Structural variability of the cerebral cortex in schizophrenia and its association with clinical symptoms

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Abstract

Background. Substantial evidence indicates structural abnormalities in the cerebral cortex of patients with schizophrenia (SCZ), although their clinical implications remain unclear. Previous case-control studies have investigated group-level differences in structural abnormalities, although the study design cannot account for interindividual differences. Recent research has focused on the association between the heterogeneity of the cerebral cortex morphometric features and clinical heterogeneity.

Methods. We used neuroimaging data from 420 healthy controls and 695 patients with SCZ from seven studies. Four cerebral cortex measures were obtained: surface area, gray matter volume, thickness, and local gyrification index. We calculated the coefficient of variation (CV) and person-based similarity index (PBSI) scores and performed group comparisons. Associations between the PBSI scores and cognitive functions were evaluated using Spearman's rho test and normative modeling.

Results. Patients with SCZ had a greater CV of surface area and cortical thickness than those of healthy controls. All PBSI scores across cortical measures were lower in patients with SCZ than in HCs. In the patient group, the PBSI scores for gray matter volume and all cortical measures taken together positively correlated with the full-scale IQ scores. Patients with deviant PBSI scores for gray matter volume and all cortical measures taken together had lower full-scale IQ scores than those of other patients.

Conclusions. The cerebral cortex in patients with SCZ showed greater regional and global structural variability than that in healthy controls. Patients with deviant similarity of cortical structural profiles exhibited a lower general intelligence than those exhibited by the other patients.

Introduction

Schizophrenia is a lifelong illness characterized by delusions, hallucinations, and cognitive impairment. Although Emil Kraepelin emphasized chronic course and poor prognosis as core features of schizophrenia (Adityanjee, Aderibigbe, Theodoridis, & Vieweg, 1999), considerable heterogeneity in the clinical manifestations and long-term course of the disease has been reported. A recent study with an approximately 30-year follow-up of patients with schizophrenia showed a heterogeneous long-term course, in which a small but notable proportion of patients experienced premature death and needed long-term support, whereas most patients lived in the community (Baltazar, De Benedictis, Abdel-Baki, Lalonde, & Lesage, 2022). Several studies have proposed patient subgroups according to the necessity of long-term antipsychotic treatments and treatment responses to antipsychotic medications. A subgroup of patients with schizophrenia who maintained recovery for several years without antipsychotic medications has been reported, whereas the majority of treatment guidelines for schizophrenia recommend long-term antipsychotic treatment for patients with multiple episodes (Correll et al., 2022; Jobe & Harrow, 2010). Categorizing patients with schizophrenia based on the resistance to antipsychotic drugs and response to clozapine has been suggested (Lee et al., 2015). Various clinical manifestations and disease courses within the same diagnosis suggest that distinct subgroups of patients with different biological predispositions have the same disorder. Studies have revealed the biological underpinnings of clinical heterogeneity, using brain morphometric features (Chand et al., 2020; Dwyer et al., 2018; Voineskos et al., 2013). However, there is no consensus on the classification of patients with schizophrenia based on morphometric features.

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Structural abnormalities of cortical structures in schizophrenia have been consistently reported. A large-scale study found that patients with schizophrenia have globally reduced thickness and surface area of the cerebral cortex, with pronounced effect sizes for decreased cortical thickness in the frontal and temporal lobe regions (van Erp et al., 2018). Associations between the cortical abnormalities and positive and negative symptoms of schizophrenia have also been reported. Two large-scale meta-analyses reported that positive and negative symptoms correlated with cortical thickness in the superior temporal gyrus and left medial orbitofrontal area, respectively (Walton et al., 2017, 2018). Despite substantial evidence of structural abnormalities in the cerebral cortex in schizophrenia, its usefulness in clinical practice remains limited, likely owing to a large variation in morphometric features within the same diagnosis, that is, schizophrenia. Neuroimaging studies have investigated group-level differences in brain morphometric measures (Thompson et al., 2020). The primary goal of this case-control approach was to identify reliable biomarkers of the disease based on the assumption that the patient and control groups were distinct entities. However, this method rarely accounts for interindividual differences and hinders the exploration of neural correlates to clinical heterogeneity of schizophrenia. Since interindividual differences have drawn attention as novel research topics (Foulkes & Blakemore, 2018; Seghier & Price, 2018), Wolfers et al. demonstrated that the group-level differences in brain cortical measures explain only a small proportion of the variance associated with schizophrenia (Wolfers et al., 2018, 2021). This indicates that the fundamental entity of a case-control design, the average patient, is non-informative at the individual level.

Recently, the variability in brain morphometric measures in patients with schizophrenia was examined using a novel metric, the person-based similarity index (PBSI). The metric quantifies the similarity of the individual's cortical and subcortical profiles within the same diagnostic group (Antoniades et al., 2021; Doucet, Glahn, & Frangou, 2020a; Doucet et al., 2020b). Studies have reported that patients with schizophrenia have lower PBSI scores for cortical thickness than those of healthy controls, and a small subset of patients with markedly deviant PBSI scores for sulcal width exhibit impaired cognitive performance (Doucet, 2020b; Janssen et al., 2021). The PBSI scores for cortical thickness, surface area, and subcortical volume are lower in patients with first-episode psychosis than in healthy controls (Antoniades et al., 2021). Despite the novelty of previous studies in investigating the heterogeneity of cortical and subcortical measures at the individual profile level, the following limit their generalizability: a relatively small sample size, limited association of the PBSI score with clinical symptoms, and use of a few conventional cortical measures. Therefore, replication and extension of the previous results are warranted.

In this study, we obtained neuroimaging data from seven studies to investigate the cerebral cortex structural variability in patients with schizophrenia when compared with healthy controls. ComBat harmonization was adopted to adjust for site differences in the neuroimaging data. We parcellated the cerebral cortex at a finer level than that of the atlas-based schemes and used the local gyrification index along with conventional morphometric measures. In comparison with age- and sex-matched healthy controls, we examined the global and regional variability of morphometric measures of the cerebral cortex in patients with schizophrenia and their association with clinical variables. We hypothesized that (1) patients with schizophrenia would have increased variability of morphometric measures of the cerebral cortex either globally or regionally, compared with healthy controls, and (2) in the patient group, a patient subset with marked deviations in terms of similarity of cortical structure profiles would exhibit poor clinical manifestations.

Methods

Study population

We included neuroimaging datasets acquired from two tertiary hospitals in the Republic of Korea, the Asan Medical Center (AMC) and Jeonbuk National University Hospital (JNUH). Several publicly available neuroimaging datasets were used in this study. From the SchizConnect database (http://schizconnect. org) (Wang et al., 2016), we obtained Center of Biomedical Research Excellence (COBRE), Neuromorphometry by Computer Algorithm Chicago (NMorphCH), MIND Clinical Imaging Consortium (MCIC), and Function Biomedical Informatics Research Network (fBIRN) datasets. Neuroimaging and clinical data from University of California Los Angeles Consortium for Neuropsychiatric Phenomics LA5c Study (UCLA) were downloaded from OpenNeuro (http://openneuro. org) with the accession number ds000030. We have briefly described the details of each neuroimaging dataset in the online Supplementary Materials. Further information on the public neuroimaging datasets is presented in the following: COBRE (Aine et al., 2017), NMorphCH (http://nunda.northwestern.edu/ nunda/data/projects/NmorphCH), MCIC (Gollub et al., 2013), fBIRN (Glover et al., 2012; Keator et al., 2016), and UCLA (Gorgolewski, Durnez, & Poldrack, 2017; Poldrack et al., 2016). The individual studies were approved by the local Institutional Review Board (IRB) and performed in accordance with the Declaration of Helsinki. The current study was approved by the IRB of the Asan Medical Center (IRB No. 2021-0423).

Clinical information, clinical symptoms, and cognitive functions

In the AMC and JNUH cohorts, the Positive and Negative Syndrome Scale (PANSS) was used to evaluate the severity of psychiatric symptoms of patients with schizophrenia. In the NMorphCH, MCIC, fBIRN, and UCLA datasets, the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were adopted. We converted the SAPS and SANS scores into the Positive and Negative Syndrome Scale (PANSS) positive and negative scores using validated equations (van Erp et al., 2014). Regarding neurocognitive functions, we selected the following neurocognitive tests, whose results were adjusted or t-scored and were available for a relatively large number of study participants: the full-scale intelligence quotient (IQ) test, color trails test 1 (CTT 1), and word fluency test. The full-scale IQ test assesses general intelligence. The CTT 1 test is developed as a culture-neutral equivalent to the Trail Making Test, which measures processing speed and executive function (Dugbartey, Townes, & Mahurin, 2000). The word fluency test is related to language deficits that are associated with executive functioning and processing speed within neuropsychiatric conditions (Harvey, 2019).

We utilized information on illness duration, positive and negative PANSS scores, and daily olanzapine equivalents in the patient

group. In both groups, the adjusted full-scale IQ scores and t scores for the CTT-1 and word fluency tests were used.

Image acquisition, preprocessing, and quality control

We obtained T1-weighted images from 540 healthy controls and 754 patients with schizophrenia from all the neuroimaging datasets. Information on the scanners and image parameters of the T1-weighted images is summarized in online Supplementary Table S1. Image analysis was performed using the FreeSurfer (version 7.1) automated pipeline (https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all) with the local GI command for the local gyrification index (Schaer et al., 2008). We included the local gyrification index because cortical gyrification is less affected by age (Sowell et al., 2003), disease processes (Cannon et al., 2015), and psychotropic drugs (Vita, De Peri, Deste, Barlati, & Sacchetti, 2015) than is the gray matter volume of the cerebral cortex. Given the better topological properties of the cortical network defined by a finer cortical scale compared to atlas-based schemes (Romero-Garcia, Atienza, Clemmensen, & Cantero, 2012), we applied an atlas with 308 cortical regions derived from the Desikan–Killiany atlas. Four morphometric features across 308 cortical structures were calculated: surface area, gray matter volume, thickness, and local gyrification index.

We performed ComBat harmonization to adjust the site differences and identified outliers on a criterion of the range of mean ± 3.5 S.D.s of each regional cortical measure across 308 cortical regions. For the age and sex matching between the control and patient groups, we subsampled the study participants in the fBIRN and UCLA datasets. We described details of the quality control processes in online Supplementary Materials. The demographic and clinical information of the final study population is presented in Table 1.

Regional variability of cortical measures

We calculated the coefficient of variation (CV) to estimate regional variability in cortical measures. The CV quantifies the extent of variability in relation to the mean of a sample. For each regional cortical measure, we calculated the CV within the same group using the following equation: CV = S.D./Mean, where Mean and S.D. denote the mean and standard deviation of the regional cortical measure, respectively.

Global variability of cortical measures

We calculated the PBSI scores to estimate the global variation in cortical measures within the same group. Following a procedure validated in previous studies (Antoniades et al., 2021; Doucet et al., 2019, 2020a, 2020b; Janssen et al., 2021), the PBSI score for the cortical measure was calculated within the same group. First, for each cortical measure, we concatenated the measurements of the 308 cortical structures into a single vector to generate a person-specific profile of cortical measures across the 308 cortical structures. In each group, the cortical structural profile of an individual correlated with the respective profiles of all other individuals within the same group using the Spearman's correlation coefficient rho. This process yielded $n - 1$ correlation coefficients per participant, where n is the number of participants in the same group. The correlation coefficients were then averaged to generate the PBSI score for the cortical measures (surface area, PBSI-SA score; gray matter volume, PBSI-GV score; thickness, PBSI-CT score; local gyrification

index, PBSI-LGI score). We also calculated the PBSI score using all cortical measures of the 308 cortical structures, a total of 1232 cortical measures per participant (PBSI-All score). To adjust for the different scales among the cortical measures, we converted the measures into z scores for each participant. The PBSI score indicates the similarity of the cortical structural profile of each participant to that of the other participants within the same group. Figure 1 illustrates the pipeline used to compute the PBSI score.

The Yeo and von Economo atlases were used to categorize the cortical structures into separate subnetworks. The atlases were based on functional magnetic resonance imaging (MRI) resting-state networks (Vasa et al., 2018; Yeo et al., 2011) and the cytoarchitectonic criteria of the cerebral cortex (Whitaker et al., 2016), respectively. We calculated the PBSI scores for the subnetworks defined by the Yeo and von Economo atlases to examine whether group differences in the PBSI scores remained in the subnetworks.

To test the robustness of the PBSI score on the effects of regional cortical measures, we applied bootstrap resampling in which the PBSI score was calculated using a randomly selected subset of 308 cortical structures in increments of 20, from 20 to 300 cortical regions. Calculation of the PBSI score was repeated 100 times for each included number of cortical regions. Furthermore, we estimated the contribution of each regional cortical measure to the PBSI score in each group using a leave-one-out approach. The absolute difference between the original and recalculated PBSI scores was considered the contribution of each regional cortical measure to the corresponding PBSI score.

Statistical analysis

All statistical analyses were performed using R software (ver. 4.0.2; R Development Core Team, Vienna, Austria). Statistical significance was determined using an alpha value of <0.05.

Group differences in continuous variables were tested using a parametric (Student's t test) or non-parametric (Mann–Whitney U test) test, as appropriate. Chi-square tests were used to evaluate group differences in categorical variables. Group differences in the CV were tested using an asymptotic test (Feltz & Miller, 1996) implemented in the *cvequality* package in R-CRAN.

Spearman's correlation was used to test the association between the PBSI score and clinical variables. Given the relationship between age and illness duration, we regressed out the effects of age on the PBSI score in the association between illness duration and the PBSI score. In the patient group, we calculated the z score of the PBSI score using the mean and s.d. of the PBSI scores in the control group. Using the z score of the PBSI score, we divided the patient group into 'deviant' and 'other patients' based on a criterion of lower than the mean − 1.5 S.D.. We compared the PANSS scores and neurocognitive results between deviant and non-deviant patients using the Mann–Whitney U test. Furthermore, we categorized the patients based on the degree of psychiatric symptom severity or cognitive impairment. We applied the upper 10th percentile values as the cutoff for PANSS scores. Regarding neurocognitive function, we regarded patients whose scores were lower than the mean − 2 S.D. in the adjusted full-scale IQ or t scores as having poor cognitive function.

The Bonferroni correction for multiple testing was used to determine statistical significance. For the group differences in the CV and contribution effects of the regional cortical measures, multiple testing correction was performed within each morphometric feature. For the associations of the PBSI scores with the clinical variables, we accounted for all tests across the

Table 1. Demographic and clinical characteristics of the study population

	AMC		COBRE		fBIRN		JNUH		MCIC		NMorphCH		UCLA		Total		Statistic	
	HC	SCZ	HC	SCZ	HC	SCZ	HC	SCZ	HC	SCZ	HC	SCZ	HC	SCZ	HC	SCZ	t/chi	p
Number of participants	21	46	77	61	27	27	190	452	22	27	41	40	42	42	420	695		
Age, mean (s.d.), years	30.9 (5)	28.7 (6.3)	39.3 (11.5)	38 (12.7)	34.9 (12.1)	40 (12.7)	37.9 (12.1)	36.6 (11.9)	35.2 (12.3)	34.4 (9.8)	31.7 (8.5)	33.4 (6.4)	36 (8.8)	36.5 (9.1)	36.7 (11.3)	36 (11.4)	0.88	0.38
Male, n (%)	8 (38.1)	18 (39.1)	56 (72.7)	49 (80.3)	20 (74.1)	21 (77.8)	99 (52.1)	216 (47.8)	12 (54.5)	20 (74.1)	19 (46.3)	27 (67.5)	32 (76.2)	31 (73.8)	246 (58.6)	382 (55)	1.24	0.27
Illness duration, mean (s.d.), years		3.6 (3.9)		16.2 (12.7)				8.8 (9.3)		10.4 (8.9)		14.8 (7.4)				9.6 (9.7)		
PANSS positive, mean (s.d.)		16.7 (7.6)		15.3 (5.2)		16.3 (3.6)		13 (5.6)		21.4 (3.3)		19.7 (6.8)		17.8 (4.7)		14.5 (6.1)		
PANSS negative, mean (s.d.)		16.8 (7.2)		17.6 (5.3)		15.8 (4.9)		11.5 (5.5)		20.9 (3.3)		21.3 (5.2)		16.2 (5.6)		13.7 (6.4)		
Cognition[a]																		
IQ, mean (s.d.)	120.4 (9.6)	97.9 (16)	111.1 (13.1)	96.5 (16.7)				80.5 (21)										
Word fluency, mean (s.d.)			41.4 (7.2)	39 (8.8)														
CTT 1, mean (s.d.)	54.2 (7.1)	45.3 (16.1)	53.9 (9.6)	39 (13.6)														
Medication																		
olanzapine equivalent, mean (s.d.), mg/day		17.1 (10.8)		16.1 (13.2)												17.0 (13.0)		
typical, n (%)		2 (4.5)		9 (15)												3 (7.7)		
atypical, n (%)		44 (100)		53 (88.3)												38 (97.4)		
lithium, n (%)		6 (13.6)		1 (1.7)												4 (10.3)		

AMC, Asan Medical Center; COBRE, Center of Biomedical Research Excellence; CTT 1, color trails test 1; fBIRN, Function Biomedical Informatics Research Network; HC, healthy control; IQ, intelligence quotient; JNUH, Jeonbuk National University Hospital; MCIC, MIND Clinical Imaging Consortium; NMorphCH, Neuromorphometry by Computer Algorithm Chicago; PANSS, positive and negative syndrome scale; SCZ, schizophrenia; UCLA, University of California Los Angeles (Consortium for Neuropsychiatric Phenomics LA5c Study).

Information on illness duration, PANSS score, IQ, CTT 1, and word fluency t-score was available for 610, 681, 267, 191, and 138 participants, respectively.

[a]Full-scale IQ scores and t scores for the word fluency test and color trails test 1 are presented. The information on full-scale IQ scores was available for all participants in the AMC and COBRE cohorts and for 62 patients in the JNUH cohort.
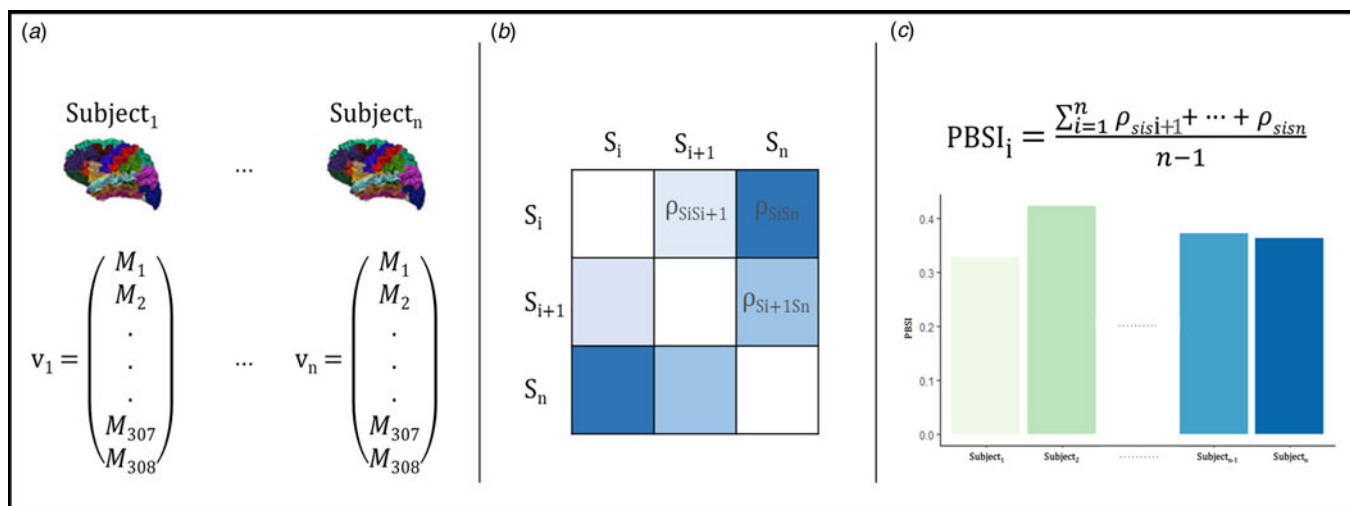
Figure 1. Pipeline for computing a person-based similarity index. (*a*) Creation of a participant-specific cortical structural profiles (v) using cortical measures (M) (for example, cortical thickness) for each participant (i). (*b*) A matrix of Spearman's correlation ρ between each pair of individual profiles. (*c*) For each individual (i), the PBSI score is calculated as the average of all pairwise correlations between the individual (i) and all other individuals within the same group.

measurement tools for clinical variables and study groups in the correction for multiple testing.

Results

Regional variability of cortical measures

To estimate the regional variability in cortical measures, we calculated the CV of cortical measures in healthy controls and patients with schizophrenia. Online supplementary Table S3 and Figure 2 show that patients with schizophrenia had a higher CV of cortical measures than that of healthy controls. In the patient group, a higher CV of the cortical surface area was observed in the left insula and the right precentral region. Regarding cortical thickness, patients with schizophrenia had a higher CV in the left precuneus, posterior cingulate, right isthmus cingulate, posterior cingulate, and superior parietal cortex.

Global variability of cortical measures

Table 2 presents the results of group comparisons of the PBSI scores between patients with schizophrenia and healthy controls. Patients with schizophrenia showed lower PBSI scores across all cortical measures compared with healthy controls. In the Yeo subnetwork (online Supplementary Table S4-1), group comparisons showed lower PBSI scores in patients with schizophrenia compared with healthy controls, except for the PBSI-SA score in subnetworks 2 (somatosensory) and 3 (dorsal attention); the PBSI-CT score in subnetwork 5 (limbic); and the PBSI-SA, PBSI-GV, and PBSI-CT scores in subnetwork 6 (fronto-parietal). In the von Economo subnetwork (online Supplementary Table S4-2), all group comparisons of the PBSI scores showed lower scores in the patient group compared with healthy controls, except for the PBSI-LGI score in subnetwork 1 (primary motor cortex), the PBSI-SA score in subnetworks 3 (association cortex 2) and 4 (primary and secondary sensory cortices), and the PBSI-CT score in subnetwork 6 (limbic cortex).

With regard to the effects of regional cortical measures on the PBSI scores, healthy controls showed higher PBSI scores for all cortical measures than those of patients with schizophrenia regardless of the number of included cortical structures (online Supplementary Fig. S3). The trend in the PBSI scores plateaued when the number of included cortical structures exceeded approximately 100. For the contribution effects of the regional cortical measures to the PBSI score, the overall spatial patterns of the contribution effects were similar between patients with schizophrenia and healthy controls (online Supplementary Fig. S4). However, there were significant group differences in the contributions of regional cortical measures (online Supplementary Table S5). Among the 308 cortical structures, significant group differences were observed in 113 cortical structures in the PBSI-SA score, 110 in the PBSI-GV score, 133 in the PBSI-CT score, 169 in the PBSI-LGI score, and 73 in the PBSI-All score.

Associations with clinical symptoms

In the patient group, no significant associations were found between the PBSI scores and illness duration (online Supplementary Table S6-1) and daily olanzapine equivalents (online Supplementary Table S6-2) after Bonferroni correction. The PANSS score positively correlated with the PBSI-GV (rho = 0.109, Bonferroni-corrected $p = 0.044$) and PBSI-All (rho = 0.110, Bonferroni-corrected $p = 0.039$) scores (online Supplementary Table S6-3). In association with cognitive function (Table 3), the PBSI-GV and PBSI-All scores positively correlated with IQ scores in the patient group.

We used a normative model in which the deviant and other patients were divided using the z scores of the PBSI scores. The clinical variables of the deviant and other patients were compared (online Supplementary Table S7-1). Regarding the PBSI-GV and PBSI-All scores, the deviant patients had lower IQ scores than those of the other patients (PBSI-GV score: $W = 2956.5$, Bonferroni-corrected $p < 0.001$; PBSI-All score: $W = 2968.5$, Bonferroni-corrected $p = 0.046$). We also categorized the patients based on their PANSS scores or neurocognitive function and compared the PBSI scores between the patients with impoverished function and other patients (online Supplementary Table 7-2). Patients with lower IQ scores had lower PBSI-SA, PBSI-GV, and PBSI-All scores than those of the other patients
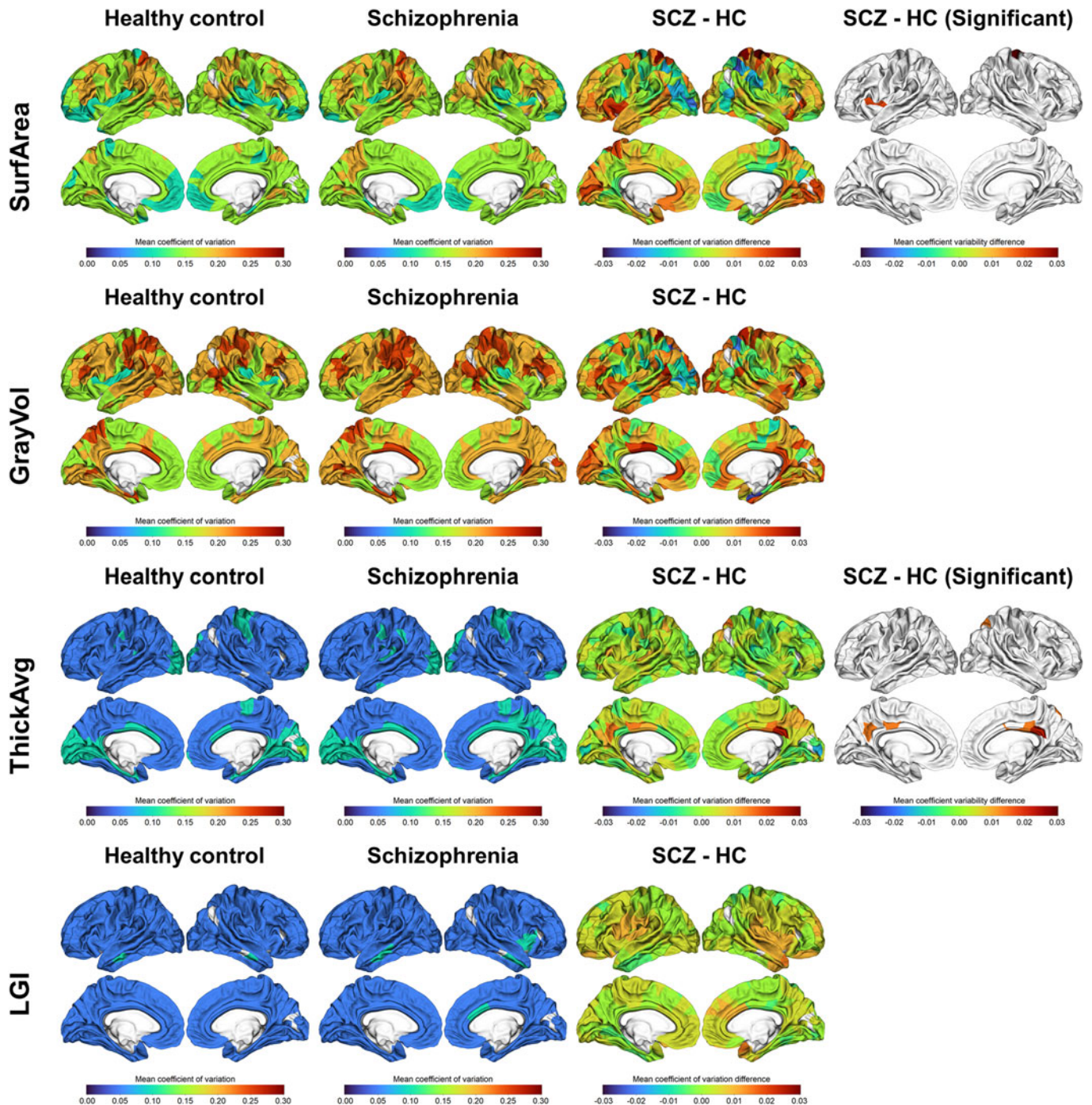
Figure 2. Coefficient of variation of regional cortical measures. Red and blue colors reflect higher and lower mean coefficients of variation, respectively. In the group comparison, red and blue colors depict higher and lower mean coefficients of variation in patients with schizophrenia compared with healthy controls. SurfArea, surface area; GrayVol, gray matter volume; ThickAvg, cortical thickness; LGI, local gyrification index; HC, healthy control; SCZ, schizophrenia.

(PBSI-SA score: $W = 2007$, Bonferroni-corrected $p = 0.024$; PBSI-GV score: $W = 2033$, Bonferroni-corrected $p = 0.015$; PBSI-All score: $W = 2099$, Bonferroni-corrected $p = 0.004$).

Discussion

We investigated the structural variability of the cerebral cortex in patients with schizophrenia using neuroimaging data from seven

studies. We used the CV and PBSI scores to estimate the regional and global structural variability of the cortex. Regarding surface area and thickness, patients with schizophrenia had a higher CV in a few cortical regions than that of healthy controls. All PBSI scores across the cortical measures were lower in the patient group than in the control group. In the patient group, the PBSI-GV and PBSI-All scores positively correlated with the IQ score and patients with deviant PBSI-GV and PBSI-All scores had lower IQ scores than those of the other patients.

Table 2. Group comparisons of the PBSI scores

	HC	SCZ	Statistic	
Modality	Mean (s.d.)	Mean (s.d.)	W	Adjusted p^a
PBSI-SA	0.383 (0.044)	0.365 (0.047)	176 621	<0.001
PBSI-GV	0.598 (0.041)	0.574 (0.043)	192 334	<0.001
PBSI-CT	0.682 (0.039)	0.660 (0.040)	198 873	<0.001
PBSI-LGI	0.919 (0.013)	0.910 (0.017)	194 635	<0.001
PBSI-All	0.650 (0.028)	0.632 (0.030)	200 449	<0.001

HC, healthy control; PBSI-All, person-based similarity index for all cortical measures; PBSI-CT, person-based similarity index for cortical thickness; PBSI-GV, person-based similarity index for gray matter volume; PBSI-LGI, person-based similarity index for local gyrification index; PBSI-SA, person-based similarity index for surface area; SCZ, schizophrenia.
^{a}The Mann–Whitney U test was used with the Bonferroni correction for multiple testing.

To determine cortex regional structural variability, we compared the CV of the regional cortical measures between patients with schizophrenia and healthy controls. A greater regional variance in cortical surface area and thickness in a few cortical regions was observed in patients with schizophrenia than in healthy controls. A recent meta-analysis by Brugger and Howes reported that patients with schizophrenia have greater variability in the volumes of the putamen, temporal lobe, and thalamus and lower variability in the volume of the anterior cingulate cortex (Brugger & Howes, 2017). A large-scale study also reported increased heterogeneity in the cortical thickness of the frontotemporal regions and the volume of the hippocampus, and a robust decrease in the mean morphometric measures (Alnaes et al., 2019). Conversely, Kuo et al. reported no significant group differences in variability in the volume of cortical gray matter and subcortical regions between patients with schizophrenia and healthy controls (Kuo & Pogue-Geile, 2019). Antoniades et al. reported no significant group differences in the CV of regional cortical measures among healthy controls, clinical high-risk cases of psychosis, and patients with first-episode psychosis (Antoniades et al., 2021). We used neuroimaging data from 420 healthy controls and 695 patients with schizophrenia, which is a larger sample size than that used by Antoniades et al., with strong statistical power to detect the subtle differences.

We used the PBSI score to estimate the similarity of individual cortical structural profiles within the same group and performed group comparisons. The PBSI scores across all cortical measures were lower in the patient group than those in the control group, indicating a greater heterogeneity in the cortex morphometric features in patients with schizophrenia. We calculated the PBSI scores in the subregions of the cerebral cortex defined by the Yeo and von Economo atlases. Except for a few group comparisons, patients with schizophrenia had lower PBSI scores than those of healthy controls in most subnetworks. A recent study with genomic, transcriptomic, and brain phenotypic data reported that the heterogeneity of cortical thickness in schizophrenia may be associated with interindividual variations in cell type-specific functions (Di Biase et al., 2022). Morgan et al. investigated the regional morphometric similarity of the cerebral cortex in patients with schizophrenia compared with healthy controls (Morgan et al., 2019). They reported that case-control differences in the regional morphometric similarity were associated with the cortical expression of schizophrenia-related genes. The previous findings suggest the association of morphometric similarity with genomic and transcriptomic expressions in the cerebral cortex of patients with schizophrenia. The current findings should be extended in future research exploring links to genomic and transcriptomic expressions.

In previous studies using the same metric for global structural variability of the brain, that is, the PBSI score, lower PBSI scores for cortical thickness and sulcal width were observed in patients with psychosis (Antoniades et al., 2021; Janssen et al., 2021). We extended previous findings by showing lower PBSI scores for surface area, gray matter volume, and local gyrification index in patients with schizophrenia. For the contributing effects of the regional cortical measures on the PBSI score, the spatial patterns of the contributing effects were similar between patients with schizophrenia and healthy controls. In contrast to previous findings (Antoniades et al., 2021; Doucet et al., 2020b), we found significant group differences in the contributing effects in a large number of cortical regions across all cortical measures. These differences may be explained by the larger sample size and finer cortical parcellation in the present study.

In the current study, no associations between the PBSI score and illness duration or daily olanzapine equivalents were found, which is consistent with previous studies (Antoniades et al., 2021; Doucet et al., 2020b). The cross-sectional design of this study should be considered when interpreting the negative association between the PBSI score and illness duration. Future longitudinal studies are required to address this issue. We showed that the PBSI-GV and PBSI-All scores positively correlated with the PANSS-positive scores in the patient group. Despite the significant association, cautious interpretation is warranted for the following reasons. First, the correlation coefficients were low and the associations were not replicated in the group comparisons in normative modeling. Second, positive symptom severity could be affected by factors other than structural variations of the cortex, such as illness duration and antipsychotic medications. We found that the PBSI-GV and PBSI-All scores positively correlated with the IQ score in patients with schizophrenia and that deviant patients had lower PBSI-GV and PBSI-All scores than those of the other patients. This implies that a greater deviation from the normative range of cortical structural similarity is associated with a lower general intelligence. Our results show significant associations between the PBSI and IQ scores, and lower IQ scores in deviant patients with lower PBSI scores. Janssen et al. reported that a subset of patients with markedly deviant PBSI scores for sulcal width had extreme deficits in cognitive performance (Janssen et al., 2021). Individuals with early psychosis whose PBSI scores markedly deviated from those of healthy controls showed a tendency towards lower nonverbal IQ and higher psychopathology (Antoniades et al., 2021).

Table 3. Association of the PBSI score with cognitive functions in healthy controls and patients with schizophrenia

Modality	Healthy control									Schizophrenia								
	IQ			CTT 1			Word fluency			IQ			CTT 1			Word fluency		
	rho	p	Adj. p	rho	p	Adj. p	rho	p	Adj. p	rho	p	Adj. p	rho	p	Adj. p	rho	p	Adj. p
PBSI-SA	0.037	0.720	1.000	0.008	0.937	1.000	−0.035	0.760	1.000	0.119	0.123	1.000	0.174	0.087	1.000	0.106	0.417	1.000
PBSI-GV	−0.071	0.489	1.000	−0.031	0.771	1.000	−0.07	0.546	1.000	0.256	0.001	0.024	0.263	0.009	0.264	0.142	0.274	1.000
PBSI-CT	0.021	0.834	1.000	−0.015	0.890	1.000	−0.011	0.926	1.000	0.197	0.010	0.312	0.252	0.012	0.371	0.111	0.393	1.000
PBSI-LGI	0.146	0.151	1.000	0.04	0.703	1.000	−0.018	0.878	1.000	0.143	0.064	1.000	0.107	0.296	1.000	0.109	0.402	1.000
PBSI-All	−0.007	0.942	1.000	0.010	0.921	1.000	−0.080	0.490	1.000	0.242	0.001	0.045	0.274	0.006	0.192	0.173	0.182	1.000

CTT 1, color trails test 1; IQ, intelligence quotient; PBSI-All, person-based similarity index for all cortical measures; PBSI-CT, person-based similarity index for cortical thickness; PBSI-GV, person-based similarity index for gray matter volume; PBSI-LGI, person-based similarity index for local gyrification index; PBSI-SA, person-based similarity index for surface area.

Several limitations should be considered when interpreting these results. First, the significant associations between the PBSI-GV, PBSI-All, and IQ scores in patients with schizophrenia was derived based on a small subset of patients for whom the IQ scores were available, and not on those of the entire population. Further studies are needed to explore the associations between the cerebral cortex structural heterogeneity and cognitive functions in schizophrenia. Second, we did not consider morphometric measure variations derived from different sample characteristics in terms of race, cognitive function, and education in the harmonization process. Previous studies have reported a relationship between cortical thickness and ethnicity, general intelligence, education, and socioeconomic status (Habeck, Gazes, Razlighi, & Stern, 2020; Kang et al., 2020; Menary et al., 2013; Piccolo et al., 2016). Although the site difference decreased after ComBat harmonization, some significant group differences in the mean cortical measures were noted. Third, cumulative exposure to antipsychotic medications was not considered. An association between cortical and subcortical morphometric measures and antipsychotic medications has been reported (Krajner et al., 2022; Roiz-Santianez et al., 2012; van Haren et al., 2011). We recognize that antipsychotic medications may also contribute to the greater heterogeneity of cortical measures in patients with schizophrenia compared with healthy controls. Follow-up studies are needed to clarify the association between structural heterogeneity of the cerebral cortex and exposure to antipsychotic medications. Fourth, we could not perform a comprehensive analysis of the associations of the PBSI scores with cognitive functions because of the limited number of cognitive tests. Further investigations should be conducted using a more comprehensive assessment tool for cognitive impairment in schizophrenia, such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery. Fifth, the study population included in the current study may not be representative of the range of patients with schizophrenia because the individual studies were conducted with the informed consent of the patients and/or their caregivers and tended to include patients with relatively stable clinical symptoms. This inherent limitation should be considered in the interpretation of our results.

We used neuroimaging data from 420 healthy controls and 695 patients with schizophrenia to evaluate the morphometric variability of the cerebral cortex in schizophrenia. An increased CV of surface area and cortical thickness was observed in patients with schizophrenia in some cortical regions. The PBSI score, which quantifies the similarity of individual cortical profiles within the same group, was lower in patients with schizophrenia than in healthy controls for all cortical measures. The PBSI-GV and PBSI-All scores positively correlated with the IQ score in the patient group, and the patient subgroup with markedly deviated PBSI-GV and PBSI-All scores had lower IQ scores than those of the other patients. Our results suggest a greater heterogeneity in the cortical morphometric profiles in patients with schizophrenia compared to those in healthy controls. We consider that the current findings provide neurobiological evidence that partially accounts for the heterogeneity of schizophrenia observed in clinical practice, particularly regarding general intelligence. There is increasing evidence on the neurobiological heterogeneity of schizophrenia and we consider that further studies focusing on personalized medicine are needed to individualize the diagnosis and treatment of schizophrenia. The identification of neurobiological biomarkers may contribute to the development of an individualized diagnostic and treatment plan for patients in the future.

References

Adityanjee, Aderibigbe, Y. A., Theodoridis, D., & Vieweg, V. R. (1999). Dementia praecox to schizophrenia: The first 100 years. *Psychiatry and Clinical Neurosciences*, 53(4), 437–448. doi: 10.1046/j.1440-1819.1999.00584.x

Aine, C. J., Bockholt, H. J., Bustillo, J. R., Canive, J. M., Caprihan, A., Gasparovic, C., … Calhoun, V. D. (2017). Multimodal neuroimaging in schizophrenia: Description and dissemination. *Neuroinformatics*, 15(4), 343–364. doi: 10.1007/s12021-017-9338-9

Alnaes, D., Kaufmann, T., van der Meer, D., Cordova-Palomera, A., Rokicki, J., Moberget, T., … Karolinska Schizophrenia Project, C. (2019). Brain heterogeneity in schizophrenia and its association with polygenic risk. *JAMA Psychiatry*, 76(7), 739–748. doi: 10.1001/jamapsychiatry.2019.0257

Antoniades, M., Haas, S. S., Modabbernia, A., Bykowsky, O., Frangou, S., Borgwardt, S., & Schmidt, A. (2021). Personalized estimates of brain structural variability in individuals with early psychosis. *Schizophrenia Bulletin*, 47(4), 1029–1038. doi: 10.1093/schbul/sbab005

Baltazar, L., De Benedictis, L., Abdel-Baki, A., Lalonde, P., & Lesage, A. (2022). Long term course and outcome of first episode schizophrenia: A 27-to-31-year follow-up. *Social Psychiatry and Psychiatric Epidemiology*, 57(7), 1319–1328. doi: 10.1007/s00127-021-02185-8

Brugger, S. P., & Howes, O. D. (2017). Heterogeneity and homogeneity of regional brain structure in schizophrenia: A meta-analysis. *JAMA Psychiatry*, 74(11), 1104–1111. doi: 10.1001/jamapsychiatry.2017.2663

Cannon, T. D., Chung, Y., He, G., Sun, D., Jacobson, A., van Erp, T. G., … North American Prodrome Longitudinal Study, C. (2015). Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biological Psychiatry*, 77(2), 147–157. doi: 10.1016/j.biopsych.2014.05.023

Chand, G. B., Dwyer, D. B., Erus, G., Sotiras, A., Varol, E., Srinivasan, D., … Davatzikos, C. (2020). Two distinct neuroanatomical subtypes of schizophrenia revealed using machine learning. *Brain*, 143(3), 1027–1038. doi: 10.1093/brain/awaa025

Correll, C. U., Martin, A., Patel, C., Benson, C., Goulding, R., Kern-Sliwa, J., … Kim, E. (2022). Systematic literature review of schizophrenia clinical practice guidelines on acute and maintenance management with antipsychotics. *Schizophrenia (Heidelb)*, 8(1), 5. doi: 10.1038/s41537-021-00192-x

Di Biase, M. A., Geaghan, M. P., Reay, W. R., Seidlitz, J., Weickert, C. S., Pebay, A., … Zalesky, A. (2022). Cell type-specific manifestations of cortical thickness heterogeneity in schizophrenia. *Molecular Psychiatry*, 27(4), 2052–2060. doi: 10.1038/s41380-022-01460-7

Doucet, G. E., Glahn, D. C., & Frangou, S. (2020a). Person-based similarity in brain structure and functional connectivity in bipolar disorder. *Journal of Affective Disorders*, 276, 38–44. doi: 10.1016/j.jad.2020.06.041

Doucet, G. E., Lin, D., Du, Y., Fu, Z., Glahn, D. C., Calhoun, V. D., … Frangou, S. (2020b). Personalized estimates of morphometric similarity in bipolar disorder and schizophrenia. *NPJ Schizophrenia*, 6(1), 39. doi: 10.1038/s41537-020-00128-x

Doucet, G. E., Moser, D. A., Rodrigue, A., Bassett, D. S., Glahn, D. C., & Frangou, S. (2019). Person-based brain morphometric similarity is heritable and correlates with biological features. *Cerebral Cortex (New York, NY)*, 29 (2), 852–862. doi: 10.1093/cercor/bhy287

Dugbartey, A. T., Townes, B. D., & Mahurin, R. K. (2000). Equivalence of the color trails test and trail making test in nonnative English-speakers. *Archives of Clinical Neuropsychology*, 15(5), 425–431. doi: 10.1016/S0887-6177(99)00034-7

Dwyer, D. B., Cabral, C., Kambeitz-Ilankovic, L., Sanfelici, R., Kambeitz, J., Calhoun, V., … Koutsouleris, N. (2018). Brain subtyping enhances the neuroanatomical discrimination of schizophrenia. *Schizophrenia Bulletin*, 44(5), 1060–1069. doi: 10.1093/schbul/sby008

Feltz, C. J., & Miller, G. E. (1996). An asymptotic test for the equality of coefficients of variation from k populations. *Statistics in Medicine*, 15(6), 646–658. doi: 10.1002/(sici)1097-0258(19960330)15:6<647::aid-sim184>3.0.co;2-p

Foulkes, L., & Blakemore, S. J. (2018). Studying individual differences in human adolescent brain development. *Nature Neuroscience*, 21(3), 315–323. doi: 10.1038/s41593-018-0078-4

Glover, G. H., Mueller, B. A., Turner, J. A., van Erp, T. G., Liu, T. T., Greve, D. N., … Potkin, S. G. (2012). Function biomedical informatics research network recommendations for prospective multicenter functional MRI studies. *Journal of Magnetic Resonance Imaging*, 36(1), 39–54. doi: 10.1002/jmri.23572

Gollub, R. L., Shoemaker, J. M., King, M. D., White, T., Ehrlich, S., Sponheim, S. R., … Andreasen, N. C. (2013). The MCIC collection: A shared repository of multi-modal, multi-site brain image data from a clinical investigation of schizophrenia. *Neuroinformatics*, 11(3), 367–388. doi: 10.1007/s12021-013-9184-3

Gorgolewski, K. J., Durnez, J., & Poldrack, R. A. (2017). Preprocessed consortium for neuropsychiatric phenomics dataset. *F1000Research*, 6(1262), 1262. doi: 10.12688/f1000research.11964.2

Habeck, C., Gazes, Y., Razlighi, Q., & Stern, Y. (2020). Cortical thickness and its associations with age, total cognition and education across the adult lifespan. *PLoS One*, 15(3), e0230298. doi: 10.1371/journal.pone.0230298

Harvey, P. D. (2019). Domains of cognition and their assessment. *Dialogues in Clinical Neuroscience*, 21(3), 227–237. doi: 10.31887/DCNS.2019.21.3/pharvey

Janssen, J., Diaz-Caneja, C. M., Alloza, C., Schippers, A., de Hoyos, L., Santonja, J., … Schnack, H. G. (2021). Dissimilarity in sulcal width patterns in the cortex can be used to identify patients with schizophrenia with extreme deficits in cognitive performance. *Schizophrenia Bulletin*, 47(2), 552–561. doi: 10.1093/schbul/sbaa131

Jobe, T. H., & Harrow, M. (2010). Schizophrenia course, long-term outcome, recovery, and prognosis. *Current Directions in Psychological Science*, 19(4), 220–225. doi: 10.1177/0963721410378034

Kang, D. W., Wang, S. M., Na, H. R., Park, S. Y., Kim, N. Y., Lee, C. U., … Lim, H. K. (2020). Differences in cortical structure between cognitively normal East Asian and Caucasian older adults: A surface-based morphometry study. *Scientific Reports*, 10(1), 20905. doi: 10.1038/s41598-020-77848-8

Keator, D. B., van Erp, T. G. M., Turner, J. A., Glover, G. H., Mueller, B. A., Liu, T. T., … Fbirn. (2016). The function biomedical informatics research network data repository. *Neuroimage*, 124(Pt B), 1074–1079. doi: 10.1016/j.neuroimage.2015.09.003

Krajner, F., Hadaya, L., McQueen, G., Sendt, K. V., Gillespie, A., Avila, A., … Egerton, A. (2022). Subcortical volume reduction and cortical thinning 3 months after switching to clozapine in treatment resistant schizophrenia. *Schizophrenia (Heidelb)*, 8(1), 13. doi: 10.1038/s41537-022-00230-2

Kuo, S. S., & Pogue-Geile, M. F. (2019). Variation in fourteen brain structure volumes in schizophrenia: A comprehensive meta-analysis of 246 studies. *Neuroscience and Biobehavioral Reviews*, 98, 85–94. doi: 10.1016/j.neubiorev.2018.12.030

Lee, J., Takeuchi, H., Fervaha, G., Sin, G. L., Foussias, G., Agid, O., … Remington, G. (2015). Subtyping schizophrenia by treatment response: Antipsychotic development and the central role of positive symptoms. *Canadian Journal of Psychiatry*, 60(11), 515–522. doi: 10.1177/070674371506001107

Menary, K., Collins, P. F., Porter, J. N., Muetzel, R., Olson, E. A., Kumar, V., … Luciana, M. (2013). Associations between cortical thickness and general intelligence in children, adolescents and young adults. *Intelligence*, 41(5), 597–606. doi: 10.1016/j.intell.2013.07.010

Morgan, S. E., Seidlitz, J., Whitaker, K. J., Romero-Garcia, R., Clifton, N. E., Scarpazza, C., … Bullmore, E. T. (2019). Cortical patterning of abnormal morphometric similarity in psychosis is associated with brain expression of schizophrenia-related genes. *Proceedings of the National Academy of Sciences of the United States of America*, 116(19), 9604–9609. doi: 10.1073/pnas.1820754116

Piccolo, L. R., Merz, E. C., He, X., Sowell, E. R., Noble, K. G., & Pediatric Imaging, N. G. S. (2016). Age-related differences in cortical thickness vary by socioeconomic status. *PLoS One*, 11(9), e0162511. doi: 10.1371/journal.pone.0162511

Poldrack, R. A., Congdon, E., Triplett, W., Gorgolewski, K. J., Karlsgodt, K. H., Mumford, J. A., … Bilder, R. M. (2016). A phenome-wide examination of neural and cognitive function. *Scientific Data*, 3, 160110. doi: 10.1038/sdata.2016.110

Roiz-Santianez, R., Tordesillas-Gutierrez, D., Ortiz-Garcia de la Foz, V., Ayesa-Arriola, R., Gutierrez, A., Tabares-Seisdedos, R., … Crespo-Facorro, B. (2012). Effect of antipsychotic drugs on cortical thickness. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Schizophrenia Research*, 141(1), 22–28. doi: 10.1016/j.schres.2012.07.014

Romero-Garcia, R., Atienza, M., Clemmensen, L. H., & Cantero, J. L. (2012). Effects of network resolution on topological properties of human neocortex. *Neuroimage*, 59(4), 3522–3532. doi: 10.1016/j.neuroimage.2011.10.086

Schaer, M., Cuadra, M. B., Tamarit, L., Lazeyras, F., Eliez, S., & Thiran, J. P. (2008). A surface-based approach to quantify local cortical gyrification. *IEEE Transactions on Medical Imaging*, 27(2), 161–170. doi: 10.1109/TMI.2007.903576

Seghier, M. L., & Price, C. J. (2018). Interpreting and utilising intersubject variability in brain function. *Trends in Cognitive Sciences*, 22(6), 517–530. doi: 10.1016/j.tics.2018.03.003

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, 6(3), 309–315. doi: 10.1038/nn1008

Thompson, P. M., Jahanshad, N., Ching, C. R. K., Salminen, L. E., Thomopoulos, S. I., Bright, J., … Consortium, E. (2020). ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. *Translational Psychiatry*, 10(1), 100. doi: 10.1038/s41398-020-0705-1

van Erp, T. G. M., Preda, A., Nguyen, D., Faziola, L., Turner, J., Bustillo, J., … Fbirn. (2014). Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophrenia Research*, 152(1), 289–294. doi: 10.1016/j.schres.2013.11.013

van Erp, T. G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., … Turner, J. A. (2018). Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium. *Biological Psychiatry*, 84(9), 644–654. doi: 10.1016/j.biopsych.2018.04.023

van Haren, N. E., Schnack, H. G., Cahn, W., van den Heuvel, M. P., Lepage, C., Collins, L., … Kahn, R. S. (2011). Changes in cortical thickness during the course of illness in schizophrenia. *Archives of General Psychiatry*, 68(9), 871–880. doi: 10.1001/archgenpsychiatry.2011.88

Vasa, F., Seidlitz, J., Romero-Garcia, R., Whitaker, K. J., Rosenthal, G., Vertes, P. E., … Bullmore, E. T. (2018). Adolescent tuning of association cortex in human structural brain networks. *Cerebral Cortex* (*New York, NY*), 28(1), 281–294. doi: 10.1093/cercor/bhx249

Vita, A., De Peri, L., Deste, G., Barlati, S., & Sacchetti, E. (2015). The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: Does the class matter? *Biological Psychiatry*, 78(6), 403–412. doi: 10.1016/j.biopsych.2015.02.008

Voineskos, A. N., Foussias, G., Lerch, J., Felsky, D., Remington, G., Rajji, T. K., … Mulsant, B. H. (2013). Neuroimaging evidence for the deficit subtype of schizophrenia. *JAMA Psychiatry*, 70(5), 472–480. doi: 10.1001/jamapsychiatry.2013.786

Walton, E., Hibar, D. P., van Erp, T. G., Potkin, S. G., Roiz-Santianez, R., Crespo-Facorro, B., … Ehrlich, S. (2017). Positive symptoms associate with cortical thinning in the superior temporal gyrus via the ENIGMA schizophrenia consortium. *Acta Psychiatrica Scandinavica*, 135(5), 439–447. doi: 10.1111/acps.12718

Walton, E., Hibar, D. P., van Erp, T. G. M., Potkin, S. G., Roiz-Santianez, R., Crespo-Facorro, B., … Ehrlich, S. (2018). Prefrontal cortical thinning links to negative symptoms in schizophrenia via the ENIGMA consortium. *Psychological Medicine*, 48(1), 82–94. doi: 10.1017/S0033291717001283

Wang, L., Alpert, K. I., Calhoun, V. D., Cobia, D. J., Keator, D. B., King, M. D., … Ambite, J. L. (2016). SchizConnect: Mediating neuroimaging databases on schizophrenia and related disorders for large-scale integration. *Neuroimage*, 124(Pt B), 1155–1167. doi: 10.1016/j.neuroimage.2015.06.065

Whitaker, K. J., Vertes, P. E., Romero-Garcia, R., Vasa, F., Moutoussis, M., Prabhu, G., … Bullmore, E. T. (2016). Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. *Proceedings of the National Academy of Sciences of the United States of America*, 113(32), 9105–9110. doi: 10.1073/pnas.1601745113

Wolfers, T., Doan, N. T., Kaufmann, T., Alnaes, D., Moberget, T., Agartz, I., … Marquand, A. F. (2018). Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. *JAMA Psychiatry*, 75(11), 1146–1155. doi: 10.1001/jamapsychiatry.2018.2467

Wolfers, T., Rokicki, J., Alnaes, D., Berthet, P., Agartz, I., Kia, S. M., … Westlye, L. T. (2021). Replicating extensive brain structural heterogeneity in individuals with schizophrenia and bipolar disorder. *Human Brain Mapping*, 42(8), 2546–2555. doi: 10.1002/hbm.25386

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., … Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, 106(3), 1125–1165. doi: 10.1152/jn.00338.2011