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Evaluation of Brain Neural Networks in Patients with Schizophrenia

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Abstract: Purpose: The purpose of this study is to clarify the relationship between the disruption of neural networks in the brain and the pathogenesis of schizophrenia and verified its clinical significance.
Materials and Methods: Using resting-state functional magnetic resonance imaging (rs-fMRI) we compared functional connectivity between patients with schizophrenia and healthy controls. The association between the severity of clinical symptoms assessed by rating scale and degree of functional connectivity in the patient group was also examined. This rs-fMRI study examined resting-state connectivity in 48 schizophrenia patients and 48 healthy controls. The schizophrenia group was assessed for symptoms using the Positive and Negative Symptom Scale. Using a five-factor model, factor scores were calculated for positive, negative, and disorganized symptoms, depression, and excitement. Using the image analysis program CONN toolbox, the connectivity of the brain functional network at rest was evaluated using region of interest (ROI) -to-ROI analysis.
Results: Compared with the healthy control group, connectivity was increased in the schizophrenia group at two clusters: the bilateral thalamus and bilateral middle temporal gyrus (cluster 1) and the bilateral thalamus and bilateral superior temporal gyrus (cluster 2). However, connectivity decreased in the bilateral thalamus and bilateral superior temporal gyrus. In the schizophrenia group, positive symptoms such as hallucination and delusion indicated a positive association between symptom severity and connectivity of the left amygdala/left nucleus accumbens and left supramarginal gyrus or bilateral amygdala/bilateral nucleus accumbens and left fusiform gyrus. No brain regions were significantly associated with negative symptoms such as blunted affect and passive apathetic social withdrawal. Symptom severity of disorganized symptoms was positively associated with connectivity of the bilateral angular gyrus, supramarginal gyrus, left middle temporal gyrus, bilateral supramarginal gyrus, left parahippocampal gyrus, left orbital gyrus, and right middle temporal gyrus.
Conclusions: We found increased thalamus-temporal connectivity and decreased thalamus-temporal lobe hemispheric connectivity in patients with schizophrenia. The results suggest that the abnormal connectivity between thalamus and temporal lobe is associated with the development of schizophrenia. Furthermore, temporal lobe and limbic system functions may be involved in the development of the core symptoms of schizophrenia, such as positive and disorganized symptoms.

Key Words: schizophrenia, resting-state functional magnetic resonance imaging, Positive and Negative Symptom Scale (PANSS), positive symptoms, disorganized symptoms

Introduction

Schizophrenia is a psychiatric disorder characterized by positive symptoms, such as hallucinations and delusions; negative symptoms, such as decreased motivation and emotional numbness; and thought disorder. The disorder has a diverse clinical course and causes impaired social functioning.

Neuroimaging studies of patients with schizophrenia have shown structural changes, such as decreased gray matter and enlarged ventricular volumes. Functional studies have focused on thalamocortical connections, mesolimbic connections that involve the amygdala, corticostriatal connections, and the default mode network and salience network visualized using resting-state

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functional magnetic resonance imaging (rs-fMRI), one of the functional imaging studies (1). In rs-fMRI studies, abnormalities in the default mode network (2), which consists of the medial prefrontal cortex, posterior cingulate gyrus, and other areas, have been frequently associated with functional connectivity in schizophrenia. While some studies have reported increased connectivity (3-6), such as a correlation between increased connectivity and the intensity of positive symptoms (7), others have otherwise shown decreased connectivity (8, 9). Decreased connectivity in thalamocortical networks occurs in the early stages of schizophrenia and is implicated in the positive, negative, and cognitive symptoms of this disorder (10). Although various reports have described increased connectivity in auditory networks (11), decreased connectivity between hemispheres (11, 12), and abnormal connectivity involving the hippocampus (13), the link between the disruption of functional connectivity in the brain and the pathogenesis of schizophrenia remains unclear.

In this study, we performed rs-fMRI and clinical symptoms assessment to compare functional connectivity in the brain between healthy subjects and patients with schizophrenia. We aimed to clarify the relationship between neural network disruption in the brain and pathophysiological manifestations of psychiatric disorders, as well as to examine its clinical significance. We mainly compared differences in neural network properties between normal subjects and patients with schizophrenia to determine the association between clinical symptom characteristics and neural network features in schizophrenia.

Most studies on functional connectivity have focused on a priori specific networks, such as the default mode or salience network. Few studies have comprehensively evaluated the network without limiting the brain regions to compare healthy subjects and patients with schizophrenia.

The five-factor model of the Positive and Negative Symptom Scale (PANSS) (14) was used to evaluate clinical symptoms. Previous factor analysis studies on the PANSS suggested that the five-factor model aptly characterizes schizophrenia symptoms (15). The five-factor model is highly useful in schizophrenia studies, such as in the evaluation of treatment responsiveness (16) and functional-level assessment (17). However, previous rs-fMRI studies of schizophrenia have not used the PANSS five-factor model to assess the main symptoms of schizophrenia, namely, positive, negative, and disorganized symptoms.

This study was conducted with the prior approval of the Ethics Committee of the Kanazawa Medical University (E241: Elucidation of Biological Features in Schizophrenia Using Brain Imaging).

Patients and methods

1. Patients

The participants included 48 patients diagnosed with schizophrenia according to ICD-10 and a corresponding number of healthy controls, for a total sample size of 96. The patients with schizophrenia were inpatients and outpatients recruited from Kanazawa Medical University Hospital, and the healthy controls included members of the university hospital staff and the general public. The healthy controls selected for inclusion had no history of psychiatric consultation or psychotropic medication. Written informed consent was obtained from all participants.

2. Clinical symptom assessment

The PANSS is a symptom-severity rating scale consisting of positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items) and is administered as a structured clinical interview by a trained interviewer. Each symptom item is scored on a scale of 1 (no symptoms) to 7 (extreme symptoms) according to the rating criteria. In the present study, two raters conducted the PANSS assessments simultaneously and independently based on the same interview and according to the PANSS manual (18). The individual scores were discussed and agreed upon. Kay et al. (14) grouped the items into three subscales. However, in the present study, the five-factor model presented by Wallwork et al. (15) was used. Symptom items were classified as positive, negative, disorganized, excited, or depressed. Factor scores were the sums of the individual component scores. Table 1 shows the PANSS five-factor model and symptom items included in each factor.

Table 1. PANSS five-factor models and symptom items included in each factor.

Factor	Symptom
Positive	Delusions(P1), Hallucinations Disorganization (P3), Grandiosity(P5), Unusual Thought(G9)
Negative	Blunted Affect(N1), Emotional Withdrawal (N2), Poor Rapport(N3), Passive/Apathetic Social(N4), Lack of Spontaneity(N6), Motor Retardation(G7)
Disorganize	Conceptual(P2), Difficulty in Abstraction Withdrawal(N5), Poor Attention(G11)
Excited	Excitement(P4), Hostility ion(P7), Uncooperative-ness(G8), Poor Impulse Control(G14)
Depressed	Anxiety(G2), Guilt Feelings(G3), Depression Posturing(G6)

3. Imaging

Functional imaging was performed using a 3T MRI system (Magnetom Trio, Siemens, Erlangen, Germany), and time series data of BOLD signals at rest were used for analysis. Two hundred sets of images were taken using the echo planar imaging method with a repetition time of 2000 ms, echo time of 30 ms, a slice thickness of 5 mm, a gap of 0 mm, and 30 slices. The total imaging time was approximately 6.6 minutes.

4. Image analysis

We analyzed the connectivity of functional brain networks in the resting state using the CONN toolbox, a Matlab-based software for the computation, display, and analysis of functional connectivity. The program has a pipeline function that can perform a series of processes, from unprocessed functional brain images, to noise removal and hypothesis testing. Spatial preprocessing, time series preprocessing, first-level individual analysis, and second-level population analysis were performed (19).

In this study, region of interest (ROI) -to-ROI analysis was performed to analyze functional connectivity. We used 164 ROIs based on the Harvard-Oxford atlas (20). In the individual analysis of functional connectivity (first-level analysis), regression analysis of the 164 ROIs was performed using the general linear model, and the correlation coefficient between ROIs was analyzed as the value of functional connectivity. This analysis determined the functional connectivity of every combination of ROIs for the subjects. The statistical model used in the population analysis was the general linear model, with control, patient, sex, and age as regressors for the comparison between healthy controls and patients. To analyze the association between functional connectivity and symptoms in the patient group, the regressors used were patient, sex, age, and PANSS items. The results were tested for significance using a corrected P value < 0.05 based on the False Discovery Rate (FDR).

Table 2. Demographic and clinical data of study participants.

		Control (n=48)	Schizophrenia (n=48)
Sex, male/female (n)		16/32	16/32
Age (years)		35.2±9.5	35.5±9.6
Handedness (right/left/mixed)		48/0/0	42/3/3
Duration of Education (years)		16.0±2.8	12.6±1.9
Duration of illness (years)			11.3±10.3
Medication dose (CPZ equivalent, mg/day)			482.6±513.5
PANSS	positive		9.9±4.8
	negative		12.4±6.1
	disorganized		6.8±3.0
	depression		6.0±2.2
	excited		7.0±3.1

Values represent the mean ± SD unless otherwise stated. CPZ, chlorpromazine; Positive and Negative syndrome Scale.

Results

1. Participant characteristics

The demographic data of the participants are shown in Table 2. The patient group had a mean ± standard deviation (SD) age of 35.5 ± 9.6 years (range 18-58 years; 16 male/32 female), whereas the mean ± (SD) age in the healthy controls was 35.2 ± 9.5 years (range, 19-54 years; 16 male/32 female). Forty-two patients were right-handed, three were left-handed, and three were ambidextrous. Conversely, all healthy controls were right-handed. The number of years of education differed between the healthy controls (16 years) and the schizophrenia group (12.6 years). In the schizophrenia group, the duration of illness ranged from 6 months to 40 years, with a mean of 11.3 years. Four patients were drug-free, and the mean chlorpromazine equivalent dose was 482.6 mg/day in patients who were under medication.

2. Group comparisons

Figure 1 shows the brain regions with significant differences between the two groups based on ROI-to-ROI analysis. Red indicates stronger connectivity in the schizophrenia group, whereas green indicates stronger connectivity in the healthy controls. Therefore, we selected the thalamus and temporal lobe as the ROIs, and examined functional connectivity between 16 ROIs in the thalamus and superior and middle temporal gyri, including the brain regions that showed significant differences.

Figure 2 shows the areas of functional connectivity that differed between the groups, which consisted of four network clusters. Cluster 1, bilateral thalamus and bilateral middle temporal gyrus ($F[3,90] = 8.01$; p-FDR = 0.000515), and cluster 2, bilateral thalamus and bilateral superior and middle temporal gyrus ($F[3,90] = 7.07$; p-FDR = 0.000766), showed higher connectivity in the schizophrenia group than in the healthy control group. Connectivity between cluster 3, bilateral thalamus ($F[1,92] = 7.95$; p-FDR = 0.010416), and cluster 4, bilateral superior and middle temporal gyrus 6 sites ($F[3,90] = 4.30$; p-FDR = 0.010416), was lower in the schizophrenia group than in the healthy control group.

3. Association between symptoms and functional connectivity

We examined the associations between functional connectivity and positive, negative, or disorganized

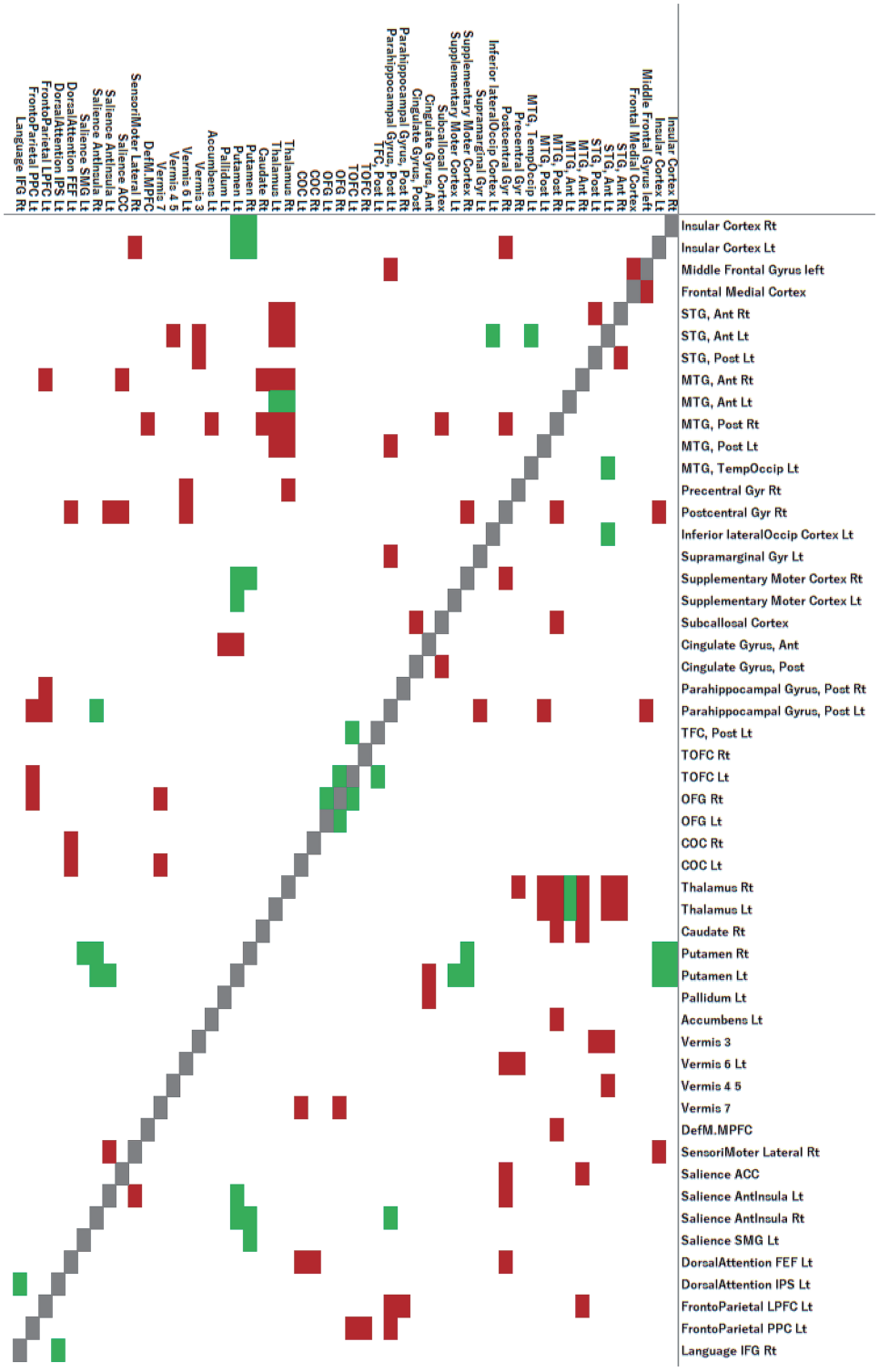


Fig.1. Two-group comparison with ROI to ROI analysis.

Abbreviation: Rt, right; Lt, left; Ant, anterior; Post, posterior; STG, Superior Temporal Gyrus; MTG, Middle Temporal Gyrus; TFC, Temporal Fusiform Cortex; TOFC, Temporal Occipital Fusiform Cortex; OFG, Occipital Fusiform Cortex; COC, Central Operculum Cortex; DefM, Default Mode; MPFC, Medial PreFrontal Cortex; ACC, Anterior Cingulate Cortex; SMG, SupraMarginal Gyrus; FEF, Frontal Eye Field; IPS, IntraParietal Sulcus; LPFC, Lateral Prefrontal Cortex; PPC, Posterior Parietal cortex; IFG, Inferior Frontal Gyrus

ROI to ROI analysis shows brain regions with significant differences between the two groups. Red indicates increased connectivity in the patient group compared to the healthy controls, and green indicates increased connectivity in the healthy controls compared to the patient group.

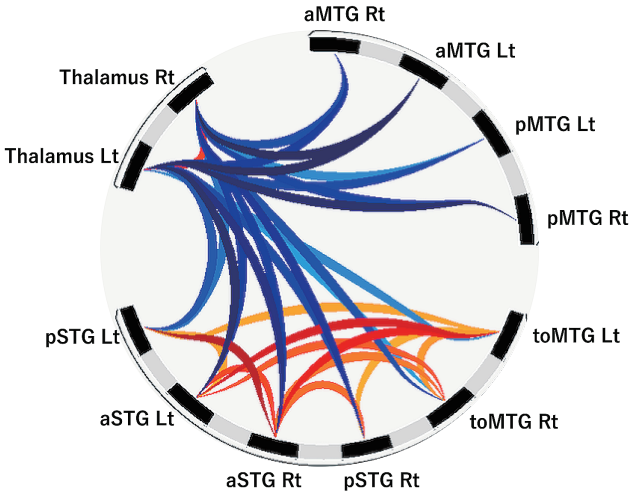


Fig2-1

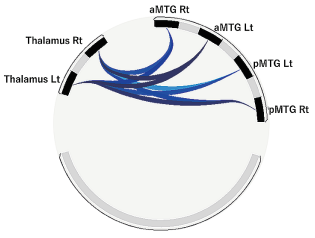
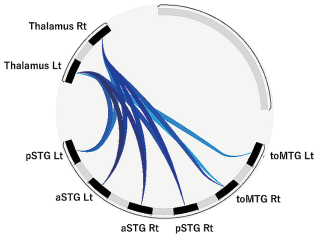


Fig2-2



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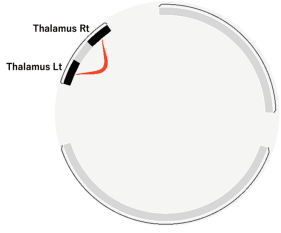

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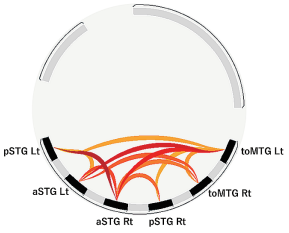

Fig2-5

Fig.2. Abbreviation: Rt, right; Lt, left; a, anterior; p, posterior; to, temporo-occipital; MTG, Middle Temporal Gyrus; STG, Superior Temporal Gyrus

Functional connectivity between 16 ROIs of the thalamus and superior and middle temporal gyrus was shown, consisting of four clusters of networks. Cluster 1, bilateral thalamus and bilateral middle temporal gyrus (4 ROIs), and cluster 2, bilateral thalamus and bilateral superior and middle temporal gyrus (6 ROIs), showed increased connectivity in the patient group compared to healthy controls. Connectivity between the bilateral thalamus (cluster 3) and between the bilateral superior and middle temporal gyrus (cluster 4) was decreased in the patient group compared to healthy controls.

Fig.2-1. Functional connectivity between 16 ROIs of the thalamus and superior and middle temporal gyrus.

Fig.2-2. Cluster 1

Fig.2-3. Cluster 2

Fig.2-4. Cluster 3

Fig.2-5. Cluster 4

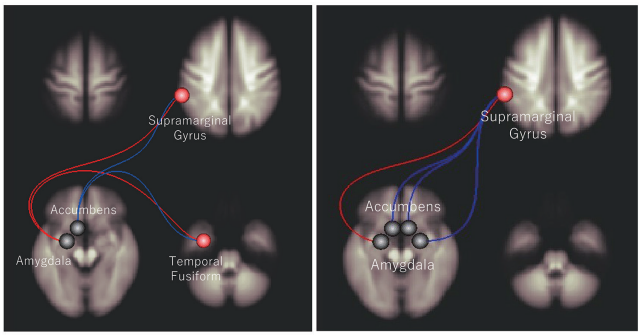

Fig.3. Relationship between positive symptom and functional connectivity.

In positive symptom, connectivity between the left amygdala and left nucleus accumbens and the left fusiform gyrus and left supramarginal gyrus was positively associated with symptom severity. Connectivity between the bilateral amygdala and bilateral nucleus accumbens and the left fusiform gyrus was positively associated with symptom severity.

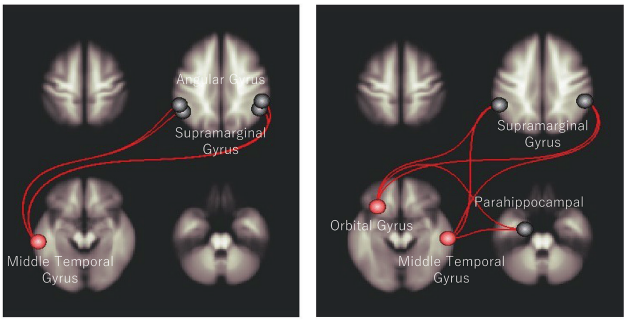

Fig.4. Relationship between disorganized symptom and functional connectivity.

In disorganized symptom, connectivity between the bilateral angular and supramarginal gyrus and the left middle temporal gyrus was positively associated with symptom severity. Connectivity between the bilateral supramarginal and left parahippocampal gyrus and the left orbital gyrus and right middle temporal gyrus was positively associated with symptom severity.

symptoms that may reflect the primary pathophysiology of schizophrenia. The severity of positive symptoms was positively associated with connectivity between the left amygdala/left nucleus accumbens and the left fusiform gyrus ($F[2,39] = 10.16$; p-FDR = 0.045472) and left supramarginal gyrus ($F[2,39] = 9.09$; p-FDR = 0.046553). The severity of positive symptoms was also positively associated with connectivity between the bilateral amygdala/bilateral nucleus accumbens and the left fusiform gyrus ($F[4,37] = 7.19$; p-FDR = 0.035028) (Fig. 3). No brain regions were significantly associated with negative symptoms.

For disorganized symptoms, connectivity between the bilateral angular gyrus/supramarginal gyrus and left middle

temporal gyrus (F[4,37] = 8.90; p-FDR = 0.006183) was positively associated with symptom severity. Connectivity between the bilateral supramarginal/left parahippocampal gyri and the left orbital gyrus (F[3,38] = 7.43, p-FDR = 0.049323) and right middle temporal gyrus (F[3,38] = 7.19; p-FDR = 0.049323) was also positively associated with symptom severity (Fig. 4).

Discussion

The results of the between-group comparison showed increased connectivity between the thalamus and superior and middle temporal gyri in the schizophrenia group. The efficient processing of sensory information may be due to the regulation between the thalamus and cortex, which may be impaired in schizophrenia (21). Increased connectivity of thalamus-related networks has also been positively associated with positive symptoms (10). Activation of the left superior and middle temporal gyri has been reported during auditory hallucinations and has been correlated with decreased gray matter volume in these regions (22).

The temporoparietal transition area is also considered an important part of the social brain (23), and a report has previously demonstrated that gray matter volume in the left superior temporal sulcus region is associated with impaired social interaction (24). In conclusion, the abnormal connectivity between the thalamus and the middle and superior temporal gyri shown in the present study may be involved in auditory hallucinations and social impairment, which are symptoms of schizophrenia. In addition, decreased connectivity between the thalamus and superior and middle temporal gyri may indicate decreased connectivity between the hemispheres. Previous rs-fMRI studies have shown that decreased interhemispheric connectivity is associated with the development of schizophrenia (11, 25, 26). In addition, a significantly higher rate of loss of interthalamic bridges has been observed in patients with schizophrenia (27), which may be a factor contributing to the decreased bilateral interthalamic connectivity observed in the present study. The temporal lobe is closely associated with auditory hallucinations (10, 28), suggesting that decreased interhemispheric connectivity in these regions is involved in the onset of hallucinations. However, interhemispheric connectivity may change depending on the disease stage (25); thus, the relationship between interhemispheric connectivity and the course of the disease, such as the number of years of illness, may need to be examined. The inclusion of three left-handed subjects in the schizophrenia group may have influenced the results, but no clear difference was observed when the two groups were compared after excluding the three left-handed subjects.

In the association between connectivity and clinical symptoms in the schizophrenia group, positive symptoms involved the fusiform and supramarginal gyri and functional brain regions, such as the amygdala and nucleus accumbens. The fusiform gyrus plays an important role in visual and sensory processing, indicating that abnormal sensory processing and speech recognition may contribute to auditory hallucinations (29). The amygdala and nucleus accumbens are emotion-related regions; the association between these regions and positive symptoms, such as hallucinations and delusions, and emotional changes, such as anxiety, agitation, and aggression, may be related to the development of schizophrenia. Previous studies have reported a positive correlation between left amygdala activity and positive symptoms; however, patients who exhibited flat affects have also shown weak amygdala activation (30). Therefore, the influence of disease stage, disease type, and medication on functional connectivity cannot be ruled out. The decreased connectivity between the temporal lobes in the two-group comparison may be related to positive symptoms such as auditory hallucinations. However, no direct association was observed between the temporal lobes and positive symptoms. Positive symptoms have also been associated with abnormal connectivity of the default mode, frontoparietal, and salience networks (7, 31-33), but no association has been found between positive symptoms and the orbitofrontal cortex, anterior and posterior cingulate gyri, or superior parietal lobes. The angular, supramarginal, parahippocampal, and middle temporal gyri were involved in disorganized symptoms. The parietal association cortex, which includes the angular and supramarginal gyri, is responsible for collecting, consolidating, and integrating information from numerous sensory areas, including visual, auditory, and somatosensory, into perceptual information, which is then abstracted and conceptualized (34). The abnormal connectivity observed in the present study between the middle temporal gyrus and these areas involved in cognitive processing is consistent with the severity of disorganized symptoms, which are composed of conceptual integration disorders. In the present study, we found an association between disorganized symptoms and abnormal connectivity of the angular and parahippocampal gyri. These results confirm those of several previous reports, including reduced activation of the right angular gyrus during social cognition-based tasks (35) and the association between abnormal activity or connectivity in the parahippocampal gyrus and misperceptions regarding information storage and extraction in patients with schizophrenia (25).

The reason why the present study did not find a brain region associated with negative symptoms may be because approximately half of patients (22 patients) had a disease duration of 5 years or less, 10 patients had disease onset within 1 year, which means that relatively more patients had acute disease, while fewer patients

showed strong negative symptoms that became more prominent in the chronic phase. In fact, the mean score for negative symptoms was not high, and few patients with pronounced negative symptoms were found in the population.

One limitation of the present study is the difference in the length of education between the healthy control and schizophrenia groups. The difference was due to the inclusion of more medical students and health care workers in the former. Therefore, differences in educational level may have affected the results. In addition, the effects of the duration of illness and history of antipsychotic treatment were not examined in the schizophrenia group. Therefore, changes in symptoms and brain structure due to chronicity of illness and antipsychotic medication were not analyzed in the study. In particular, the possibility that antipsychotics may affect functional connectivity in the amygdala has been previously reported (36), and the possibility that antipsychotics may affect functional connectivity cannot be ruled out.

In conclusion, comparisons between healthy controls and patients with schizophrenia showed increased thalamus-temporal lobe connectivity and decreased thalamus-temporal lobe hemispheric connectivity in patients with schizophrenia. These results suggest that sensory information and language-related areas are associated with the development of schizophrenia. In relation to clinical symptoms in the patient group, connectivity between the fusiform, supramarginal, and parahippocampal gyri and the amygdala and nucleus accumbens was associated with symptom severity in positive symptoms. Furthermore, connectivity between the angular, supramarginal, and parahippocampal gyri and the middle temporal and orbital gyri was associated with severity of disorganized symptoms. Our results suggest that temporal lobe and limbic system functions are involved in the development of the core symptoms of schizophrenia, such as positive and disorganized symptoms.

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Disclosure of conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

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