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Thalamocortical dysrhythmia in patients with schizophrenia spectrum disorder and individuals at clinical high risk for psychosis

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Thalamocortical dysrhythmia (TCD) is a model characterized by abnormal resting-state thalamic oscillatory patterns where the alpha rhythm is replaced by cross-frequency coupling of low- and high-frequency rhythms. Although disrupted thalamic function is a suggested important pathophysiological mechanism underlying schizophrenia, knowledge regarding the TCD model in schizophrenia spectrum disorder (SSD) patients and individuals at clinical high risk (CHR) for psychosis is limited. A total of 169 SSD patients, 106 individuals at CHR for psychosis, and 105 healthy controls (HCs) underwent resting-state electroencephalography recordings. We performed mean global field power (MGFP) spectral analysis between 1 and 49 Hz as well as source-level theta phase-gamma amplitude coupling (TGC) analysis and compared resting-state oscillatory patterns across groups. Correlations between altered TGC values and psychotic symptom severity in the patient group were investigated. Spectral MGFP of low- and high-frequencies was larger in the SSD and CHR groups than in the HC group. The TGC of SSD patients was greater than that of HCs in the right frontal, right parietal, and left and right limbic lobes. Greater TGC in the right frontal and limbic lobes was associated with positive symptom severity in SSD patients. However, TGC in the CHR group was comparable to that in the HCs and was smaller than that in the SSD group in widespread cortical regions. The TCD pattern may be apparent after frank psychotic disorder onset in tandem with overt positive symptoms. A psychosis-risk state without overt psychotic symptoms could be characterized by abnormally increased low- and high-frequency activities with relatively preserved TGC.

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INTRODUCTION

The thalamus is one of the key brain regions of schizophrenia pathophysiology, especially for psychotic symptoms and cognitive impairments, due to its role in integrating and connecting information flow across the brain regions affected in psychotic disorders, as suggested in Andreasen's cognitive dysmetria [1]. Previous studies reporting abnormal structural and functional connectivity of the thalamus in patients with schizophrenia spectrum disorder (SSD) and in individuals at clinical high risk (CHR) for psychosis support the importance of the role of the thalamus in the pathophysiology of schizophrenia [2–5]. However, given that neural activity occurs instantaneously with moment-by-moment changes, the role of abnormal thalamocortical information flow in schizophrenia pathophysiology needs to be further clarified by evaluating neural oscillatory activities captured by resting-state electroencephalography (EEG) with a very high temporal resolution [6–8].

Thalamocortical dysrhythmia (TCD) has been suggested as a disease model that illustrates the abnormal resting-state oscillatory patterns found in neurological disorders and psychiatric disorders that share thalamic dysfunctions [9–13]. In the TCD model, a dysfunctional thalamocortical circuit centering thalamic reticular nuclei slows the normal resting-state alpha rhythm to a low frequency (i.e., delta and theta rhythms). Then, low-frequency activity results in an increase in surrounding high-frequency activity (i.e., beta and gamma rhythms) by a reduction in collateral inhibition, which is called the edge effect; this outcome is presented as increased theta-gamma coupling [9, 10]. Considering that the thalamus is the hub of neural communication and thalamic dysfunction has been suggested as a neural mechanism underlying schizophrenia [1, 2], the TCD model could explain the abnormalities in the instantaneous thalamocortical information flow underlying psychotic symptoms and its pathophysiological mechanisms [14, 15]. However, no previous study showed abnormal TCD patterns in SSD or discussed its relationship with psychotic symptoms.

It has been consistently reported that SSD patients present abnormally increased low- and high-frequency spectral powers or cross-frequency coupling of these spectral powers in the resting state [13, 16–19]. In individuals at CHR for psychosis, the existing literature is scarce, and the results are inconsistent. Two studies reported that abnormal brain oscillatory activities during the

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resting state shown in individuals at CHR for psychosis were predictive of transition to psychotic disorder [20, 21], while another study reported no such alteration in brain activity [22]. It has been suggested that dysfunctional brain oscillations found in SSD patients were due to abnormalities in rhythm-generating γ-aminobutyric acid (GABA) interneurons and their connections to cortical areas [14, 23–26]; these characteristics are closely related to the thalamic dysfunction of information flow evident in schizophrenia [1, 27, 28]. Despite the suggested usefulness of the TCD model in investigating the pathophysiological mechanism of schizophrenia, only one study reported abnormally increased low- and high-frequency spectral powers in a small number of SSD patients [13], and a study investigating individuals at CHR for psychosis has not yet been reported.

In the current study, we aimed to investigate whether the abnormal oscillatory pattern suggested as a model of TCD (i.e., increased low- and high-frequency spectral powers and theta phase-gamma amplitude coupling [TGC]) is apparent after the onset of overt psychotic symptoms or is present from the at-risk stage of psychotic disorder by investigating resting-state EEG in a large number of SSD and CHR participants. We hypothesized that the pattern of TCD would be present in SSD patients and that a significant relationship between TGC and psychotic symptom severity would be found. Because several reports of resting-state EEG findings in individuals at CHR for psychosis have been inconsistent, we hypothesized that the TCD pattern in individuals at the risk stage of psychosis could be less prominent than that in patients with frank psychotic disorders.

MATERIALS AND METHODS

Participants

A total of 169 SSD patients, 106 individuals at CHR for psychosis, and 105 healthy controls (HCs) participated in resting-state EEG recordings. The data of 59 SSD patients and 50 HCs were used in our previously published study [18]. Patients with SSD were recruited from an inpatient and outpatient clinic of the Department of Neuropsychiatry at the Seoul National University Hospital (SNUH). SSD patients satisfied the diagnosis criteria of schizophrenia, schizoaffective disorder, or schizophreniform disorder when assessed with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders (SCID-I). Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Subjects at CHR for psychosis were recruited from the Seoul Youth Clinic, a center for early detection and intervention of psychosis [29], in SNUH. The Structured Interview for Prodromal Symptoms (SIPS) [30] was used to confirm the CHR status of the participants. The psychosis-risk symptoms were assessed using the validated Korean version of the Scale of Prodromal Symptoms (SOPS) [31, 32]. HCs were recruited via internet advertisement and were screened using the SCID-I Nonpatient Edition (SCID-NP). Potential HC participants were excluded when they had any first- to third-degree biological relatives with a psychotic disorder. Common exclusion criteria included substance abuse or dependence (except nicotine), neurological disease or significant head trauma, medical illness that could accompany psychiatric symptoms, and intellectual disability (intelligence quotient [IQ] <70).

Written informed consent was received from all participants after they were provided with a thorough explanation of the study procedure (IRB no. H-1110-009-380). For the minors, informed consent was obtained from both the participants themselves and their parents. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of SNUH (IRB no. H-2103-073-1204).

EEG acquisition

The participants were instructed not to drink coffee or tea or to have other stimulants, including cigarettes, within 2 h before the EEG recording session. Participants were seated comfortably in a quiet, electrically shielded room with their eyes closed and were instructed not to fall asleep. Resting-state EEG recording was conducted for 5 min using a Neuroscan 64-Channel SynAmps2 system equipped with a 64-channel Quick-Cap based on the modified 10–20 international system (Compumedics, Charlotte, NC, USA). The EEG data were digitized at a 1000 Hz sampling rate, and an online low pass filter of 100 Hz was used. The reference electrodes were placed on both mastoids, and the ground electrode was placed on AFz. Vertical and horizontal electrooculograms were recorded using the electrodes below and on the outer canthus of the left eye to monitor eye movement artifacts. The resistance of all electrode sites was below 5 kΩ.

Preprocessing and power spectrum analysis

EEG data analysis was performed using MATLAB R2019b (MathWorks, Natick, MA, USA) and the EEGLAB toolbox [33]. After a bandpass filter of 0.5–50 Hz was applied, bad channels were replaced by the linear interpolation of the adjacent channels (up to 7% per participant). For artifact reduction, independent component analysis (ICA) using the second-order blind identification algorithm implemented in the EEGLAB toolbox was performed [34, 35]. Ocular artifact removal was conducted using the SASICA toolbox [36] and visual inspection. EEG recordings were rereferenced to the common average reference data and segmented into 4 s epochs; then, 25 artifact-free epochs were selected by careful visual inspection. Selected epochs underwent fast Fourier transformation with a Hamming window, and EEG spectral power (μV^2) of 1–49 Hz was acquired for each electrode. The mean global field power (MGFP) was calculated by the arithmetic mean values of EEG spectral powers for each frequency from all 62 electrodes.

Source reconstruction and TGC analysis

Source reconstruction of 100 s resting-state EEG data was performed using the standardized low-resolution electromagnetic tomography (sLORETA) method with the LORETA-KEY alpha software program [37]. Based on the Brodmann area (BA) information, a total of 82 cortical regions of interest (ROIs) except for two sublobar ROIs were evaluated, and source signals were extracted from the centroid voxel of each BA. Source signals were converted into theta (4–7 Hz) and gamma (30–50 Hz) ranges using the basic finite impulse response filter embedded in the EEGLAB toolbox. After obtaining the phase of the theta band and the amplitude of the gamma band using the Hilbert transform, the phase of the theta band was divided into 18 bins with a range of 20 degrees, and the average of the gamma band amplitudes corresponding to each bin was calculated as a TGC modulation index (MI) value [38]. Permutation tests of the individual EEG data of each participant were performed to verify that significant TGC was present within each of the 82 cortical ROIs. Each theta phase and gamma amplitude data in each cortical ROI were randomly matched on 1000 iterations, and the MI distribution was calculated and compared to the MI distribution of actual data. We found that the MI distribution of the actual data was more than 1.96 standard deviation away from the MI distribution obtained from the permutation test. The permutation test revealed that local TGC values of the 82 ROIs were significantly greater than randomly obtained TGC values in all individuals and thus confirmed as actual TGC. Then, TGC MI values of 10 lobar ROIs (i.e., the frontal, parietal, temporal, occipital, and limbic lobes of the left and right hemispheres) were calculated by the arithmetic mean values of the TGC MI from the corresponding 82 cortical ROIs (Table S1 in the Supplementary Material).

Statistical analysis

The demographic and clinical characteristics of the participants were compared using analysis of variance or independent *t* test across the groups for continuous variables. A Bonferroni test was used for post hoc analysis. Chi-square tests were used for categorical variables. In all group comparison analyses of the EEG spectra and TGC MI values, age, sex, and lorazepam equivalent dose of benzodiazepines [39] were used as covariates. To compare the EEG power spectra across the SSD, CHR, and HC participants, we performed multivariate analysis of covariance (MANCOVA) with group as the independent variable and frequency (1–49 Hz) as the dependent variable. Based on a general significant effect, we performed a univariate analysis of covariance (ANCOVA) to define specific frequencies showing group differences. For the group comparison of TGC MI values, MANCOVA with group as the independent variable and the ten lobar ROIs as the dependent variable was performed. Based on a general significant effect, a univariate ANCOVA was used to find specific ROIs with group differences. We performed a Pearson's correlation analysis to investigate the relationship between the altered TGC MI values in the patient group and psychotic symptom severity as measured by the PANSS positive and negative subscale scores. False discovery rate (FDR) correction

Table 1. Demographic and clinical characteristics of patients with schizophrenia spectrum disorder (SSD), subjects at clinical high risk (CHR) for psychosis, and healthy controls (HCs).

	SSD	CHR	HC	Statistical analysis[a]	
	(*N* = 169)	(*N* = 106)	(*N* = 105)	F or T or χ^2	*P*
Sex (male/female)	79/90	75/31	75/30	23.234	<0.001**
Handedness (right/left)	158/11	100/6	97/8	0.332	0.847
Age (years)	25.9 ± 6.9	20.2 ± 4.0	22.5 ± 4.3	35.704	<0.001**
IQ[b]	99.8 ± 14.6	105.2 ± 14.1	113.7 ± 13.4	30.431	<0.001**
Education (years)	13.9 ± 2.5	12.5 ± 1.8	14.2 ± 1.6	21.079	<0.001**
DOI (months)	51.9 ± 72.1	–	–		
PANSS					
Positive symptoms	15.6 ± 5.7	–	–		
Negative symptoms	16.5 ± 5.9	–	–		
General symptoms	32.2 ± 8.9	–	–		
SOPS					
Positive symptoms	–	9.8 ± 3.7	–	–	–
Negative symptoms	–	14.0 ± 6.4	–	–	–
Disorganization	–	4.1 ± 2.8	–	–	–
General symptoms	–	7.0 ± 4.0	–	–	–
Prescribed medication[c]					
Antipsychotics	156 (92.3)	16 (15.1)	–	165.785	<0.001**
Antidepressants	33 (19.5)	23 (21.7)	–	0.189	0.663
Mood stabilizers	28 (16.6)	4 (3.8)	–	10.371	0.001**
Benzodiazepines	74 (43.8)	26 (24.5)	–	10.441	0.001**
Benzodiazepine dose[d]	0.4 ± 0.6	0.3 ± 0.5	–	2.241	0.026*

Data are given as the mean ± standard deviation.
IQ intelligence quotient, *DOI* duration of illness, *PANSS* Positive and Negative Syndrome Scale, *SOPS* Scale of Prodromal Symptoms.
*Statistical significance is at $p < 0.05$.
**Statistical significance is at $p < 0.005$.
[a]Analysis of variance, independent *t* test or Welch's *t* test if the variances were not equal, χ^2 analysis or Fisher's exact test for categorical data.
[b]The number of missing data is 13 in the SSD group.
[c]Number (percentage) of participants who were prescribed each medication at the time of resting-state electroencephalography (EEG) measurement.
[d]Lorazepam equivalent dose of benzodiazepines prescribed at the time of resting-state EEG measurement.

was applied to correct for multiple comparisons in all group comparison and correlation analyses. Statistical analyses were performed using R (×64, 3.53 version), and statistical significance was set at $p < 0.05$.

RESULTS

Participant characteristics

The demographic and clinical characteristics of SSD patients, CHR individuals, and HCs are summarized in Table 1. There were more females in the SSD group than in the CHR and HC groups ($\chi^2 = 23.234$, $p < 0.001$). Age was lowest among CHR subjects, was intermediate among HCs, and highest among SSD patients ($F = 35.704$, $p < 0.001$; SSD vs. CHR, $p < 0.001$; SSD vs. HC, $p < 0.001$; CHR vs. HC, $p = 0.008$). Subjects at CHR for psychosis were less educated ($F = 21.079$, $p < 0.001$) than SSD patients ($p < 0.001$) and HCs ($p < 0.001$). IQ was highest in HCs, intermediate in individuals at CHR for psychosis, and lowest in the SSD group ($F = 30.431$, $p < 0.001$; SSD vs. CHR, $p = 0.007$; SSD vs. HC, $p < 0.001$; CHR vs. HC, $p < 0.001$).

MGFP spectral analysis results

MANCOVA comparing the MGFP spectra across the SSD, CHR, and HC groups showed a significant effect of group ($F = 4.975$, $p = 0.007$; Fig. 1). ANCOVAs with FDR correction showed significantly larger MGFP in SSD patients than in HCs at 3–9 and 16–17 Hz. The MGFP of subjects at CHR for psychosis was significantly greater than that of HCs at 1–4, 9–11, and 14–49 Hz. There was no frequency range with a significant group difference in MGFP between the SSD and CHR groups.

TGC MI results

TGC MI results are presented in Fig. 2 and Table 2. MANCOVA comparing the TGC MI values of 10 lobar ROIs, which were calculated by arithmetic mean values of TGC MI from the corresponding 82 cortical ROIs, across the SSD, CHR, and HC groups showed a significant effect of group ($F = 9.894$, $p < 0.001$). ANCOVAs with FDR correction revealed that SSD patients showed significantly larger TGC MI values in four lobar ROIs, which were the right frontal and parietal lobes and limbic lobes of both hemispheres, compared to HCs. There were no lobar ROIs with significant group differences in TGC MI values between the CHR and HC groups. TGC MI values of CHR individuals were significantly smaller than those of SSD patients in eight lobar ROIs except for the left frontal lobe and right temporal lobe. Results of the exploratory group comparison of TGC MI values in 82 cortical ROIs across the SSD, CHR, and HC groups are provided in the Supplementary Material (Table S1 and Fig. S1).

Correlation with psychotic symptoms

Pearson's correlation analyses were performed to investigate the relationship of TGC MI values from 4 lobar ROIs, which were significantly higher in SSD patients than in HCs, with positive and

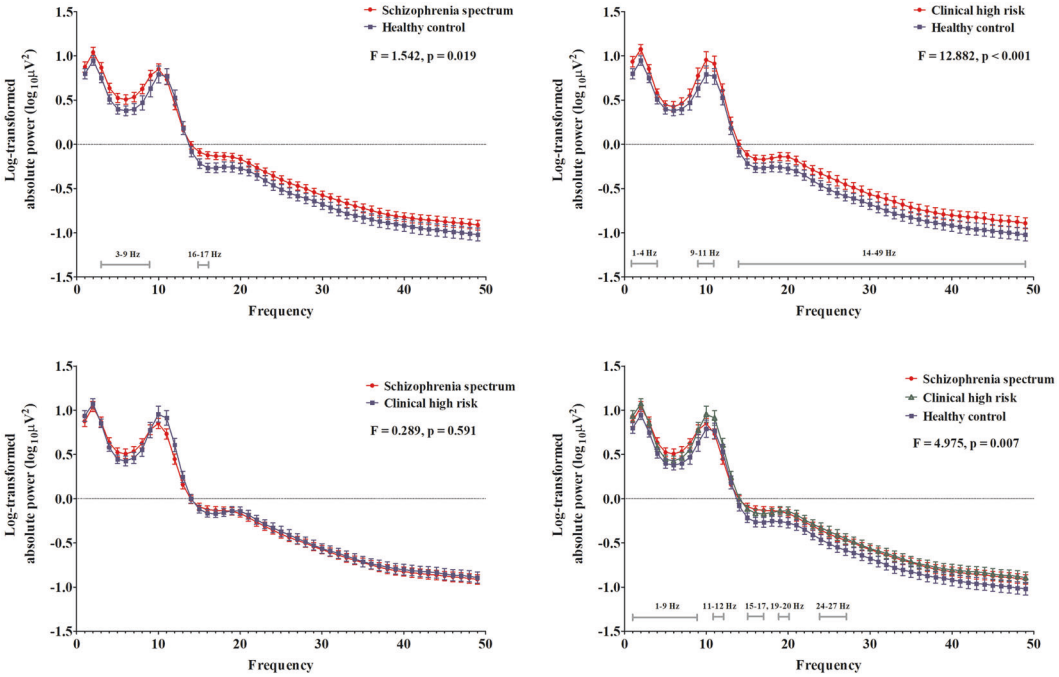

Fig. 1 A comparison of the power spectrum of patients with schizophrenia spectrum disorder, individuals at clinical high risk for psychosis, and healthy controls. Whiskers in the graph indicate 95% confidence intervals. Gray bars in the figure indicate specific frequencies showing significant group differences. Statistical significance was set at false discovery rate-corrected $p < 0.05$.

negative symptom scores on the PANSS in SSD patients. After FDR correction, positive correlations between PANSS positive symptom scores and the TGC MI values of the right frontal lobe ($r = 0.319$, $p_{FDR} = 0.044$) and right limbic lobe ($r = 0.320$, $p_{FDR} = 0.008$) were found (Fig. 3). There was no significant correlation between the PANSS negative symptom scores and the TGC MI values. The results are summarized in Table S2 in the Supplementary Material.

DISCUSSION

This study is the first to evaluate a large number of SSD patients and individuals at CHR for psychosis to investigate whether the pattern of TCD in resting-state EEG occurs after the onset of frank psychotic disorder or originates in the psychosis-risk state. Larger MGFP in low- and high-frequency rhythms were observed in both the SSD and CHR groups compared to the MGFP in the HC group. In addition, greater TGC values in the right frontal, right parietal, and both limbic lobes were observed in SSD patients than in HCs, and greater TGC in the right frontal and limbic lobes were associated with more severe positive symptoms in those patients. However, in individuals at CHR for psychosis, TGC values were not different from those in HCs and were smaller than those in SSD patients. These results not only highlight that the TCD pattern is apparent after the onset of frank psychotic disorder in tandem with overt positive symptoms but also support the importance of the role of the thalamus in dysfunctional information flow in the pathophysiological mechanism of schizophrenia.

The current study first reported that the pattern of TCD characterized by abnormally increased delta, theta, and beta spectral powers as well as elevated TGC values was present in SSD patients. Consistent with the current study results, the increased resting-state delta and theta activity in the SSD patients were the most consistent findings of previous studies [19], and an increase in beta activity has also been reported [13, 17]. Two previous studies, including our own study using data partially overlapping with those used in the current study, reported an abnormally increased TGC in the resting state in SSD patients [18, 40]. The modulation of the gamma amplitude by the theta phase is suggested as a mechanism of neural communication [8, 41], and the resting-state TGC is thought to be reflective of the neural excitation/inhibition (E/I) balance [42]. Given that the thalamus is a hub of neural communication, the thalamic dysfunction and E/I imbalance produced by N-methyl-D-aspartate receptor (NMDAr)-GABA hypofunction are suggested as neural mechanisms of schizophrenia [1, 15, 26, 43]; hence, the current study results support that abnormal moment-by-moment neural communications centering on the thalamus, as explained by the TCD model, are present in SSD patients.

In their seminal study, Vanneste et al. [11] showed that TCD was spectrally equivalent across various neurological disorders and depression, but increased cross-frequency coupling was found in distinct brain areas related to each disorder. For example, increased TGC in depression was observed in cingulate cortices, which have been investigated as major brain regions affected in the disorder [44, 45]. Similarly, we observed increased TGC in the frontal, parietal, and limbic lobes in SSD patients, which is in line with previous studies reporting thalamic disconnections to the frontal, parietal, and limbic cortices in SSD patients [3, 5, 46, 47]. In addition, we found a significant relationship between greater TGC in the right frontal and limbic lobes and more severe positive symptoms, although the association was relatively weak. The development of positive symptoms has been explained by abnormal neural oscillatory network-dopaminergic interactions in the prefrontal cortex during adolescence [43, 48, 49]. Furthermore, an altered natural frequency of the frontal/thalamocortical circuit was reported to be correlated with positive symptom severity in SSD patients [28]. In the limbic cortex, abnormally elevated glutamate levels in the anterior cingulate cortex (ACC) and parahippocampal cortex as well as altered thalamo-ACC functional connectivity have been reported to be related to positive symptoms in SSD patients [47, 50, 51]. Therefore, the current study findings may provide a biological background for future studies to bridge the gap between the molecular mechanisms of glutamate, brain circuits centering the thalamus, and positive symptoms of psychotic disorder. However, the relationship between TGC and positive symptoms should be

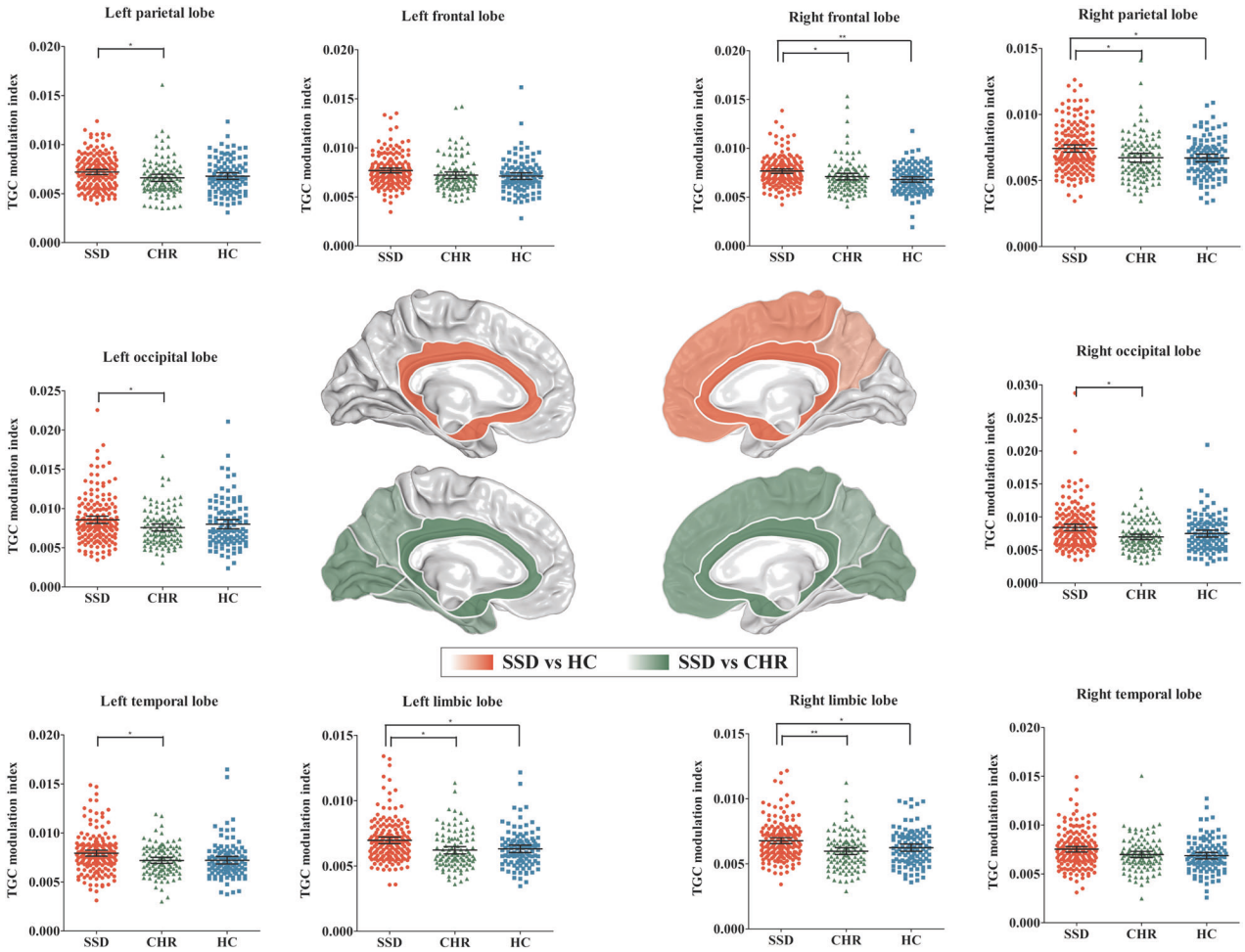

Fig. 2 Group comparison results of theta phase-gamma amplitude coupling (TGC) across patients with schizophrenia spectrum disorder (SSD), individuals at clinical high risk (CHR) for psychosis, and healthy controls (HCs). The horizontal and vertical lines in the group indicate the mean and 95% confidence interval of TGC values. Asterisk symbol (*) indicates that the statistical significance is false discovery rate (FDR)-corrected $p < 0.05$. Double asterisk symbol (**) indicates that the statistical significance is FDR-corrected $p < 0.005$.

Table 2. The group comparison results of theta phase-gamma amplitude coupling (TGC) across patients with schizophrenia spectrum disorder (SSD), subjects at clinical high risk (CHR) for psychosis, and healthy controls (HCs) in ten lobar regions of interest (ROIs).

Lobar ROI	SSD	CHR	HC	Statistical analysis (P_{FDR})[a]				
	($N = 169$)	($N = 106$)	($N = 105$)	F	P_{FDR}	SSD vs. HC	CHR vs. HC	SSD vs. CHR
	TGC modulation index[b]							
Left frontal lobe	7.694 ± 1.607	7.208 ± 1.694	7.122 ± 1.749	2.900	0.062	0.052	0.806	0.079
Left parietal lobe	7.198 ± 1.717	6.606 ± 1.886	6.790 ± 1.741	2.973	0.062	0.111	0.806	0.035*
Left temporal lobe	8.078 ± 2.746	7.203 ± 1.554	7.218 ± 1.949	4.074	0.030*	0.091	0.857	0.035*
Left occipital lobe	8.930 ± 4.633	7.576 ± 2.342	8.020 ± 3.018	3.398	0.048*	0.164	0.517	0.035*
Left limbic lobe	6.965 ± 1.636	6.212 ± 1.432	6.316 ± 1.431	6.485	0.007*	0.040*	0.806	0.013*
Right frontal lobe	7.657 ± 1.490	7.093 ± 1.770	6.800 ± 1.459	8.072	<0.001**	<0.001**	0.548	0.035*
Right parietal lobe	7.419 ± 1.797	6.727 ± 1.721	6.706 ± 1.495	5.523	0.008*	0.040*	0.857	0.013*
Right temporal lobe	7.531 ± 1.863	6.989 ± 1.656	6.872 ± 1.717	2.607	0.075	0.061	0.806	0.070
Right occipital lobe	8.423 ± 3.374	6.990 ± 2.148	7.482 ± 2.691	6.022	0.008*	0.061	0.390	0.013*
Right limbic lobe	6.778 ± 1.474	5.971 ± 1.376	6.247 ± 1.407	9.182	<0.001**	0.040*	0.517	<0.001**

Data are given as the mean ± standard deviation.
FDR false discovery rate.
*FDR-corrected *p* value is at <0.05.
**FDR-corrected *p* value is at <0.005.
[a]Analysis of variance with age, sex, and lorazepam equivalent dose of benzodiazepines as covariates.
[b]Data are multiplied by e^{-3}.

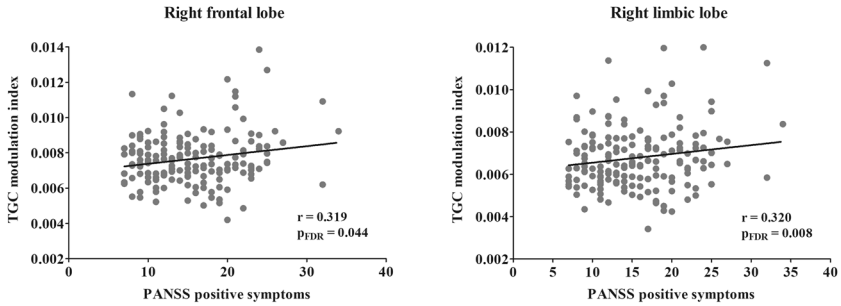

Fig. 3 Correlation between theta phase-gamma amplitude coupling (TGC) of the right frontal/limbic lobes and Positive and Negative Syndrome Scale (PANSS) positive symptom scores. Statistical significance was set at false discovery rate (FDR)-corrected $p < 0.05$.

interpreted with caution considering the relatively weak association found in the current study.

The pattern of TCD was less apparent in individuals at CHR for psychosis than in SSD patients in that low- and high-frequency activities were elevated but TGC was not different from that of HCs. Two previous studies reported that subject at CHR for psychosis who later transitioned to psychotic disorder showed increased low- and high-frequency activities compared to HCs [20, 21]. The current study results support their findings that elevated low- and high-frequency activities may serve as a neurophysiological marker for psychosis risk. A cross-sectional study reported no group difference between patients at CHR for psychosis and HCs, but the small sample size ($n = 33$) may be a cause of the small effect [22]. Because this study is the first to investigate resting-state TGC in individuals at CHR for psychosis, our findings that TGC was not different from HCs and was smaller than that in SSD patients should be interpreted in consideration of the characteristics of being at CHR. First, CHR is mostly defined by attenuated positive symptoms with a progressive nature [52]; thus, biomarkers related to frank psychotic disorder or overt positive symptoms such as resting-state TGC may not be apparent in the CHR state. Other electrophysiological markers reflecting the NMDAr-GABA system, such as mismatch negativity and gamma auditory steady-state response, were found to be reduced in the CHR group, but the effect sizes were smaller than those in SSD patients [53–56]. Second, with a declining transition rate and increasing psychiatric comorbidities [57–59], growing heterogeneity in the CHR group may have blurred the effect of increased TGC in a small number of individuals at CHR for psychosis who are closer to becoming SSD patients.

This study has several limitations. First, although TCD is suggested as a spectrally shared phenomenon across various neurological and psychiatric disorders [11], we only looked at TCD in the psychosis spectrum. From the perspective of cross-disorder biotyping to provide better treatment based on the biological mechanism [60, 61], other psychiatric disorders, such as mood, anxiety, and developmental disorders, should be further investigated together with psychotic disorders. Second, the participants in the current study were not matched by age, sex, or benzodiazepine use. Thus, we controlled those variables by using them as covariates in every group comparison analysis. Third, many SSD patients were taking antipsychotics and benzodiazepines, which may have had an effect on the brain oscillatory activities of these patients. Fourth, although we interpreted the negative TGC results in individuals at CHR for psychosis with CHR heterogeneity, we could not perform a group comparison of TGC between homogeneous subgroups of individuals at CHR for psychosis mainly due to the limited sample size and lack of clinical information. Future multicenter longitudinal studies with large sample sizes should be performed to determine whether TGC differs between homogeneous subgroups of individuals at CHR for psychosis with distinct biological and prognostic characteristics.

In conclusion, the present study suggests that the pattern of TCD in resting-state EEG signals may occur after the onset of frank psychotic disorder in tandem with overt psychotic symptoms. By showing that dysfunctional neural activity centering around the thalamus is present in SSD patients using resting-state EEG signals with very high temporal resolution, our results support previous neuroimaging studies reporting disruption in the thalamus and thalamocortical connectivity as an important pathophysiological mechanism of psychotic disorders [2, 5, 46, 51, 62]. More research is needed to validate the current study findings in other psychiatric disorders and in homogeneous subgroups of psychosis spectra to achieve cross-disorder and within-diagnosis biotyping for effective treatment based on distinct biotypes.

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AUTHOR CONTRIBUTIONS

MK: Conceptualization, methodology, formal analysis, data curation, writing—original draft, and visualization. THL: Formal analysis, investigation, data curation, writing—review and editing, and visualization. HP: Investigation, writing—review and editing, and visualization. SYM: Investigation and writing—review and editing. SKL: Investigation and writing—review and editing. JSK: Conceptualization, methodology, writing—review and editing, supervision, and project administration.

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COMPETING INTERESTS

The authors declare no competing interests.

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