Research Paper

Meta-analysis of cortical thickness reduction in adult schizophrenia

Shilin Sun, MD; Shu Xiao, PhD; Zixuan Guo, PhD; Jiaying Gong, PhD; Guixian Tang, PhD; Li Huang, PhD; Ying Wang, PhD

Background: Numerous neuroimaging studies using surface-based morphometry analyses have reported altered cortical thickness among patients with schizophrenia, but the results have been inconsistent. We sought to provide a whole-brain meta-analysis, which may help enhance the spatial accuracy of identification. **Methods:** We conducted a meta-analysis of whole-brain studies that explored cortical thickness alteration among adult patients with schizophrenia, including first-episode patients with schizophrenia, and patients with chronic schizophrenia, compared with healthy controls by using the seed-based d mapping with permutation of subject images (SDM-PSI) software. **Results:** A systematic literature search identified 25 studies (33 data sets) of cortical thickness, including 2008 patients with schizophrenia and 2004 healthy controls. Overall, patients with schizophrenia showed decreased cortical thickness in the right inferior frontal gyrus (IFG) and bilateral insula extending to the superior temporal gyrus (STG). Subgroup meta-analysis reported that patients with chronic schizophrenia showed decreased cortical thickness in the right insula extending to the right IFG. There was no significant cortical thickness difference between first-episode patients with schizophrenia and healthy controls. **Limitations:** The results of meta-regression analyses should be viewed cautiously since they were driven by a small number of studies or did not overlap with the between-group differences found in the primary analyses. **Conclusion:** The meta-analysis suggested robust cortical thickness reduction in the IFG, insula and STG among adult patients with schizophrenia, particularly in those with chronic schizophrenia. The results provide useful insights to understanding the underlying pathophysiology of schizophrenia.

Introduction

Schizophrenia is a severe psychiatric disease characterized by cognitive impairment, auditory hallucination, delusions, abnormal behavioural disorders and poor long-term prognosis, leading to adverse effects on quality of life and social function of patients with schizophrenia.[1–4] Schizophrenia affects about 1% of the general population in the world,[5] places a tremendous burden on patients, families and society, and remains a debilitatingly progressive and incurable disease. It is recognized globally as the most notable reason for a chronic psychiatric disability. However, the specific pathophysiology and neuroanatomical biomarkers of schizophrenia remain elusive.

Structural magnetic resonance imaging (MRI) is a noninvasive neuroimaging technique used to research brain structural abnormalities in schizophrenia, improving our understanding of the neurobiological characteristics of schizophrenia.[6,7] Grey matter volume is the most commonly used structural index, measured through whole-brain voxel-based morphometry (VBM) or region-of-interest analysis.[8] Several VBM meta-analyses have shown abnormalities in grey matter volume in the superior temporal gyrus (STG),[9] inferior frontal gyrus (IFG), cingulate cortex[10] and insula[11] in schizophrenia. Recently, several studies reported that surface-based morphometry appears more sensitive to studying subtle structural differences in the cortex than VBM.[12] Surface-based morphometry can be used for probing cortical thickness, and alignment precision is improved across the entire cortex.[13] Cortical thickness represents the size, density, arrangement of neurons, neuroglia and nerve fibers; cortical thinning may demonstrate a loss of dendrites and dendritic spines and changes in myelination within brain regions.[14] In addition, previous studies have shown that cortical thickness is a significant indicator of brain degeneration in schizophrenia.[15,16] Some studies reported decreased cortical thickness in the anterior cingulate cortex,[16,17] occipital cortex,[14] several subregions of the temporal cortex,[18,19] insula,[20] and

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IFG[21] relative to healthy controls. Other studies have reported increased cortical thickness among patients with schizophrenia in the cingulate gyrus,[22,23] and no apparent differences in cortical thickness.[24] These inconsistencies may be due to differences between studies in sample characteristics (such as age and sex), subtypes,[25] illness duration and stages, medications, compensatory brain adaptations,[26] flexible analyses and statistical methods. Thus, a quantitative assessment of cortical thickness abnormalities using neuroimaging meta-analysis is needed to overcome such divergence in the schizophrenia literature.

Coordinate-based meta-analysis combines individual neuroimaging studies to identify brain regions consistently involved in neuropsychiatric disorders using peak coordinates located in 3-dimensional anatomical spaces (x, y, z). Through technical advancements, coordinate-based meta-analysis has been widely applied to identify consistent alterations in cortical thickness in psychiatric disorders such as bipolar disorder, major depressive disorder and posttraumatic stress disorder.[8,27,28] Only 1 coordinate-based meta-analysis has explored cortical thickness abnormalities among patients with schizophrenia, which included 671 patients with first-episode psychosis (FEP) and 579 patients with chronic schizophrenia; it found decreased cortical thickness in the STG, anterior cingulate cortex, insula, IFG and temporal pole.[29] However, this study of FEP data sets did include first-episode schizophrenia and psychotic, schizoaffective and adolescent patients with schizophrenia, which might have contributed to some bias. Therefore, we sought to perform a coordinate-based meta-analysis of surface-based morphometry studies using seed-based d mapping with permutation of subject images (SDM-PSI) to investigate alterations in cortical thickness in schizophrenia. We also sought to conduct a subgroup meta-analysis to estimate the heterogeneity and robustness of the main findings, including patients of different status (i.e., first-episode schizophrenia, chronic schizophrenia and unmedicated schizophrenia). Finally, we sought to use meta-regression analysis to identify the potential associations of clinical variables (i.e., age, sex distribution, age of onset, illness duration and symptom score). Given previous empirical studies investigating schizophrenia, we hypothesized that analyses would primarily find abnormal cortical thickness in brain regions related to affective and cognitive function, such as the insula and the frontal and temporal lobe. By providing correspondingly robust neuroimage biomarkers, the present study may contribute to a comprehensive understanding of the neuroanatomical and neurobiological mechanisms of schizophrenia.

Methods

Literature search

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist[30] and registered it with the PROSPERO database (no. CRD42022328696). Our study adhered to the most recent guidelines and recommendations in the field. We performed comprehensive and systematic searches to identify studies in PubMed, Embase, Web of Science, SinoMed, Chinese National Knowledge Infrastructure and WanFang databases through Aug. 11, 2022, using keywords related to schizophrenia ("schizophrenia" OR "schizophrenic disorder" OR "disorder, schizophrenic") and terms related to cortical thickness ("cortical thickness" OR "cortical thinning" OR "freesurfer" OR "AFNI" OR "CIVET" OR "ANTs").

Study selection criteria

We included original studies according to the following conditions: studies used coordinate-based analyses to compare cortical thickness between patients with schizophrenia and healthy controls at the whole-brain level; patients and healthy controls were between the ages of 18 and 60 years, and patients had a primary diagnosis of schizophrenia; studies reported peak coordinates of results in Talairach or Montreal Neurological Institute (MNI) coordinates; studies published in peer-reviewed journals in English or Chinese; when the details of original manuscripts were not reported, we could retrieve these by making a reasonable request to the corresponding author.

We excluded studies if they reported region-of-interest analyses only instead of whole-brain analysis; if they reported follow-up data only without baseline data; if peak coordinates of effects were not available (e.g., missing neuroanatomical coordinates), even after contact with the authors by email; or if the samples obviously overlapped with those of other included studies, in which case we included the study with largest sample size.

Quality assessment and data extraction

Based on previous meta-analyses of cortical thickness,[28,31] we used a 12-point checklist (details in Appendix 1, Table S1, www.jpn.ca/lookup/doi/10.1503/jpn.230081/tab-related-content) to assess the quality of each study. The checklist was divided into 3 parts: participants (items 1–6), imaging methodology and analysis (items 7–10) and results and conclusions (items 11–12). We included any study scoring more than 6.0 points in the present meta-analysis. Two authors (G.X.T. and J.Y.G.) conducted the literature search, study selection and quality assessment independently, and a third investigator (Y.W.) would make the final decision if any disagreements occurred.

For each eligible study, we extracted the peak coordinates, the name of the first author, year of publication, demographic and clinical characteristics (sample size, mean age, sex distribution, age of onset, illness duration, the Positive and Negative Syndrome Scale [PANSS] score, medication status, Wechsler Abbreviated Scale of Intelligence [WASI] score) and basic information on imaging, as well as statistical methods (magnetic field strength, statistical software, statistical threshold and correction methods of main results). Some studies included more than 1 patient group, and we included each comparison of patient versus healthy control group as separate contrasts.

Pooled meta-analysis of cortical thickness

We conducted a meta-analysis of cortical thickness to investigate cortical thickness alterations in schizophrenia using SDM-PSI software (version 6.21, https://www.sdmproject.com/).[32] Briefly, the SDM-PSI, a voxel-based meta-analysis software, used reported peak coordinates and their statistics (e.g., *t* values) to recreate an effect-size signed map of the difference between patients with schizophrenia and healthy controls for each original study.[33] We selected the modality for VBM of grey matter, the correlation template for grey matter and the FreeSurfer mask to improve the accuracy of effect size maps by restricting them to the cortical grey matter.[29] Next, we then consolidated the maps in a standard random-effects model weighing sample size (i.e., studies with larger sample size or lower variability contributed more), intra-study variability and between-study heterogeneity, and pooled multiple imputations according to Rubin's rules.[34] Finally, we applied a subject-based permutation test to calculate the family-wise error (FWE) rate of the results. We carried out analyses as described in the SDM-PSI tutorial and previous publications.[32,35] We reported results using a threshold of p less than 0.05 after a correction for the FWE rate, and a minimum cluster extent of at least 10 voxels with a peak SDM-Z greater than 1. We used the MRIcron software package (www.mricro.com/mricron/) to visualize SDM-PSI maps.

Subgroup meta-analysis

To explore brain alterations in different stages of schizophrenia, we performed analyses for 3 clinical subgroups (first-episode schizophrenia; chronic schizophrenia, defined as illness duration > 2 yr; and unmedicated, including patients who underwent a medication wash-out period of longer than 4 wk). Furthermore, we conducted 2 subgroup analyses (studies from Eastern and Western countries) to explore the effects of cultural and geographic differences. We also conducted a subgroup analysis excluding the studies with an insufficient sample size ($n < 10$) or those uncorrected for statistics to estimate the heterogeneity and robustness of the main findings.

Analyses of jackknife sensitivity, heterogeneity and publication bias

To estimate the replicability of the results, we conducted a jackknife sensitivity analysis in the pooled and subgroup meta-analyses by repeating the main analysis in accordance with the number of total data sets included, discarding 1 study at a time to determine whether the results remained detectable.

We extracted the values from peak coordinates for information to assess heterogeneity and publication bias. We evaluated heterogeneity between studies to assess robustness of findings using the I^2 statistic, whereby an I^2 less than 50% indicates low heterogeneity.[36] To determine potential publication bias, we created funnel plots for visual inspection and performed Egger tests.[37] An asymmetric plot and p value less than 0.05 suggested a significant publication bias.

Meta-regression analyses

It should be noted that relevant demographic and clinical variables (i.e., age, percentage of males, age of onset, illness duration, PANSS total scores and WASI score) may have potential effects on the results of the analysis. In accordance with previous meta-analyses,[28,38] we used a threshold of p less than 0.05 (corrected for FWE) with a minimum cluster extent of at least 10 voxels to determine statistical significance, and discarded findings in regions other than those detected in the main analyses. We reported results in MNI space.

Results

Figure 1 displays the process of the systematic literature search and assessment of eligible studies. Twenty-five studies — with 33 group comparisons of patients with schizophrenia versus healthy controls (i.e., experiments) — met the inclusion criteria, including 2008 patients with schizophrenia (1277 males and 716 females, mean age 33.00 yr) and 2004 healthy controls (1086 males and 904 females, mean age 32.51 yr). Age did not differ significantly between patients and controls ($t = 0.23$, $p = 0.93$) but there was a significant difference in sex distribution ($\chi^2 = 37.25$, $p < 0.001$). In different clinical statuses, 7 experiments from 7 studies included patients with first-episode schizophrenia (462 patients and 708 healthy controls); 17 experiments from 14 studies included patients with chronic schizophrenia (847 patients and 708 healthy controls); and 6 experiments from 6 studies included patients with unmedicated schizophrenia (419 patients and 419 healthy controls). We excluded 29 experiments from 22 studies because of the insufficient number of participants ($n < 10$) or because they were uncorrected for statistics. The demographic and clinical characteristics of participants are presented in Table 1; imaging parameters, statistical thresholds and quality scores of each identified study in our meta-analysis are presented in Table 2.

Pooled meta-analysis

Compared with healthy controls, patients with schizophrenia had decreased cortical thickness in 3 clusters including the right IFG and bilateral insula extending to the bilateral STG. None of the regions showed increased cortical thickness (Figure 2A and Table 3).

Subgroup meta-analysis

Compared with healthy controls, there was no significant cortical thickness difference among patients with first-episode schizophrenia or those with unmedicated schizophrenia. In addition, patients with chronic schizophrenia showed decreased cortical thickness in the right insula extending to the right IFG (Figure 2B and Table 3).

Moreover, the subgroup analysis excluding the studies with an insufficient number of participants ($n < 10$) or uncorrected for results exhibited decreased cortical thickness in the right IFG and bilateral insula (Appendix 1, Figure S2 and Table S3).

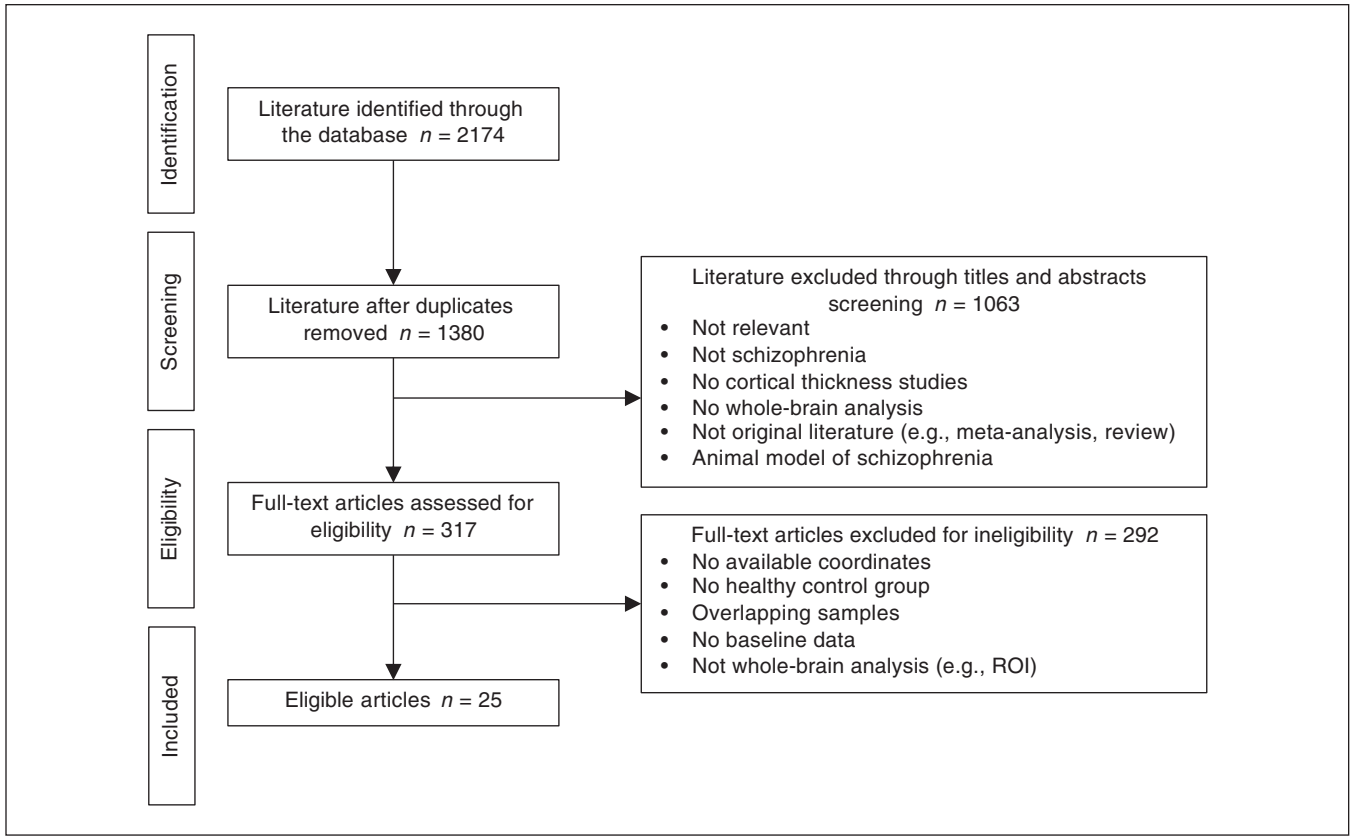

Figure 1: Flow chart of meta-analysis of cortical thickness studies involving patients with schizophrenia. ROI = region of interest.

Jackknife sensitivity analysis

In the main analysis of jackknife sensitivity, results of the right IFG and right insula were preserved throughout all combinations, and the left insula was preserved throughout 31 combinations of 33 experiments. Thus, the results of right IFG and bilateral insula were all highly replicable.

Heterogeneity and publication bias

No regions with abnormal cortical thickness showed significant heterogeneity (all $I^2 < 50\%$) in the pooled meta-analysis (Table 3). Furthermore, in the analysis of publication bias, the Egger test of funnel plot asymmetry was not statistically significant in the right insula ($Z = -1.39$, $p = 0.16$), left insula ($Z = 0.74$, $p = 0.46$) or right IFG ($Z = 0.78$, $p = 0.43$) in the main analysis (Appendix 1, Figure S4).

Meta-regression analyses

Illness duration was negatively associated with cortical thickness in the right IFG. In addition, the WASI score was positively associated with cortical thickness in the right IFG and left insula, although only 9 experiments drove this analysis. We detected no significant effect of mean age, sex distribution, age of onset and symptom score (PANSS total score) on cortical thickness abnormalities (Table 4).

Discussion

In this large meta-analysis of the whole brain, we explored abnormal cortical thickness among adult patients with schizophrenia. This study included 25 studies with 33 data sets including 2008 patients with schizophrenia and 2004 healthy controls to precisely localize regions with abnormalities in cortical thickness among patients with schizophrenia. Compared with healthy controls, patients with schizophrenia displayed decreased cortical thickness in the right IFG and bilateral insula extending to the bilateral STG. The subgroup meta-analysis found decreased cortical thickness in the right insula extending to the right IFG among patients with chronic schizophrenia. In contrast, we found no significant differences among patients with first-episode schizophrenia and patients who were unmedicated. Meta-regression analyses demonstrated that the illness duration was negatively associated with cortical thickness in the right IFG, and the WASI score was positively associated with cortical thickness in the right IFG and left insula. These findings may offer insights into the pathophysiology of schizophrenia.

Our meta-analysis found decreased cortical thickness in the right IFG among patients with schizophrenia, and the subgroup analysis found decreased cortical thickness in the right IFG among those with chronic schizophrenia. In addition, meta-regression analysis indicated longer illness duration and lower WASI scores was associated with more pronounced

Table 1: Demographic and clinical characteristics of participants in the 25 included studies

	Demographic characteristics					Clinical characteristics among patients with schizophrenia						
	No. of participants		Age, yr, mean									
Study	SCZ	HC	SCZ	HC	Age of onset, yr	Illness duration, mo, mean*	Medication status (%)	Chlorpromazine equivalent, mg	FE or chronic	PANSS total score	WASI score	Study country
Barry et al., 2019[39]	42	23	41.4	38.4	26.85	177.6	Yes (NA)	331.9	Chronic	61.6	94.5	England
Besteher et al., 2016[19]	37	50	30.9	29.5	NA	NA	Yes (NA)	403.5	NA	78.5	NA	Germany
Boos et al., 2012[40]	155	186	26.9	27.5	NA	NA	Yes (90)	NA	NA	62.2	93.3	Netherlands
Boos et al., 2012[40]	155	122	26.9	27.5	NA	NA	Yes (90)	NA	NA	62.2	93.3	Netherlands
Chen et al., 2016[41]	30	30	23.2	22.4	NA	NA	No	NA	FE	95.7	NA	China
Feng et al., 2021[42]	67	170	24.8	24.8	NA	9.6	Yes (NA)	NA	FE	NA	NA	China
Green et al., 2016[43]	22	22	38.9	39.6	22.89	165.4	Yes (100)	NA	Chronic	73.9	NA	Australia
Jamea et al., 2021[44]	15	15	33.9	28.8	NA	NA	NA	NA	NA	NA	NA	Arabia
Kong et al., 2015[45]	22	20	54.0	52.8	NA	378.5	Yes (NA)	NA	Chronic	NA	NA	Germany
Madre et al., 2020[46]	128	127	41.0	39.0	22	216	Yes (95)	585	Chronic	NA	NA	Spain
Penades et al., 2016[47]	35	15	37.0	34.8	NA	139.1	Yes (14)	269	Chronic	NA	NA	Spain
Quide et al., 2018[48]	214	94	38.1	37.0	NA	171.1	Yes (100)	NA	Chronic	NA	105.7	Germany
Romreo et al., 2017[49]	44	45	43.2	43.0	NA	242.2	Yes (100)	709.0	Chronic	NA	NA	Spain
Storvestre et al., 2019[50]	11	19	33.2	33.2	18.1	NA	Yes (100)	NA	Chronic	NA	94.4	Norway
Storvestre et al., 2019[50]	17	19	34.3	33.2	21.9	NA	Yes (100)	NA	Chronic	NA	101.2	Norway
Swam et al., 2012[51]	10	10	40.0	40.0	27.4	164.4	Yes (100)	411.6	Chronic	76.9	NA	Switzerland
Swam et al., 2012[51]	10	10	36.3	40.0	29.1	93.6	Yes (100)	583.1	Chronic	76.1	NA	Switzerland
Takayanagi et al., 2020[52]	102	79	25.5	24.3	22	43.2	Yes (98)	NA	Chronic	NA	NA	Japan
Takayanagi et al., 2020[52]	46	79	25.0	24.3	NA	NA	Yes (85)	NA	NA	NA	NA	Japan
Tao et al., 2013[53]	29	26	26.0	25.0	NA	1–132	NA	NA	NA	NA	NA	China
Tully et al., 2014[54]	26	29	38.7	33.8	22.2	196.8	Yes (96)	461.1	Chronic	NA	108.1	America
Voineskos et al., 2013[55]	18	18	49.0	50.0	21	336	Yes (100)	430	Chronic	NA	NA	Canada
Voineskos et al., 2013[55]	18	18	49.0	50.0	22	336	Yes (100)	408	Chronic	NA	115	Canada
Wang et al., 2018[56]	21	22	21.2	22.7	NA	21.8	Yes (29)	NA	FE	NA	99.0	China
Wei et al., 2022[57]	117	98	24.7	26.5	NA	1–24	No	NA	FE	91.5	102.8	China
Xiao et al., 2015[58]	128	128	24.3	26.1	NA	11.5	No	NA	FE	96.4	NA	China
Zeng et al., 2016[59]	55	61	25.0	25.3	25.0	NA	No	NA	FE	NA	NA	China
Zhang et al., 2022[60]	44	48	24.7	24.8	NA	NA	Yes (95)	573.8	FE	75.3	81.9	China
Zheng et al., 2014[61]	95	98	27.0	25.5	NA	NA	NA	NA	NA	NA	NA	China
Zheng et al., 2014[61]	67	63	29.5	24.6	NA	NA	NA	NA	NA	NA	NA	China
Zheng et al., 2014[61]	100	100	26.0	24.5	NA	NA	NA	NA	NA	NA	NA	China
Zugman et al., 2013[62]	61	80	33.8	33.5	NA	154.8	Yes (NA)	NA	Chronic	63.4	NA	Brazil
Zugman et al., 2013[62]	67	80	35.8	33.5	NA	146.5	Yes (NA)	NA	Chronic	54.6	NA	Brazil

FE = first-episode; HC = healthy control; NA = not available, PANSS = The Positive and Negative Syndrome Scale; SCZ = schizophrenia; WASI = Wechsler Abbreviated Scale of Intelligence.
*Range provided if mean was not available.

reduction of cortical thickness in the IFG. Consistent with our findings, a recent meta-analysis reported lower cortical thickness in the IFG among patients with chronic schizophrenia (n = 579) relative to healthy controls.[29] The IFG, the ventrolateral part of the prefrontal cortex, plays an important role in executive function (such as cognitive inhibition) and affect modulation.[63,64] A task-based functional MRI meta-analysis reported activation decreases in the IFG among patients with schizophrenia during neurocognitive-related processing.[65] Another resting-state functional MRI meta-analysis reported that regions of IFG had increased amplitude of low-frequency fluctuation among patients with schizophrenia,[66] which may be interpreted as reflecting a compensatory effect for reduced cortical thickness.

Table 2: Imaging characteristics of the 25 included studies

Study	Imaging characteristics				Quality score
	Scanner field strength, T	Software	FWHM, mm	Threshold	
Barry et al., 2019[39]	3.0	FreeSurfer	10	$p < 0.05$, RFT	11.5
Besteher et al., 2016[19]	1.5	FreeSurfer	NA	$p < 0.001$, corrected	11
Boos et al., 2012[40]	1.5	FreeSurfer	20	$p < 0.05$, FDR	11
Chen et al., 2016[41]	3.0	FreeSurfer	10	$p < 0.05$, corrected	12
Feng et al., 2021[42]	3.0	FreeSurfer	10	$p < 0.05$, FDR	11.5
Green et al., 2016[43]	1.5	FreeSurfer	NA	$p < 0.05$, corrected	11
Jamea et al., 2021[44]	3.0	CAT12	15	$p < 0.05$, corrected	10
Kong et al., 2015[45]	3.0	FreeSurfer	10	$p < 0.05$, FDR	11.5
Madre et al., 2020[46]	1.5	FreeSurfer	20	$p < 0.05$, corrected	11
Penades et al., 2016[47]	3.0	FreeSurfer	15	$p < 0.05$, corrected	11.5
Quide et al., 2018[48]	1.5	CAT12	8	$p < 0.05$, FWE	11
Romreo et al., 2017[49]	NA	FreeSurfer	15	$p < 0.05$, FWE	11
Storvestre et al., 2019[50]	3.0	FreeSurfer	10	$p < 0.05$, corrected	11
Swam et al., 2012[51]	3.0	Brain Voyager QX	NA	$p < 0.05$, uncorrected	10.5
Takayanagi et al., 2020[52]	1.5	FreeSurfer	10	$p < 0.005$, AFNI	11*
Tao et al., 2013[53]	3.0	FreeSurfer	NA	$p < 0.01$	11
Tully et al., 2014[54]	3.0	FreeSurfer	10	$p < 0.05$, corrected	11.5
Voineskos et al., 2013[55]	1.5	FMRIB	NA	$p < 0.05$, FDR	11
Wang et al., 2018[56]	3.0	CAT12	8	$p < 0.001$, uncorrected	11
Wei et al., 2022[57]	3.0	CAT12	15	$p < 0.05$, FWE	12
Xiao et al., 2015[58]	3.0	CIVET	20	$p < 0.05$, FDR	11.5
Zeng et al., 2016[59]	3.0	FreeSurfer	NA	$p < 0.05$, FWE	11.5
Zhang et al., 2022[60]	3.0	FreeSurfer	15	$p < 0.05$, FDR	11.5
Zheng et al., 2014[61]	3.0	FreeSurfer	NA	$p < 0.05$, RFT	11
Zugman et al., 2013[62]	1.5	FreeSurfer	15	$p < 0.01$, corrected	11

AFNI = Analysis of Functional NeuroImages; CAT = The Computational Anatomy Toolbox; CIVET = Montreal Neurological Institute at McGill University, Montreal, Canada; FDR = false discovery rate; FSL = FMRIB's Software Library, the University of Oxford; FWE = family-wise error; FWHM = full-width at half maximum; NA = not available; RFT = random field theory.
*The quality score was 11 for the sample of 102 patients with chronic schizophrenia, and was 10.5 for the sample of 46 schizotypal disorder patients.

Furthermore, increasing evidence indicates structural abnormalities in the IFG among patients with schizophrenia; for example, meta-analysis of VBM studies has reported decreased grey matter volume in the right IFG among patients with schizophrenia.[10,65,67] A previous MRI study had reported a decrease in grey matter volume in the IFG among patients with schizophrenia and a similar decrease in the IFG among their unaffected siblings, suggesting that the structure of IFG grey matter volume may be associated with genetic susceptibility in schizophrenia.[68] Grey matter volume is the mathematical product of the cortical surface area and thickness, meaning that both cortical thickness and surface area affect the measurement of grey matter volume.[69] In addition, a previous review study reported that, in schizophrenia, the prefrontal cortex showed deficits in basilar dendritic spines of layer-3 pyramidal neurons and disruptions in inhibitory input.[70] Taken together, different methodologies have found abnormalities of the IFG, suggesting structural disruption of the IFG among patients with schizophrenia.

The insula cortex is part of the salience network and has widespread connections to the anterior cingulate cortex, temporal lobe, amygdala, thalamus and other limbic areas.[71–73] Previous review studies have reported that the insular-anchored salience network plays a central role in the abnormal mapping of salient external and internal events in schizophrenia,[73] and the structure of the salience network is affected at an early stage of development, predating the onset of psychosis.[74] We found decreased cortical thickness in the bilateral insula extending to the bilateral STG among patients with schizophrenia. Moreover, our subgroup meta-analysis displayed decreased cortical thickness in the right insula among those with chronic schizophrenia, but not among those with first-episode schizophrenia or unmedicated schizophrenia. Meta-regression analysis found that the

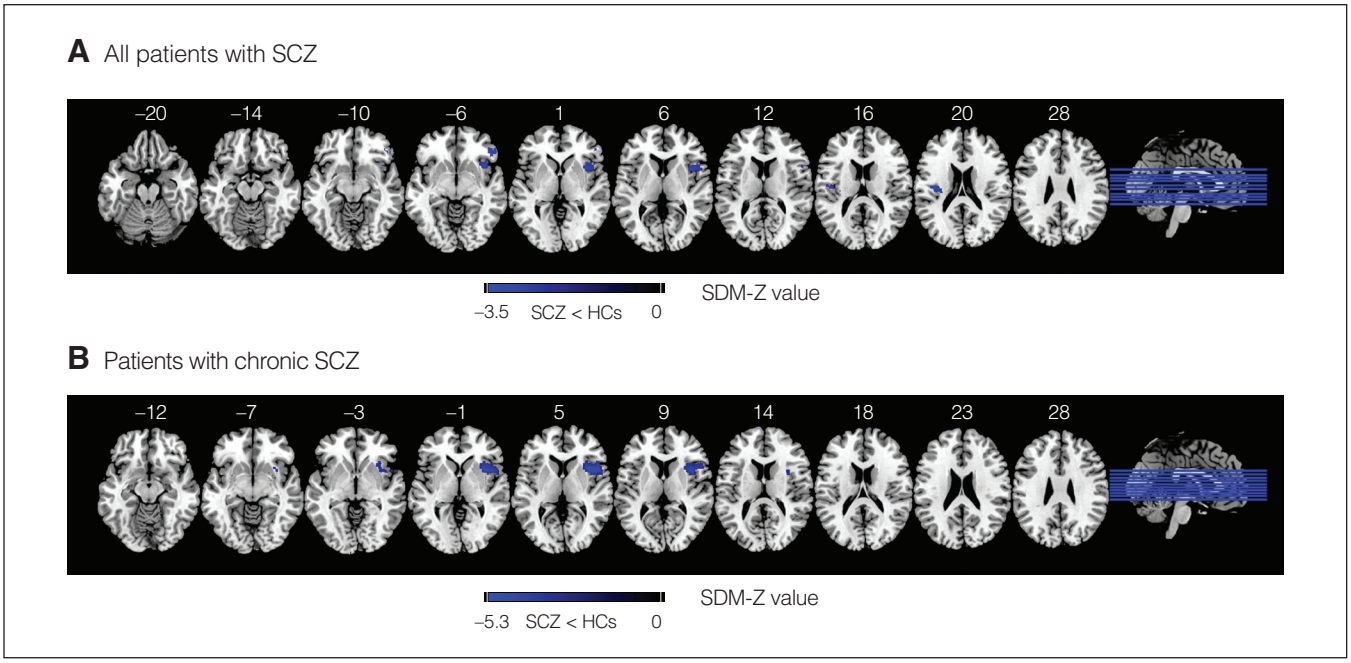

Figure 2: Alterations of cortical thickness among (A) all patients with schizophrenia (SCZ) and (B) those with chronic SCZ, compared with healthy controls (HCs). Areas with decreased cortical thickness are displayed in blue. The colour bar indicates the maximum and minimum seed-based d mapping (SDM) Z values.

Table 3: Cortical thickness alterations among patients with schizophrenia

Region	MNI coordinate			SDM Z score	*p* value	No. of voxels in cluster	Cluster breakdown (no. of voxels)	Egger test *p* value	Heterogeneity, I^2
	x	*y*	*z*						
All patients with schizophrenia									
Right insula, BA 48	38	12	−2	−3.475	0.029	332	Right insula, BA 48 (190) Right inferior frontal gyrus, opercular part, BA 48 (94) Right inferior frontal gyrus, triangular part, BA 45 (9) Right superior temporal gyrus (16)	0.164	13.47%
Left insula, BA 48	−40	−16	18	−3.216	0.029	99	Left insula, BA 48 (42) Left superior temporal gyrus (30)	0.343	33.08%
Right inferior frontal gyrus, orbital part, BA 47	48	36	−4	−3.120	0.036	91	Right inferior frontal gyrus, orbital part, BA 47 (68) Right inferior frontal gyrus, triangular part, BA 45 (21)	0.481	20.85%
Patients with chronic schizophrenia									
Right insula, BA 48	46	10	2	−5.228	< 0.001	618	Right insula, BA 47, 48 (291) Right inferior frontal gyrus, opercular part, BA 48 (145) Right inferior frontal gyrus, triangular part, BA 45 (28) Right lenticular nucleus, putamen, BA 47, 48 (32)	0.204	39.40%

BA = Brodmann area; MNI = Montreal Neurological Institute; SDM = seed-based d mapping.

WASI score was positively associated with cortical thickness in the left insula, suggesting that lower WASI scores may be associated with thinner cortical thickness in the insula among those with schizophrenia. A recent large-sample study supported our regression results, finding that a lower intelligence quotient (IQ) was correlated with smaller insula volume among patients with schizophrenia, which may explain the disruption of insula structure leading to IQ impairment.[75] A systematic review and meta-analysis found cortical thinning in the right insula among individuals in the first

Table 4: Factors affecting decreased cortical thickness in studies involving patients with schizophrenia

Factor	Region	MNI coordinate			SDM Z score	*p* value	No. of voxels in cluster
		x	*y*	*z*			
Illness duration	Right inferior frontal gyrus, BA 48	36	12	–4	–4.476	0.003	361
WASI score	Left insula, BA 48	–42	–30	18	7.122	< 0.001	2957
	Right inferior frontal gyrus, BA 47	44	40	–12	5.387	0.027	78

BA = Brodmann area; MNI = Montreal Neurological Institute; SDM = seed-based d mapping; WASI = Wechsler Abbreviated Scale of Intelligence.

episode of psychosis and in the long-term illness stages of schizophrenia.[29] They used an uncorrected threshold of *p* less than 0.005. Although previous studies have shown that this threshold adequately controls the false-positive rate,[33] it remains an approximation of corrected results. A study from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium also reported finding a thinning of the insular cortex among patients with schizophrenia, but they used data from participating sites rather than from published literature.[76] Our recent multimodal voxel-based meta-analysis also found decreased regional homogeneity and grey matter volume in the insula of patients with schizophrenia,[10] which suggested both functional and structural impairment. Postmortem studies have reported a reduction in the size of neurons and glia in layer 2 of the insular cortex among patients with schizophrenia.[77] In addition, a systematic review reported that the insula is a critical brain region for electroconvulsive therapy for patients with schizophrenia.[78] Moreover, structural alterations in grey matter volume and the cortical thickness of the insula and IFG have been reported across several mental disorders. For example, a previous meta-analysis of bipolar disorder reported cortical thinning in the insula and IFG.[27] Several meta-analyses of VBM found grey matter loss in the insula and IFG in schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder and anxiety.[65,79–81] The presence of similar structural deficits in the insula and IFG across different psychiatric disorders suggests potential shared neural substrates across psychopathologies.

Our findings also revealed decreased cortical thickness in the bilateral STG among patients with schizophrenia. The STG includes the primary auditory cortex (the Heschl gyrus), responsible for processing auditory information, and the Wernicke area, for understanding spoken language.[82] Moreover, the left STG plays a pivotal role in processing cognitive and affective theories of mind.[83,84] Deficits in the STG are associated with a series of symptoms, and abnormalities of the STG have been significantly implicated in auditory hallucinations, sensory disturbances and thought disorders among patients with schizophrenia,[85,86] which are core symptoms of schizophrenia. A postmortem study reported decreased levels of *N*-acetylaspartate and *N*-acetylaspartylglutamate in the STG among patients with schizophrenia, which indicates neuronal dysfunction or damage in the STG.[87] In addition, a meta-analysis from Zhao and colleagues[29] recently reported that patients with FEP showed cortical thinning in the right lateral STG, right anterior cingulate cortex and right insula. However, we did not find a significant difference in cortical thickness among patients with first-episode schizophrenia (7 studies) and unmedicated patients with schizophrenia. This may be caused by the limited sample size in this study, and future verification could involve a more substantial sample size.

Limitations

This study was based on summarized data (e.g., reported coordinate and effect sizes from published studies) instead of raw data, and results with few or moderate effect sizes may be missed. The studies included in the meta-analysis used different statistical thresholds and multiple comparison corrections, and we excluded comparisons with fewer than 10 participants. Some participants took psychotropic medicines, so whether medicines or the illness caused the alteration of cortical thickness in schizophrenia remains unknown. Furthermore, the results should be treated with caution, given the limited number of studies, potential limitations in statistical power and the presence of numerous datasets in chronic schizophrenia. Future studies should investigate the neuropathologic mechanism of cortical thinning.

Conclusion

This meta-analysis suggested robust reductions in cortical thickness in the IFG, insula and STG among adult patients with schizophrenia, particularly those with chronic schizophrenia. The results provide useful insights to understanding the underlying pathophysiology of schizophrenia.

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