between the thalamus and the left auditory cortex in SZ patients, which was associated with functional connectivity in the ASSR task state. This result supports the insightful hypothesis proposed by Northoff and Gomez-Pilar (2021), under which reduced shifts in resting-state and task-related connectivity, potentially linked to abnormal differentiation of internally and externally oriented cognition, may underlie SZ pathology. We propose that the disrupted shift between resting state and task-related connectivity within the thalamo-auditory network might reflect impaired sensory filtering within the auditory regions around the sensory thalamus. In the auditory system, auditory information ascends from the cochlea toward the auditory cortex through the medial geniculate body in the thalamus (Farahani et al., 2019). The thalamus plays an important role in relaying auditory information from the peripheral nervous system to the cortex while regulating the activity of those regions. Notably, thalamic inhibition is believed to facilitate goal-directed noise filtering, enabling efficient sensory

processing (Nakajima et al., 2019). Given the role of the thalamus in sensory information processing, the increased resting-state connectivity observed in the thalamo-auditory network in SZ patients may result from the failure of thalamic inhibition, leading to unnecessary noise transmission. Thus, it is conceivable that this heightened network activity may interfere with auditory information processing. Therefore, SZ patients may exhibit hypoconnectivity in the thalamo-auditory network and reduced activation in the bilateral auditory cortex during the ASSR task.

4.4 | Abnormal shifts between resting-state and task-related gamma-band oscillatory functions

Given the close association between the BOLD signal and gamma-band oscillations (Hall et al., 2014), it may be assumed that an impairment within the thalamo-auditory network could be linked to disrupted gamma-band oscillations in SZ patients. Consistent with our findings, previous EEG studies on SZ (Hirano et al., 2015; Parker et al., 2019; Spencer, 2011) have consistently indicated an inverse correlation between spontaneous and task-related gamma-band dysfunctions. A meta-analysis by Thuné et al. (2016) illustrated that impairments in gamma-band evoked power and phase-locking factors serve as robust markers of neural circuit dysfunctions in SZ patients. The present study suggested a potential neural pathway that implicates gamma-band ASSR deficits in SZ patients, thus providing invaluable insights into the pathophysiology of SZ.

4.5 | Limitations

This study has several limitations that warrant further investigation. First, our measurements were limited to fMRI data, which prevented us from establishing a robust relationship between the BOLD response and gamma-band oscillations. Therefore, it is crucial to confirm the correlation between these variables in future studies (which are currently in progress) utilizing simultaneous EEG-fMRI methods. Second, the different designs employed for collecting resting-state and task-related fMRI data made it difficult to compare the two types of data. Specifically, we employed the sparse sampling method to minimize the impact of scan noise on BOLD signal activation during the ASSR task. However, during resting-state fMRI, participants were continuously exposed to acoustic noise generated by the MRI device, which could affect resting-state network connectivity

(Pellegrino et al., 2022). Third, the sample size in our study was relatively small. Future investigations with larger sample sizes are necessary to enhance the generalizability of our findings.

5 | CONCLUSION

This study highlighted a potential link between disruptions in thalamo-auditory networks in patients with SZ and an abnormal dependence of task-related activity on resting-state activity. Furthermore, these network abnormalities may reflect deficits in the modulation of gamma-band oscillations between the resting state and task state in SZ patients. The diminished modulation observed across the entire brain is believed to contribute to the abnormal differentiation between internally and externally oriented cognition, a characteristic feature associated with various symptoms of SZ, such as auditory hallucinations, delusions, passivity phenomena and ego disturbances (Northoff & Gomez-Pilar, 2021). Further investigations into the ‘dysconnection’ of brain networks underlying these deficits in switching between the resting state and task state will advance our understanding of the pathophysiology of SZ.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16298>.

DATA AVAILABILITY STATEMENT

The data used in this study are not available publicly due to the restriction of sharing research data from the Research Ethics Committee but are available upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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