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The Structural Covariance Analysis in Schizophrenia Patients: A Multisite Study Utilizing T1-Weighted Image

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Multiple brain imaging parameters have been used to study the pathophysiology of schizophrenia; however, the difficulties in data collection often limit the size of the sample. The purpose of this study was to compare the brain networks of schizophrenia patients and healthy controls using structural covariance analysis of datasets from multiple sites. We obtained a total sample of 652 patients and 415 healthy controls. When comparing schizophrenia patients and controls, 36 correlation coefficients between two ROIs exhibited significant group difference, including 23 out of the 68 brain regions defined in this study. The brain regions that demonstrated between-group differences in structural covariance were also associated with the symptom severity of schizophrenia and deficits in neurocognitive function in the patient group. Rather than focusing solely on brain deterioration and reduction to understand schizophrenia, the results of this study emphasize the need to consider the complex patterns of brain networks and explore how these structural relationships correlate with the clinical symptoms and cognitive impairment in schizophrenia patients.

Keywords: schizophrenia, neuroimaging, structural covariance, t1-weighted image

Introduction

Schizophrenia is a major psychiatric disorder characterized by psychotic symptoms such as delusions and hallucinations, disorganized speech and behavior, as well as negative symptoms such as avolition and anhedonia. Research using structural and functional brain imaging has previously shown significant differences between the brains of patients with schizophrenia and those without (Honea et al., 2005; Van Den Heuvel & Fornito, 2014; Wannan et al., 2019; Wright et al., 2000).

Neuroimaging studies have also shown that patients with schizophrenia have abnormalities in their brain networks (Fitzsimmons et al., 2013; Lynall et al., 2010; Pankow et al., 2015; Yang et al., 2014). These changes go beyond the overall reduction and degeneration of the brain to include a complex pattern of change in brain connectivity (Jo et al., 2020; Joo et al., 2021; Ribolsi et al., 2014; Skudlarski et al., 2010). These differences are associated with clinical and functional changes in schizophrenia patients, which means that abnormalities in the brain network are possibly linked to the symptoms

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and cognitive impairment of the disorder (Ehrlich et al., 2012; Prasad et al., 2022a). However, neuroimaging studies have often been limited by sample sizes (Prasad et al., 2022a, 2022b; Van Den Heuvel & Fornito, 2014). A larger sample size achieved by merging multisite data will permit the study's replicability (Schnack et al., 2010).

We used structural covariance analysis to study brain networks with T1-weighted images. T1-weighted images have a high resolution and are widely available, making them a valuable tool for studying the brain in larger sample sizes. Structural covariance analysis assumes that brain areas are significantly correlated if a morphological measure in one brain region covaries with another. With structural covariance analysis of T1-weighted images, previous research studied brain networks using morphometric parameters, such as gray matter volume and cortical thickness (Alexander-Bloch et al., 2013; Mechelli et al., 2005).

This research was designed to compare the brains of schizophrenia patients and normal controls and find the anatomical regions where structural covariance revealed significant differences between the two groups. We also examined the correlation between cortical thickness of the selected brain regions, clinical symptoms, and cognitive function in schizophrenia patients to explore the association between the differences in the brain and the symptomatic aspects of schizophrenia.

Methods

Study Participants and Image Processing

This research used datasets from four study sites: Asan Medical Center (AMC), Jeonbuk University Hospital (JUH), Center of Biomedical Research Excellence (COBRE), and the University of California Los Angeles Consortium for Neuropsychiatric Phenomics LA5c Study (UCLA). We sought to achieve a homogeneous patient population and excluded patients diagnosed with schizophrenia spectrum disorders apart from schizophrenia.

All brain images were visually inspected for image quality control, and we excluded subjects whose signal dropouts or artifacts prevented further analysis. T1-weighted images underwent parcellation and segmentation using FreeSurfer ver. 7.1. A total of 68 ROIs were defined using the Desikan-Killiany atlas. The cortical thickness of each ROI was automatically estimated using FreeSurfer, and the standard deviation of cortical thickness was considered as the variability of cortical thickness.

Data collection from all four study sites was approved by the relevant Institutional Review Boards (IRBs) and followed the Declaration of Helsinki guidelines. AMC IRB approved the current study (IRB Number: 2021-0423).

AMC

Study participants were recruited from Asan Medical Center, Seoul, Korea. Data collection was approved by the Institutional Review Board of Asan Medical Center (2012-0485). The schizophrenia diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria, and healthy controls were defined as those without any diagnosis of Axis I disorders and without any first-degree relative diagnosed with Axis I disorders. All brain images were acquired using a 3T scanner with an 8-channel SENSE head coil (Achieva; Philips Healthcare, Best, The Netherlands). T1-weighted images were acquired using a turbo field echo sequence (TR[repetition time]/TE[echo time] = 4.9/4.6 ms; field of view = 240 × 240 × 170 mm; and voxel size = 1 mm^3).

JUH

Study participants were recruited from Jeonbuk University Hospital, Jeonju, Korea. Schizophrenia diagnoses were based on DSM-IV-TR, according to the Structured Clinical Interview for DSM-IV (SCID). Patients with drug or alcohol dependence within the previous six months, and those with intellectual disabilities, serious medical illnesses, neurological disorders, or pregnancy were excluded. Healthy controls were defined as those without prior or present mental illness, neurological disease, or significant medical condition. This study was approved by the Institutional Review Board of JUH. Brain images were acquired using a 3T scanner (MAGNETOM Verio; Siemens, Erlangen, Germany).

COBRE

The COBRE project integrates data acquired using multiple neuroimaging techniques and psychiatric, neuropsychological, and genetic test measures. We obtained publicly available data from SchizConnect (http://schizconnect.org) (Wang, 2016). Diag-

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nostic information regarding schizophrenia was collected using the Structured Clinical Interview used for DSM disorders (SCID). Brain imaging was conducted using a 3T scanner (Trio, Siemens Healthcare, Erlangen, Germany). T1-weighted images were collected using a multi-echo MPRAGE sequence (TE = 1.64, 3.5, 5.36, 7.22, and 9.09 ms; TR = 2.53 s; TI = 1.2 s; flip angle = 7°; number of excitations = 1; slice thickness = 1 mm; field of view = 265 mm; and resolution = 256 × 256).

UCLA

The UCLA project compares the dimensional structure of memory and cognitive control functions in healthy individuals and psychiatric patients. We obtained the dataset of this project from OpenNeuro (https://openneuro.org) with accession number ds000030. The diagnosis was made based on DSM-IV-TR, using the Structured Clinical Interview for DSM-IV (SCID). A 3T scanner was used to image the brain (Trio, Siemens Healthcare, Erlangen, Germany), and T1-weighted images were collected using an MPRAGE sequence (TE = 34 ms; TR = 5,000 ms; flip angle = 90°; slice thickness = 1 mm; field of view = 250 mm; and matrix = 256 × 256).

Measurement of Symptoms and Neurocognitive Function

The psychiatric symptoms and neurocognitive functions of both schizophrenia patients and normal controls were examined using standardized tools. The Positive and Negative Syndrome Scale (PANSS) measured the severity of psychiatric symptoms of the patients (Kay et al., 1987). In the UCLA project, the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were used instead of PANSS (Andreasen, 1984, 1989). We converted the SAPS and SANS scores into PANSS scores using equations validated by previous studies (Van Erp et al., 2014).

We used the outcome measures that were included in common for each dataset: Wechsler Adult Intelligence Scale-IV (WAIS-IV), the Vocabulary and Block Design subtest of the Wechsler Abbreviated Scale of Intelligence-II, the Phonemic Fluency Test, the Category Fluency Test, the Auditory Continuous Performance Test (CPT), and Part 1 of the Color Trails Test (CTT-1) or Part A of the Trails Making Test (TMT-A).

Statistical Analyses

All statistical analyses were performed using R (ver. 4.1.3), and statistical significance was set as $p < .05$. Comparisons of demographic measures between the patient and control groups were made using Welch's *t-test*, except for categorical variables such as sex, which underwent a Chi-squared test. We compared neurocognitive test scores between groups using linear regression, adjusting for age, sex, years of education, and illness duration. Multiple comparisons were adjusted by Bonferroni correction.

For the brain imaging data, a correlation matrix of the cortical thickness of 68 ROIs from the Desikan-Killiany atlas was constructed for the patient and control groups, adjusting for sex and age. Cortical thickness was the common brain morphological data available for individual subjects across the datasets. This yields a 68 × 68 correlation matrix for each group, showing how each brain region covaries with other regions. We compared the correlation coefficients in these matrices between the schizophrenia patient and control groups using Fisher's *Z-test*. Then, using the cortical thickness of the brain regions that survived this comparison between structural covariance, we analyzed its association with the clinical characteristics of schizophrenia to search for a link between the brain characteristics and the symptoms and cognitive function in schizophrenia patients. The latter part of the analysis involving the clinical characteristics of schizophrenia was undertaken only for the patient group.

Table 1. *Demographic and Clinical Characteristics of Participants*

	Patients (n = 652)	Controls (n = 415)	t / χ^2	adjusted p
	Mean [Standard deviation]			
Age	36.5 [12.6]	35.5 [11.4]	-1.306	.192
Sex (male)	344	235	1.375	.241
Education (years)	13.1 [2.76] (n = 597)	14.5 [2.04] (n = 392)	8.919	< .001
Duration of illness (years)	9.24 [9.94] (n = 583)	-		
PANSS-P	13.7 [5.96] (n = 651)	-		
PANSS-N	12.3 [5.85] (n = 594)	-		
PANSS-G	26.6 [7.80] (n = 547)	-		
PANSS-Total	52.0 [16.3] (n = 547)	-		

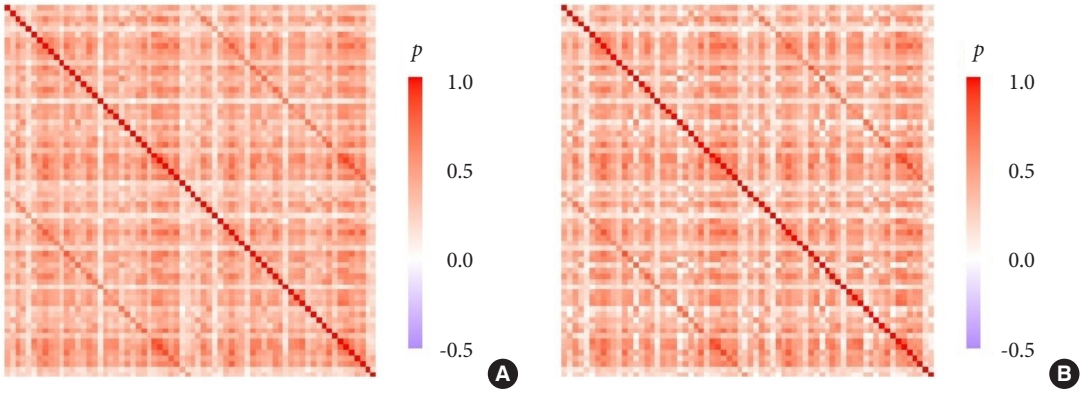

Figure 1. *Correlation matrices between the cortical thickness of 68×68 ROIs. (A) is the correlation matrix of patients with schizophrenia; (B) is that of normal controls.*

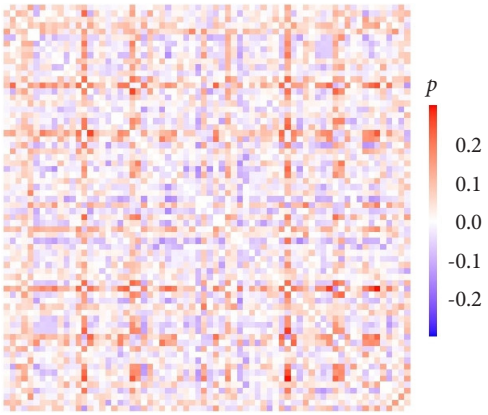

Figure 2. *The between-group difference (Patients-Controls) of correlation matrices between each ROIs, in a matrix form of 68×68.*

Results

Demographics

The final study sample included 652 patients with schizophrenia and 415 healthy controls: 48 patients and 23 healthy controls from AMC, 501 patients and 204 healthy controls from JUH, 57 patients and 73 healthy controls from COBRE, and 46 patients and 115 healthy controls from UCLA. The average duration of illness was 9.2 years for the schizophrenia patient group, and the average total PANSS score was 52.0. There were no significant differences between the schizophrenia and control groups in age and sex, but the patients with schizophrenia received less education than the controls ($p < .001$). More demographic information is provided in Table 1.

Structural Covariance Analysis

The correlation matrix for each group was created by structural covariance analysis, as depicted in Figure 1. Figure 1(A) shows the correlation matrix of the 68 brain regions of patients with schizophrenia, and Figure 1(B) shows that of normal controls. Figure 2 depicts the difference in correlation coefficients between brain regions in the schizophrenia patient and control groups (Patient-Control).

Significant explanatory power is provided by the structural covariance of brain regions that differs between patients and controls. A total of 36 correlation coefficients between two brain ROIs showed a significant group difference after Bonferroni correction for multiple comparisons ($p < .001$). The group differences found in structural covariance consisted of 23 brain ROIs among the 68 brain regions used in this study (Table 2).

Association Between Significant Brain Regions and Clinical Characteristics

This part of the analysis examined whether brain characteristics in the selected brain regions were also associated with clinical features in schizophrenia patients, using the cortical thickness of the 23 brain regions that survived structural covariance analysis. The following part of the analysis involved only the schizophrenia patient group.

Symptoms of Schizophrenia

Using the brain regions selected from structural covariance analysis, there was a significant correlation between the cortical thickness of several brain areas and PANSS scores (Table 3). Negative

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Table 2. *Significant Differences in Structural Covariance*

ROI – ROI	*rho* (Patient-Control)	adjusted *p*
Rt lingual cortex – Rt superior frontal cortex	.298	< .001
Rt lingual cortex – Rt pars triangularis	.272	< .001
Lt medial orbitofrontal cortex – Lt pericalcarine cortex	.265	< .001
Rt lingual cortex – Rt rostral middle frontal cortex	.252	< .001
Lt lingual cortex – Rt superior frontal cortex	.250	< .001
Lt pericalcarine cortex – Rt superior frontal cortex	.243	< .001
Lt pars triangularis- Rt lingual cortex	.232	< .001
Lt medial orbitofrontal – Rt pericalcarine cortex	.229	< .001
Rt pericalcarine cortex – Rt superior frontal cortex	.228	< .001
Lt lingual cortex – Rt pars triangularis	.228	< .001
Lt lingual cortex- Rt caudal anterior cingulate cortex	.227	< .001
Rt medial orbitofrontal cortex – Rt postcentral cortex	.225	< .001
Rt lateral orbitofrontal cortex – Rt pericalcarine cortex	.225	< .001
Lt lateral orbitofrontal cortex – Rt lingual cortex	.224	< .001
Lt caudal anterior cingulate – Lt lingual cortex	.224	< .001
Rt lateral orbitofrontal cortex – Lt pericalcarine cortex	.223	< .001
Lt rostral middle frontal cortex – Rt lingual cortex	.223	< .001
Lt lingual cortex – Lt lateral orbitofrontal cortex	.219	< .001
Lt lingual cortex – Rt lateral orbitofrontal cortex	.217	< .001
Lt lingual cortex – Rt rostral middle frontal cortex	.217	< .001
Rt caudal anterior cingulate – Rt pericalcarine cortex	.214	< .001
Rt lateral orbitofrontal cortex – Rt lingual cortex	.213	< .001
Rt lingual cortex – Lt medial orbitofrontal cortex	.210	< .001
Rt lingual cortex – Rt frontal pole	.208	< .001
Lt lateral orbitofrontal cortex – Lt pericalcarine cortex	.208	< .001
Rt superior temporal cortex – Lt lingual cortex	.207	< .001
Lt pars orbitalis- Rt lingual cortex	.207	< .001
Lt fusiform cortex – Lt lingual cortex	.205	< .001
Rt lingual cortex – Rt medial orbitofrontal cortex	.205	< .001
Lt lingual cortex – Lt pars triangularis	.204	< .001
Rt postcentral – Ltrostralanteriorcingulate cortex	.202	< .001
Rt lingual cortex – Lt inferior temporal cortex	.201	< .001
Rt lingual cortex – Rt superior temporal cortex	.197	< .001
Lt fusiform cortex – Rt lingual cortex	.180	< .001
Rt superior frontal cortex – Rt superior parietal cortex	.130	< .001
Lt rostral middle frontal – Lt inferior temporal cortex	-.146	< .001

Note. Rt = right; Lt = left.

symptoms of schizophrenia (PANSS-N) were associated with a reduction in cortical thickness in the left and right rostral middle frontal cortex, left inferior temporal cortex, pars orbitalis, rostral anterior cingulate, right frontal pole, lateral orbitofrontal cortex, medial orbitofrontal cortex, pars triangularis, superior frontal, parietal, and temporal cortices. The composite PANSS score was negatively correlated with cortical thickness in the left rostral middle frontal cortex, right frontal pole, and superior frontal cortex.

Neurocognitive Function

Significant differences were found between the schizophrenia and control groups when measuring neurocognitive functions, adjusting for age, sex, years of education and duration of illness, as presented in Table 4 ($p < .001$). Patients with schizophrenia had lower full-scale IQ (FSIQ) and subtest scores on the Vocabulary and Block Design in the Wechsler Intelligence Tests. These patients also scored lower on both the Phonemic and Category Fluency tests.

More omission and commission errors on the auditory CPT were found in schizophrenia patients, but there was no significant difference between the groups when comparing CPT reaction time. There was no group difference in the time spent completing CTT-1.

Age, sex, years of education, and the chronicity of the disorder as measured by years of duration were controlled as covariates in the analysis involving neurocognitive function and cortical thickness of the brain regions selected through structural covariance analysis. The correlation between cognitive function that showed significant group difference and cortical thickness of the chosen brain regions was significant in several ROIs (Table 5).

The FSIQ scores were negatively correlated with cortical thickness in the right medial orbitofrontal cortex and cuneus, while the Phonemic and Category Fluency test results were negatively correlated with the cortical thickness of the right pericalcarine cortex. CPT omission errors were negatively associated with cortical thickness in the left fusiform and lingual cortex, while CPT commission errors were also negatively correlated with cortical thickness in the left fusiform and lingual cortex, with the addition of the left inferior temporal cortex. The Block Design subtest was an exception, as it did not exhibit a significant association with any of the selected ROIs.

Table 3. *Cortical thickness of ROIs Correlated with Schizophrenia Symptoms*

Scale	ROI	*rho*	adjusted *p*
PANSS-N	Lt inferior temporal cortex	-.155	< .001
	Lt pars orbitalis	-.201	< .001
	Lt rostral anterior cingulate cortex	-.140	< .001
	Lt rostral middle frontal cortex	-.157	< .001
	Rt frontal pole	-.125	< .001
	Rt lateral orbitofrontal cortex	-.166	< .001
	Rt medial orbitofrontal cortex	-.122	< .001
	Rt pars triangularis	-.152	< .001
	Rt rostral middle frontal cortex	-.191	< .001
	Rt superior frontal cortex	-.217	< .001
	Rt superior parietal cortex	-.160	< .001
	Rt superior temporal cortex	-.171	< .001
PANSS-Total	Lt rostral middle frontal cortex	-.125	< .001
	Rt frontal pole	-.154	< .001
	Rt superior frontal cortex	-.121	< .001

Note. Rt = right; Lt = left; PANSS = Positive And Negative Syndrome Scale.

Discussion

This study analyzed differences in the structural covariance in the

Table 5. *Cortical thickness of ROIs Correlated with Neurocognitive Function in Patients*

Neurocognitive Test	ROI	*rho*	adjusted *p*
FSIQ	Right medial orbitofrontal cortex	-.330	.005
Phonemic fluency	Right pericalcarine cortex	-.152	.007
Category fluency	Right pericalcarine cortex	-.130	.041
Auditory CPT:	Left fusiform cortex	-.138	.039
Omission Errors	Left lingual cortex	-.175	.002
Auditory CPT:	Left fusiform cortex	-.148	.019
Commission Errors	Left inferior temporal cortex	-.145	.023
	Left lingual cortex	-.157	.009

Note. Age, sex, years of education, and illness duration were included as covariates in this analysis.

Table 4. *Group Differences in Neurocognitive Measures*

	Patients (n = 652)	Controls (n = 415)	t	adjusted p
	Mean [Standard deviation]			
FSIQ	90.9 [20.1] (n = 168)	113.8 [11.9] (n = 96)	7.073	< .001
Vocabulary test	31.7 [11.9] (n = 94)	44.2 [8.53] (n = 138)	5.134	< .001
Block design test	36.1 [15.7] (n = 105)	50.3 [13.7] (n = 96)	4.530	< .001
Phonemic fluency	28.6 [12.2] (n = 575)	38.1 [11.4] (n = 296)	11.055	< .001
Category fluency	15.3 [5.01] (n = 536)	21.0 [5.24] (n = 276)	14.503	< .001
Auditory CPT: Omission Errors	18.5 [22.9] (n = 526)	5.48 [7.61] (n = 224)	-7.101	< .001
Auditory CPT: Commission Errors	12.2 [14.0] (n = 526)	4.42 [7.27] (n = 224)	-6.651	< .001
Auditory CPT: Reaction Time	0.767 [0.725] (n = 526)	0.721 [0.0607] (n = 224)	-0.970	.332
CTT-1	41.1 [31.8] (n = 179)	28.4 [11.4] (n = 206)	-1.554	.121

Note. Age, sex, years of education, and illness duration were included as covariates in this analysis.

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brains of patients with schizophrenia compared to healthy controls. We successfully built a conceptual brain network via structural covariance analysis and acquired a large study sample by merging T1-weighted images from multiple study sites. The main finding of this study is that schizophrenia patients have a different pattern of structural covariance compared to healthy controls. Significant differences in the correlation between the two ROIs were found in 23 brain regions. Cortical thickness of the brain areas that survived the structural covariance analysis further showed a negative correlation with symptom severity and a mixed relationship with neurocognitive function in the schizophrenia patient group.

Structural covariance analysis revealed that patients with schizophrenia have a significant difference from healthy controls in the ROI-to-ROI correlation, including 23 brain regions that encompass parts of the frontal, temporal, and parietal areas, the lingual cortex, and anterior cingulate cortex. Previous research has found increased structural covariance in regions with significant cortical thickness reductions in chronic and treatment-resistant schizophrenia patients compared with healthy controls (Wannan et al., 2019). These brain regions also overlap with findings from previous research that showed structural and functional brain abnormalities in schizophrenia patients across different imaging parameters (Kim et al., 2019; Oertel-Knöchel et al., 2013; Van Erp et al., 2018).

Among the statistically significant correlation coefficients, the lingual cortex appeared most frequently and exhibited large effect sizes. The lingual cortex in patients with schizophrenia has been found to have reduced gray matter volume and cortical thickness, and is also suggested to be associated with problems in cortical maturation in relation to the disorder (Horn et al., 2010; Schultz et al., 2010a; Schultz et al., 2020b). This region is also found to hyperactivate during the resting-state in schizophrenia patients compared to normal controls even though the functional meaning remains unclear, and an altered activity in the lingual cortex in cortical regions was related to formal thought disorder (Cavelti et al., 2018; Kühn & Gallinat, 2013). The results of this study suggest that the lingual cortex may be an important feature in how the brain networks differ in schizophrenia patients compared to those without the disease.

The frontal lobe of the brain, such as the medial and lateral orbitofrontal cortex, superior frontal cortex, and rostral middle frontal cortex, also frequently showed a significant group difference in structural covariance with other brain regions. These results are consistent with prior research showing that the frontal regions of patients with schizophrenia have the greatest differences in brain structure and function compared to the normal population (Fitzsimmons et al., 2013; Kim et al., 2020; Van Erp et al., 2018; Wannan et al., 2019).

Also of note is that regarding the frontal areas of the brain, there was a significant difference in structural covariance either with the lingual cortex or the pericalcarine cortex. Stronger long-range connections between the lingual and prefrontal gyri were previously found in schizophrenia patients, supporting the above phenomenon in this study (Wang et al., 2014). The connotation of this correlation needs further study, and future research would be able to explore the role of, and the complex relationship between, brain regions in the pathophysiology of schizophrenia, focusing on the regions found in this study.

The severity of schizophrenia symptoms strongly correlated with the cortical thickness of the brain regions that survived the between-group structural covariance analysis and many brain regions exhibited a negative correlation with the negative symptoms of schizophrenia (PANSS-N). Although few studies specifically focus on finding the neural correlates of negative symptoms of schizophrenia, the prefrontal deficit is often pointed out as being related to the pathology, while the chronicity of the negative symptoms in turn may influence brain morphology and function (Hare et al., 2019; Walton et al., 2018). The results of this study also add to the importance of negative symptoms of schizophrenia in relation to the brain abnormalities found in patients with schizophrenia.

The symptom severity in general as measured by PANSS total score was correlated to the cortical thickness in the left rostral middle frontal cortex, right frontal pole, and superior frontal cortex, all three of which were also associated with PANSS-N scores. This suggests the importance of frontal areas in the symptomatology of schizophrenia, as established by other studies (Oertel-Knöchel et al., 2013; Schultz et al., 2010b; Van Erp et al., 2018). The prefrontal cortex and cortical midline structures located in the frontal lobe have shown robust associations with impaired self-reference in patients with schizophrenia, indicating the possible role of these brain regions in psychotic symptoms (Larivière et al.,

2017; Raju et al., 2021).

Patients with schizophrenia also experience cognitive impairment, significantly affecting their ability to function normally (Fett et al., 2011; Hill et al., 2013; Schaefer et al., 2013). Auditory CPT omission and commission errors, implying deficits in sustained attention, were negatively connected with cortical thickness in the lingual, fusiform, and temporal cortex, among the brain regions that explained the group differences in the brain network. Attention is one of the core cognitive deficits in schizophrenia, and is the foundation of many intelligent activities (Elvevåg & Goldberg, 2000; Knowles et al., 2010). In short, this study found that attentional problems in schizophrenia patients were linked to some brain regions that have significant group difference in structural covariance. This suggests that clinical outcomes are also associated with brain network differences.

Negative correlation was found between the right medial orbitofrontal cortex and the full-scale IQ, and the right pericalcarine cortex and Phonemic and Category Fluency test scores. One reason for this discrepancy may lie in the relatively small number of participants who completed all the neurocognitive measures analyzed in the study, and the relationships between the cortical thickness and cognitive function may vary in their strength. These results need to be interpreted with caution, and further research equipped with more data and adjusting for the limitations listed below is needed.

There are limitations to this study. The subjects studied in the COBRE project and UCLA datasets were predominantly Caucasian, while those in AMC and JUH were Korean. Although structural covariance analysis calculates and reduces data into a group-level matrix, ethnicity can lead to substantial differences in brain measurements, including cortical thickness (Kang et al., 2020).

The study also did not consider the age at schizophrenia onset and chronicity of the disease in the structural covariance analysis. These factors can lead to different results in morphological characteristics and the structural covariance of the brain and may provide a chronological aspect of the pathophysiology of schizophrenia. Regarding the potential effect on the brains of schizophrenia patients, medication history was also not accounted for in the present study.

Instead of standardized scores, raw scores were used in this study due to the lack of sufficient information for each neurocognitive test. Although analyses involving neurocognitive test data were adjusted for sex, age, years of education, and illness duration, this is a weakness of this study. Also, since the multiple datasets had little overlapping neurocognitive data, only limited aspects of cognitive function were covered in this study. Essential abilities regarding the daily life of schizophrenia patients, such as executive function, were not included.

In conclusion, this study suggests that schizophrenia may have a complex pathophysiology involving significant differences in structural covariance among different brain regions, rather than simple deterioration or reduction in brain structure and function. Structural covariance analysis is an effective and valuable method for studying and analyzing brain imaging data from large sample sizes and allows for more reproducible and reliable research on schizophrenia's brain network. Cortical thickness of the brain areas found to account for the differences between the patient and control groups was negatively correlated with symptom severity of the disease and sustained attention, providing a link between brain characteristics and the clinical aspects of schizophrenia.

Author contributions statement

EL, a clinical psychology resident in the Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, statistically analyzed the data and wrote the original manuscript. SWJ and HK, who are clinical fellows, SA, YC, and WC, who are residents of the Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, participated in data collection and data curation. JSL, a professor in the Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, was the principal investigator and supervised the research process. JYC, a professor in the Department of Psychiatry, Jeonbuk National University Hospital, Jeonbuk National University Medical School, supervised data collection and image processing. YTJ, previously a clinical fellow in the Department of Psychiatry at Asan Medical Hospital, University of Ulsan College of Medicine, now a clinical assistant professor in the Department of Psychiatry, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, collected data from multiple study sites, significantly contributed to data analysis and interpretation, and reviewed and finalized the manuscript. All authors provided critical feedback, participated in the revision of the manuscript, and approved the final submission.

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