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Thinning of the temporal and insular cortex is associated with negative symptoms and impaired attention in Chinese chronic schizophrenia patients with deficit syndrome

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Abstract

Background The considerable clinical heterogeneity of schizophrenia poses significant challenges for elucidating its neurobiology. The concept of deficit schizophrenia (DS) is a valuable framework for addressing the heterogeneity of schizophrenia. Growing evidence suggests notable differences between deficit (DS) and nondeficit (NDS) schizophrenia, indicating that DS could represent a separate disease entity.

Methods We aimed to use FreeSurfer to identify specific changes in cortical thickness among NDS patients and healthy controls (HCs) in a Chinese sample. Furthermore, we examined the potential relationships between changes in cerebral cortical thickness and negative symptoms and attention deficits in DS patients. A total of 142 subjects (48 HCs, 50 NDSs, and 44 DSs) underwent MRI scans and completed the assessment of psychopathological severity and cognitive performance.

Results Compared with HCs, DS and NDS patients presented common cortical thinning in the right insula, whereas cortical thinning in the left supramarginal cortex was more prominent in DS patients. We also found that thinning of the temporal and insular cortex was correlated with negative symptoms and impaired attention in DS patients.

Conclusions Cortical thinning in specific brain regions in DS patients was found to be correlated with specific clinical and cognitive symptoms.

Keywords Deficit schizophrenia, Nondeficient schizophrenia, Brain cortical thickness, Negative symptoms, Neuropsychological assessment

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Background

The concept of deficit schizophrenia (DS) was first proposed by Carpenter in 1988 [1]. Categorizing patients into those with deficit and nondeficit subtypes of schizophrenia helps to reduce heterogeneity in describing the disease [2]. DS, with predominantly negative symptoms [1], can be differentiated from nondeficit schizophrenia (NDS) by greater impaired cognition, a longer disease course and poorer functional outcomes [3]. Based on estimates from the literature, the prevalence of DS is 25–30% or greater in the chronic schizophrenia population [4]. DS is stable long-term, and the severity of the deficit syndrome is closely related to cognitive impairment. Compared with NDS patients, DS patients perform worse in all major cognitive domains, providing reliable evidence for the deficit/nondeficit classification [2, 5]. However, the prognostic value of classifying patients based on clinical manifestations remains limited.

Advancements in magnetic resonance imaging (MRI) technology provide researchers with a widely available and biologically safe method for investigating potential neurobiologically distinguished subgroups in patient populations. Therefore, neurobiological markers may be used to differentiate these two subtypes of schizophrenia [6].

Structural MRI enables the quantification of brain anatomical features. Research on deficit schizophrenia has revealed that DS patients differ from NDS patients in several aspects. These differences include a decrease in grey matter volume in the brain regions of DS patients compared with those of NDS patients [7]. Compared with healthy controls, DS patients exhibit more prevalent brain structural abnormalities, especially in the left frontal, temporal, and marginal structures [8]. Cortical thinning is a well-established feature of schizophrenia, with the potential to predict the risk of developing psychosis among first-degree unaffected adolescent relatives of SZ patients [9]. Although cortical thinning is one of the most common findings associated with cognitive impairment in schizophrenia patients [10, 11], it is also observed in schizophrenia patients without cognitive impairment [12].

To date, only three studies have examined cortical thickness in patients with DS and NDS [13–15]. Takayanagi and colleagues identified thinning of the anterior cingulate cortex in DS patients via FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) [13], whereas using the CIVET pipeline method, Voineskos et al. reported cortical thinning in parts of the frontal and temporal regions in both DS and NDS patients, although no significant difference was detected between the groups [14]. Moreover, cortical thinning in the inferior frontal gyri and superior temporal gyrus in DS patients was observed by Xie et al., again via the CIVET pipeline approach [15]. Therefore, whether the cortical thickness of DS patients differs from that of NDS patients or healthy controls (HCs) remains to be studied. Compared with prior research [15], we have increased the sample size (44 DS patients, 50 NDS patients, and 48 HCs). Unlike the CIVET pipeline used in previous studies (version 1.1.9), this analysis employed FreeSurfer 7.2.0. Compared with CIVET, FreeSurfer 7.2.0 provides improvements in multiple aspects, including the following: (1) **Higher resolution**: FreeSurfer typically offers higher spatial resolution, allowing for more accurate capture of subtle structural changes in the cerebral cortex. (2) **Improved cortical segmentation**: This software adopts more advanced algorithms in cortical segmentation, which can more effectively distinguish different brain regions and reduce the occurrence of misclassification. (3) **Automated processing flow**: This version enhances automation functionality, significantly reduces processing time, and improves the consistency and repeatability of results.

To address this question [16], this study included MRI and a neurocognitive battery for 142 male participants (44 DS patients, 50 NDS patients, and 48 HCs) to calculate the cortical thickness, psychopathology, neurocognitive battery, and relationships among them. This study contributes to a deeper understanding of the relationships among cortical thickness, psychopathology and cognitive function in DS patients.

Methods

The sample size was determined to be 120 subjects for an effect size of 0.25 based on a previous study that investigated cortical thickness in deficit schizophrenic patients [15] via the G*Power 3.1 program, with a power of 0.8 and a significance level of 0.05. However, considering a 15% dropout rate, 142 male participants were recruited and allocated into three groups (44 DS patients, 50 NDS patients, and 48 HCs). This study included 44 DS patients (mean age = 47.82 ± 7.75 years), 50 NDS patients (mean age = 47.50 ± 6.32 years), and 48 HCs (mean age = 45.04 ± 9.68 years), all of whom were recruited from The Affiliated Guangji Hospital of Soochow University (Jiangsu Province, China). The patient groups were all long-term (> 1 year) inpatients at the psychiatric hospital. These patients met the criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and the DSM-IV Structured Clinical Interview (SCID-I) [17]. Additionally, patients with a Hamilton Depression Scale score ≥ 7 were excluded. The patients were classified as DS or NDS via the Chinese version of the Deficit Syndrome Scale (SDS) [18]. The screening criteria for DS were a deficit syndrome rated as at least moderate according to the SDS, lasting longer than 12 months, and including at least 2 of the following symptoms: restricted affect, diminished

affective range, paucity of speech, restricted interests, diminished sense of purpose, and diminished social drive. Each patient was taking antipsychotic medications and had not changed their treatment regimen for at least 12 months prior to the study. All patients were right-handed and physically healthy. We excluded candidates with severe head trauma, neurological illnesses, or substance abuse disorders.

The HCs were matched for age, handedness, and education and included individuals from the broader community and the university. None of the HCs had any cognitive, psychiatric, or physical comorbidities.

The authors assert that all procedures contributing to this work comply with the ethical standards set by the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the WuTaiShan Hospital Ethics Committee for clinical research (Approval No. 2018-056). Written informed consent was obtained from all participants.

Imaging

The subjects were scanned using a 3.0T MRI scanner (GE HDx) with T1-weighted high-resolution three-dimensional brain volume imaging, resulting in 172 contiguous T1-weighted slices. The scanning parameters were as follows: TR = 11.94 ms; TE = 5.044 ms; flip angle = 15°; field of view = 240 × 240 mm; matrix size = 256 × 256; slice thickness = 1 mm without gaps; voxel size = 1 × 1 × 1 mm^3; and number of slices = 172.

We used FreeSurfer 7.2.0 (http://surfer.nmr.harvard.edu/) to process the magnetic resonance images. Cortical thickness was calculated via FreeSurfer's standard automated reconstruction algorithm to reconstruct the cortical surface. First, the images were visually inspected by an experienced researcher (Jin Li) for the presence of any artefacts that might interfere with further analyses. The 3D-MPRAGE image series was then manually reoriented to the anterior–posterior commissure (AC–PC) line. Each sample was projected onto the fsaverage template and smoothed using a 30 mm Gaussian kernel.

Standardized pipeline for group analysis

Following the acquisition of T1-weighted structural imaging data, the processing pipeline involved automated segmentation of cortical and subcortical structures to generate surface-based models incorporating quantitative cortical thickness measurements and topological anatomical features. Cortical thickness, as a core morphometric parameter, has been extensively employed in neuroimaging research. Individual-space cortical thickness data were spatially normalized to the standardized brain template (fsaverage) through nonlinear registration algorithms to enable population-level analyses. Within the fsaverage coordinate system, whole-brain intergroup comparisons were conducted based on vertexwise topological correspondence. This methodology fundamentally differs from traditional predefined anatomical label-based region of interest (ROI) analysis. Each cerebral hemisphere contains 163,842 topologically defined vertices, necessitating 327,684 independent hypothesis tests for two-sample comparisons. Notably, conventional manual ROI annotation approaches prove technically infeasible for such high-dimensional analytical frameworks. For details, see Fig. 1.

GLM

The implementation of generalized linear models (GLMs) enables simultaneous statistical comparisons across all vertices. While GLMs inherently possess statistical complexity, their conceptual framework can be simplified for practical interpretation. Consider a scenario comparing cortical thickness between two groups (GROUP1 and GROUP2). A common analytical challenge arises when confounding variables, such as age disparities between cohorts, may bias intergroup comparisons. To mitigate this, the GLM framework incorporates both group membership (independent variable) and confounding factors (e.g., age) into the design matrix.

The resulting model yields two beta coefficients:

- $\boldsymbol{\beta_1}$ quantifies the group effect, where $\beta_1 \neq 0$ indicates significant intergroup differences.
- $\boldsymbol{\beta_2}$ represents the confounding factor's contribution, with $\beta_2 \neq 0$ confirming its confounding influence. For primary hypothesis testing (intergroup differences), interpretation focuses on β_1, irrespective of β_2's significance.

The GLM architecture permits scalable integration of additional confounders (e.g., sex, intracranial volume) by appending columns to the design matrix. While comprehensive mathematical derivations exceed this practical guide, we emphasize implementation in FreeSurfer:

1. **Design matrix specification**: Include categorical group variables and continuous covariates (e.g., age).
2. **Statistical inference**: Utilize clusterwise correction methods (e.g., Monte Carlo simulations) to address multiple comparisons across vertices.
3. **Visualization**: Thresholded statistical maps (e.g., $p < 0.05$, cluster-corrected) localize regions exhibiting significant group effects.

For details, see Fig. 2.

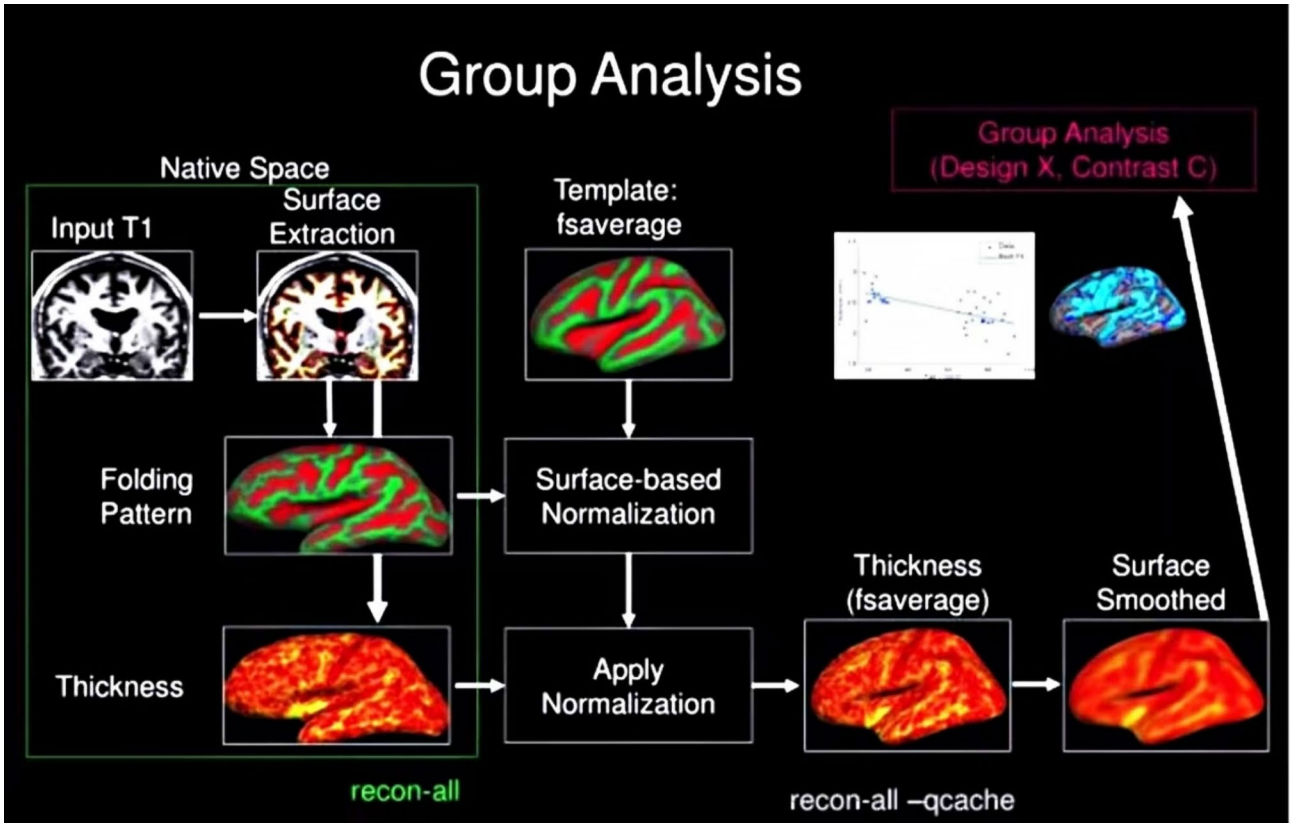

Fig. 1 Standardized Pipeline for Group Comparisons in FreeSurfer

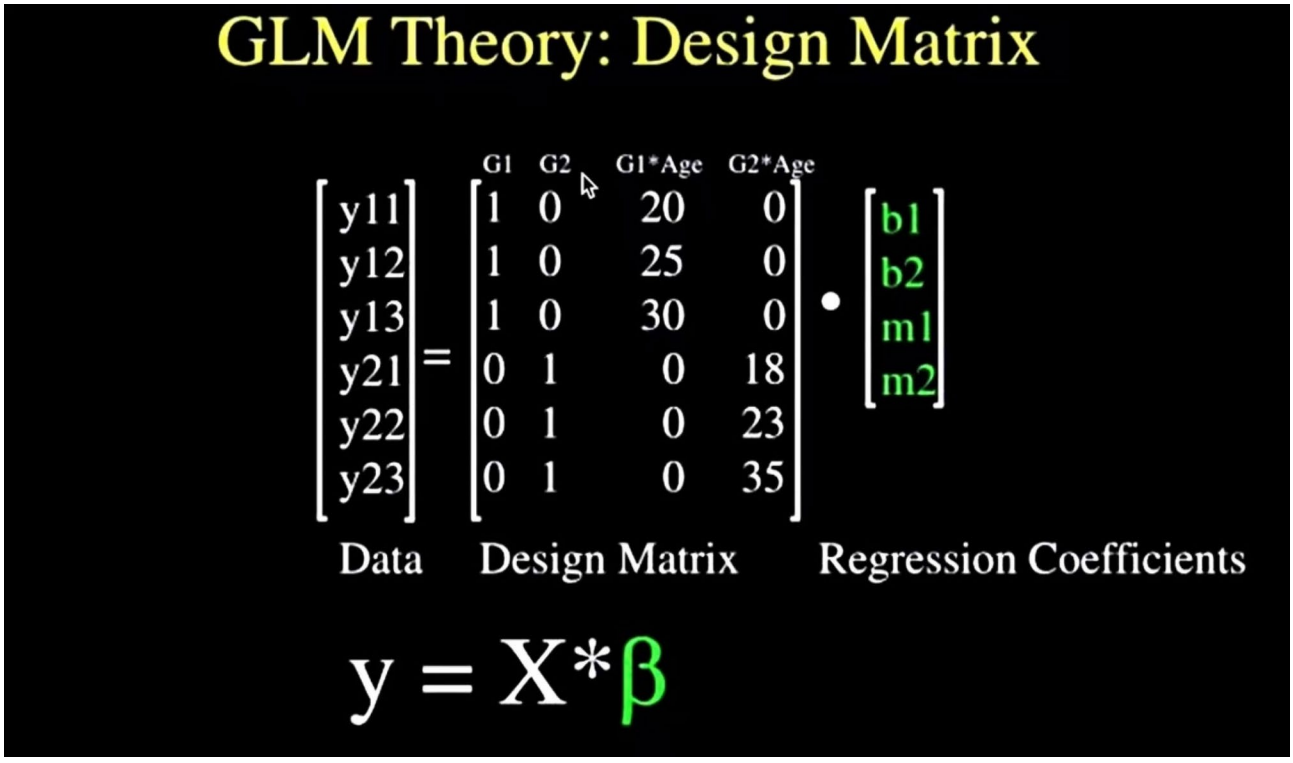

Fig. 2 Fundamental Principles of the General Linear Model (GLM)

Multiple comparison correction

In neuroimaging data analysis, the issue of multiple comparison correction holds significant statistical importance. Taking the typical resolution of cerebral cortical surface models as an example, a single cerebral hemisphere contains 163,842 vertices, necessitating statistical testing at this magnitude during whole-brain analysis. When conventional significance thresholds ($\alpha = 0.05$) are employed, approximately 8,192 false-positive results ($163{,}842 \times 0.05$) are theoretically expected. This random error generation mechanism primarily stems from the cumulative effect of Type I errors. Specifically, as the number of statistical tests increases, the familywise error rate (FWER) exhibits exponential growth, substantially compromising the reliability of statistical inferences.

The permutation test, as a nonparametric statistical method, provides an effective correction strategy for this issue. Its core principle lies in constructing an empirical null distribution: through random reassignment of subjects between experimental and control groups (typically involving 1,000–10,000 iterations), each iteration calculates maximum cluster statistics, ultimately determining the corrected significance threshold via Monte Carlo simulation. This method effectively reduces false-positive rates caused by multiple comparisons through strict control of the FWER. Notably, permutation testing maintains rigorous error control when the original data satisfy the exchangeability assumption. In neuroimaging analysis tools such as FreeSurfer, the implementation of this method incorporates topologically constrained cluster inference, which simultaneously accounts for spatial neighbourhood correlations and preserves statistical power, thereby providing crucial safeguards for the reliability analysis of neuroimaging data.

Clinical assessments

The severity of the clinical symptoms was assessed via the Positive and Negative Syndrome Scale (PANSS) [19].

Neurocognitive assessments

Two highly trained psychiatrists conducted seven different neuropsychological tests on all the subjects, including the digit cancellation test (DCT), the animal naming test (ANT), the controlled oral word association test (COWAT), the spatial span test (SS), the two-part trail-making task (TMT-A and TMT-B), the block design test (BDT) and the Stroop colour-word test (SCWT).

The neurocognitive battery assessed the following:

Executive functions: The ANT, COWAT, TMT-B and SCWT were used to assess executive functions.

Sustaining and focusing attention: The DCT and TMT-A were used to assess attention.

Memory functions: The SS and BDT (visuospatial functions) were used to assess memory functions.

The tests used in this study are described below:

DCT

The DCT task includes a page with 20 lines, each containing 25 digits. The participant is required to quickly cross out all the numbers that match the first digit of each line and record the total time spent in seconds. The DCT is considered a test for sustained attention and focus [20].

ANT

The animal naming test requires participants to say as many words as possible within 60 s that belong to a specific semantic category (animal). It tests and evaluates language fluency, such as recalling words [21].

COWAT

A speech or word fluency test that requires participants to say as many words as possible, starting with Chinese characters such as “fa, da, yi” within 60 s.

SS

The spatial span (SS) testing tool consists of 10 irregularly arranged blue blocks fixed on a whiteboard [22]. In this test, participants are asked to repeat the exact order from memory after observing the experimenter tapping the blue blocks in a prearranged order. This test assesses spatial working memory ability.

TMT-A and TMT-B

TMT-A: This test involves connecting the circle numbers 1 to 25 in numerical order as quickly as possible while recording the completion time.

TMT-B: The circles containing numbers or letters must be connected in alternating order (1-a, 2-B, etc.) as quickly as possible.

This test is used to evaluate attention and psychomotor speed.

BDT

The block design test (BDT) [23] requires participants to use wooden blocks to assemble patterns based on the provided images within a specified time frame. After applying standardized scoring criteria, the scores reflect an individual’s spatial perception, visual analysis ability, and speed of information output.

Stroop colour-word test (SCWT)

The Stroop colour-word test [24] is a type of cognitive aptitude test. In accordance with the Stroop effect principle, the test examines participants’ ability to overcome the influence of font colour when naming colour nouns written in conflicting colours. The test is generally divided into three parts: (1) quick naming of colour patches; (2) rapid recitation of colour names; and (3)

Table 1 Demographics and clinical characteristics of the DS, NDS, and HC groups

	DS ($n=44$)	NDS ($n=50$)	HC ($n=48$)	*P* value
Age	47.82 ± 7.75	47.50 ± 6.32	45.04 ± 9.68	0.187
Education years	8.73 ± 2.89	9.32 ± 1.87	10.10 ± 2.75	0.034
BMI	24.56 ± 3.31	25.62 ± 2.94	23.78 ± 2.06	0.010
Age at onset	22.23 ± 2.45	22.38 ± 3.27	-	0.558
Duration	25.59 ± 7.24	25.12 ± 6.74	-	0.428
CPZ-equivalent dose (mg/day)	475.57 ± 220.18	529.00 ± 213.56	-	0.927
PANSS total score	64.75 ± 9.40	50.80 ± 7.26	-	0.170
Positive syndrome	11.36 ± 2.93	10.74 ± 2.42	-	0.779
Negative syndrome	23.48 ± 6.41	14.74 ± 3.85	-	0.000
General Psychopathology syndrome	29.89 ± 3.45	25.32 ± 2.97	-	0.109

presenting a set of cards with nouns representing colour names written in different colours and checking the participants' ability to distinguish between colour names and actual colours, as well as their ability to quickly recite nouns representing colour names. The degree of influence of font colour on participants was used as an indicator of their cognitive control.

Statistical analysis

The Kolmogorov–Smirnov test was performed to assess the normality of the data, and the continuous variables were found to be normally distributed. Demographic data among the HC, DS, and NDS groups were compared via *analysis of variance* (ANOVA), and clinical symptoms among the patient groups were compared via two-sample t tests, whereas differences in cognitive test scores among the HC, DS, and NDS groups were assessed via ANOVA.

We used FreeSurfer's general linear model to compare differences in cortical thickness among the three groups: DS vs. HC, NDS vs. HC, and DS vs. NDS. Cortical thickness was associated with the PANSS negative symptom score and DCT, with age, body mass index (BMI), and years of education included as control variables. Correlation analyses were performed on the DS and NDS groups separately. To correct for multiple comparisons, a permutation test (Monte Carlo simulation) was applied. To determine the associations between symptom measures, neurocognitive assessment scores, and cortical thickness, we calculated Spearman's rho and applied Bonferroni correction for multiple comparisons. The P value was set at 0.05.

Results

Table 1 presents the demographic and clinical characteristics of all 142 participants. Significant differences were observed in years of education and BMI among the DS, NDS, and HC groups, but post hoc analysis revealed no differences in these variables between the DS and NDS groups. No significant difference was found in the type of antipsychotic treatment between the DS and NDS groups (conventional antipsychotics: 42.4% [$n=19$] vs. 31.7% [$n=16$]; novel antipsychotics: 30.3% [$n=13$] vs. 34.1% [$n=17$]; combination: 27.3% [$n=12$] vs. 34.1% [$n=17$], respectively).

The groups did not differ in age at onset, disease duration, or the equivalent dose of chlorpromazine (CPZ) (*DS* vs. *NDS*). The negative symptoms were more severe in the DS group, whereas the positive symptoms, the general psychopathological syndrome subscores of the PANSS, and the total PANSS scores did not differ between the two groups.

The values are presented as the means ± standard deviations. DS, deficit schizophrenia; NDS, nondeficit schizophrenia; HC, healthy control; PANSS, Positive and Negative Syndrome Scale; CPZ, chlorpromazine; BMI, body mass index.

Compared with the HCs, the DS group presented cortical thinning primarily in the left precuneus and right insula (Table 2; Fig. 3). Cortical thicknesses in the left superior temporal gyrus and right insula were significantly lower in the NDS group than in the HCs (Table 3; Fig. 4). In addition, the cortex of the left supramarginal area was thinner in the DS group than in the NDS group (Table 4; Fig. 5). Owing to software limitations, we were unable to derive effect size data for the differences observed in cortical thickness.

Schizophrenic patients performed significantly worse than HCs did on all the cognitive tests, and the neurocognitive test results of the DS group were significantly worse than those of the NDS group. ANCOVA results revealed differences in cognitive test scores among the three groups (48 HCs, 50 NDSs, and 44 DSs) after adjusting for age, education, and BMI (Table 5).

Table 2 Cortical thickness in the DS group compared with the HC group

Cluster no.	Cluster size (mm2)	Clusterwise *P*	MNI coordinates (maximum vertex)			Annotation
			x	y	z	
1	30.69	0.04547	-8.4	-59.0	31.3	Left precuneus
2	73.87	0.00200	38.6	-16.4	-8.7	Right insula

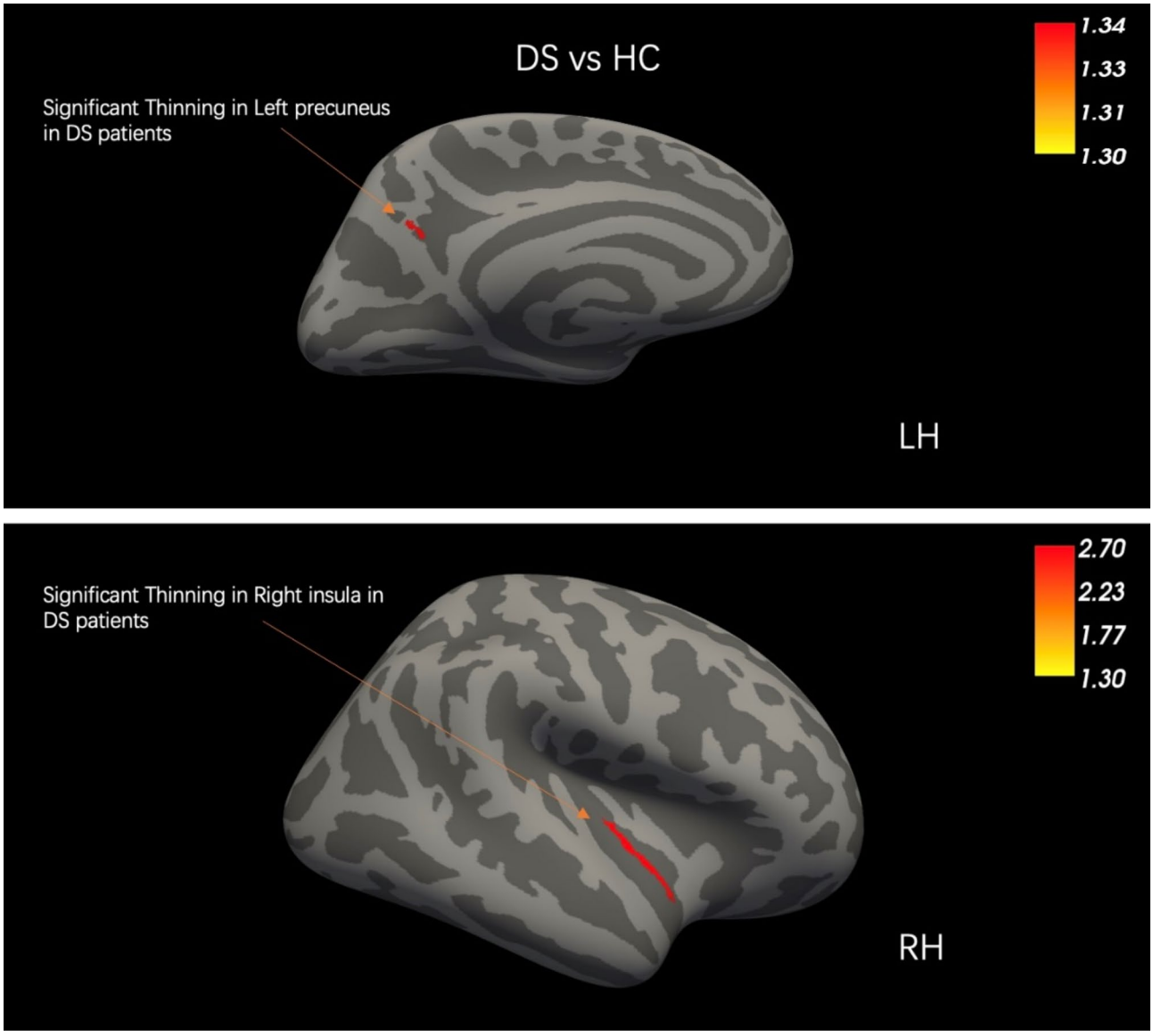

Fig. 3 Cortical statistical maps comparing the cortical thickness between deficit schizophrenia (DS) patients and healthy controls (HCs) are shown. The maps are shown for the left (upper) and right (bottom) hemispheres. The colour bar indicates the P value (< *0.005*, *corrected*). LH, *left hemisphere*; RH, *right hemisphere*. The red highlighted area of the LH, *left precuneus*; the red highlighted area of the RH, *right insula*

Table 3 Reduced cortical thickness in NDS patients compared with HCs

Cluster no.	Cluster size (mm2)	Clusterwise *P*	MNI coordinates (maximum vertex)			Annotation
			x	y	z	
1	36.40	0.02583	-45.3	-20.8	-5.2	Left superior temporal
2	35.00	0.04156	37.3	-25.4	1.6	Right insula

BMI is related to the cortical thickness of patients with schizophrenia and can also predict the thickness of the prefrontal cortex in patients with schizophrenia [25, 26]. The number of years an individual completes formal education positively correlates with their cognitive function throughout adulthood [27]. Partial correlation analysis was conducted, with age, BMI, and years of education as control variables, to examine the relationships between cortical thickness and the PANSS negative symptom score. After Bonferroni correction, we found that rh_G_temporal_inf_thickness (rho = – 0.632, $P = 0.002$) and rh_G_temporal_middle_thickness (rho = – 0.560, $P = 0.026$) were significantly correlated with the PANSS negative symptom score in DS patients but not in NDS patients.

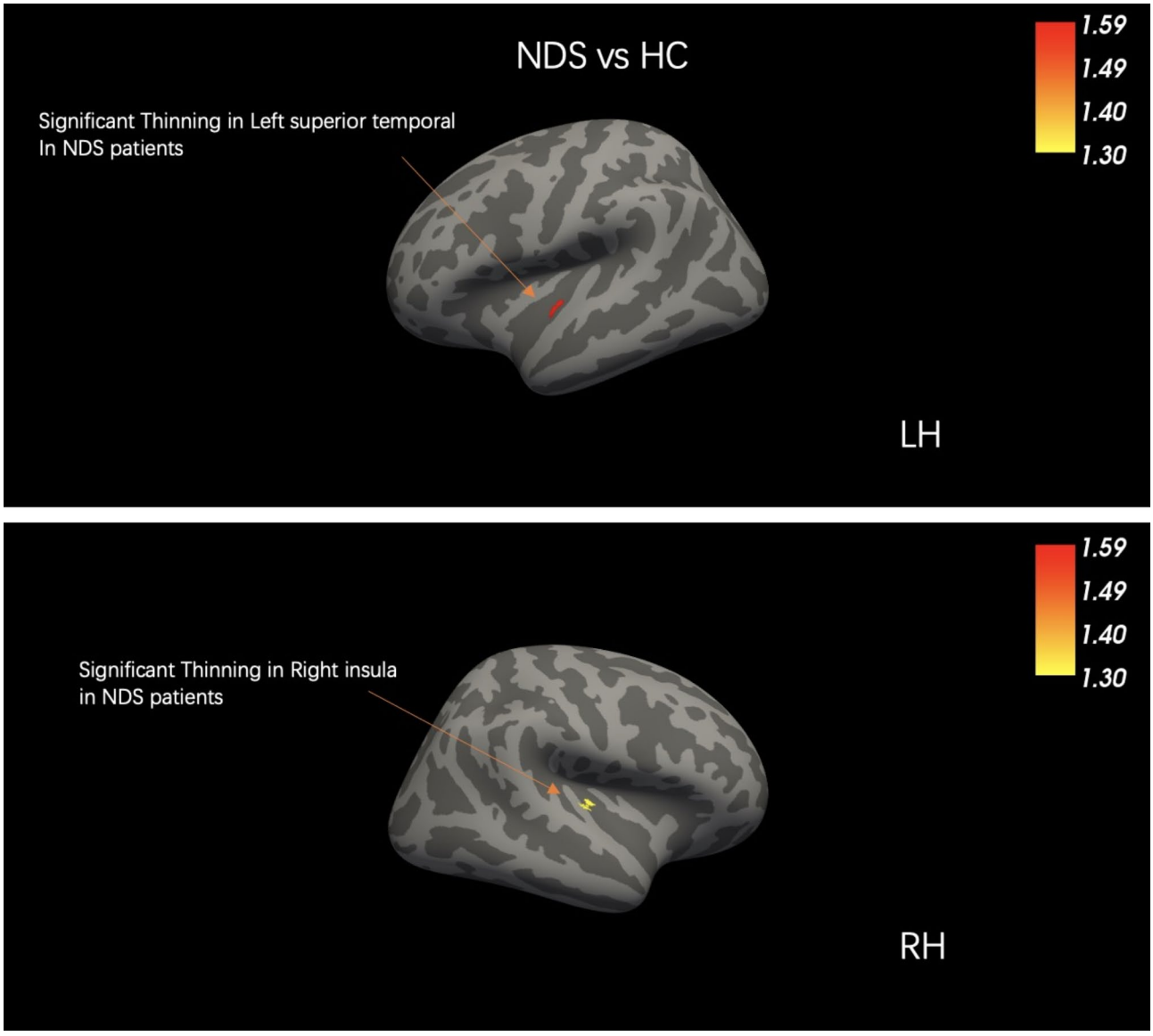

Fig. 4 Cortical statistical maps comparing the cortical thickness between nondeficit schizophrenia (NDS) patients and healthy controls (HCs) are shown. The maps are shown for the left (upper) and right (bottom) hemispheres. The colour bar indicates the P value (< *0.005*, *corrected*). LH, *left hemisphere*; RH, *right hemisphere*. The red highlighted area of the LH, *left superior temporal*; the yellow highlighted area of the RH, *right insula*

Table 4 Cortical thickness in NDS patients compared with that in DS patients

Cluster no.	Cluster size (mm2)	Clusterwise *P*	MNI coordinates (maximum vertex)			Annotation
			x	y	z	
1	33.72	0.03764	-49.7	-41.5	28.8	Left supramarginal

Partial correlation analysis was conducted, with age, BMI and years of education as control variables, between cortical thickness and the DCT score. After Bonferroni correction, we found that lh_S_circular_insula_ant_ thickness (rho = – 0.612, $P = 0.042$) was significantly correlated with the DCT score in DS patients *but not in* NDS patients or HCs.

Discussion

In this study, we investigated the relationships among severe negative symptoms, poor cognitive performance, and cortical thickness in *deficit schizophrenia* (DS) patients. Compared with HCs, both groups showed common cortical thinning in the right insula, whereas cortical thinning in the left supramarginal area was most pronounced in DS patients. We also found that thinning of the temporal and insular cortices was associated

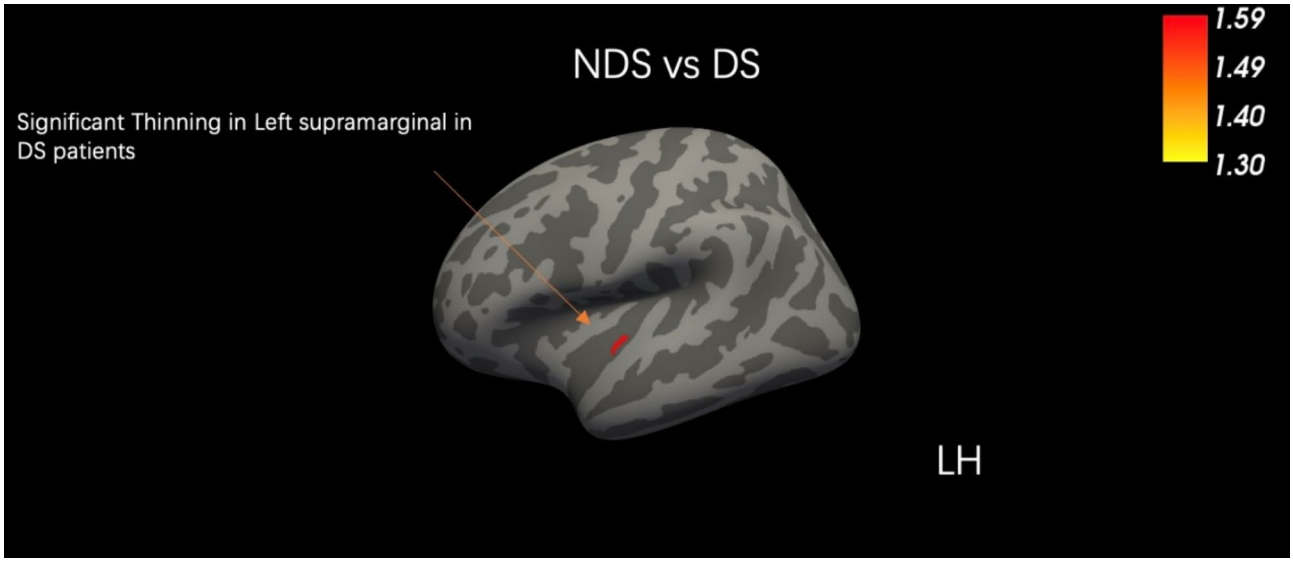

Fig. 5 Cortical statistical maps comparing the cortical thickness between nondeficit schizophrenia (NDS) patients and deficit schizophrenia (DS) patients are shown. Maps are shown for the left hemisphere. The colour bar indicates the P value (*< 0.005, corrected*). LH, *left hemisphere*. The red highlighted area of the LH, *left superior supramarginal*

Table 5 Cognitive test scores for the DS, NDS, and HC groups

	DS (*n* = 44)	NDS (*n* = 50)	HC (*n* = 48)	*P* value
DCT [b]	305.78 ± 230.22	187.31 ± 67.52	136.76 ± 44.64	0.000[e]
ANT	12.21 ± 7.27	12.58 ± 4.95	20.35 ± 5.68	0.000[c]
COWAT [a]	4.37 ± 3.18	6.84 ± 3.27	8.17 ± 2.62	0.000[d]
Category fluency score	16.97 ± 5.38	18.35 ± 6.17	28.47 ± 5.32	0.000[d]
Spatial span total	11.90 ± 4.53	12.67 ± 3.66	17.69 ± 3.54	0.000[c]
TMT-A(s) [b]	132.73 ± 75.08	86.77 ± 40.29	48.83 ± 23.43	0.000[d]
TMT-B(s)	310.33 ± 122.45	188.34 ± 50.14	125.17 ± 60.78	0.000[d]
Block design	15.29 ± 9.41	20.29 ± 7.26	28.56 ± 8.87	0.000 [d]
SCWT				
Stroop-words	45.34 ± 16.26	59.26 ± 14.28	76.32 ± 15.18	0.000[d]
Stroop-colours	22.14 ± 11.75	34.39 ± 12.47	51.18 ± 11.76	0.000[d]
Stroop-interference	12.56 ± 11.55	22.39 ± 7.89	31.45 ± 9.68	0.000[c]

Deficit schizophrenia; NDS, nondeficit schizophrenia; HC, healthy control; DCT, digit cancellation test; ANT, animal naming test; COWAT, controlled oral word association test; TMT, trail-making test; SCWT, Stroop colour-word test; education could not be excluded as a confounding factor, so one-way ANOVA was used to compare scores among groups; [b] Not meeting homogeneity of variances using Welch's test. All other cognitive test scores were compared by analysis of covariance, controlling for age, education and BMI. All the statistical test results were adjusted for multiple comparisons via Bonferroni correction. [c] Post hoc comparisons revealed that the scores of the neurocognitive battery in the DS and NDS groups were significantly lower than those in the HC group, but there was no significant difference between the DS and NDS groups. [d] Post hoc comparisons revealed that the scores of the neurocognitive battery in the DS and NDS groups were significantly lower than those in the HC group and that the scores of the neurocognitive battery in the DS group were significantly lower than those in the NDS group. [e] Post hoc comparisons revealed that the DCT scores in the DS groups were significantly lower than those in the HC and NDS groups, but there was no significant difference between the HC and NDS groups

with negative symptoms and impaired attention in DS patients.

Brain MRI studies of brain volume in DS and NDS patients have revealed that the frontal and temporal lobes are particularly susceptible to cortical thinning [28, 29]. Cortical thinning, rather than cortical surface contraction, has been shown to drive brain volume loss in patients with *schizophrenia* [30]. The three studies on cortical thickness in DS and NDS undertaken to date [13–15] revealed that areas of cortical thinning primarily involved the frontal and temporal lobes. Some researchers have reported that the insula plays a crucial role in various cognitive functions supported by the human brain [31].

To date, the diagnosis of schizophrenia is still based on clinical interviews and careful observation, which are subjective and variable and potentially lead to misdiagnosis and/or delayed diagnosis. Owing to the importance of early intervention for improving outcomes in patients with schizophrenia, there is a great need for objective testing that can be used for both the diagnosis and treatment monitoring of patients with schizophrenia. Identifying each patient's neurobiological subtypes and progression patterns could lead to new biomarkers. Researchers have used data-driven machine learning techniques to determine the progression patterns of brain morphological changes in schizophrenia patients and to investigate their associations with treatment resistance [32]. The current findings provide new insights related to novel biomarkers that could be useful for the diagnosis and treatment monitoring of schizophrenia

and may lead to the identification of clinically useful personalized biomarkers.

Negative symptoms are a core and persistent characteristic of deficit schizophrenia (DS). Several studies have assessed the brain correlates of negative symptoms in patients with *schizophrenia*. In a large meta-analysis investigating negative symptoms and brain structure, thinning of the left medial orbitofrontal cortex was associated with negative symptom severity in patients with *schizophrenia* [33]. A first-episode psychosis MRI study examining visual cortical deficits and their associations with clinical symptoms revealed that decreased thickness of the middle temporal visual cortex is associated with more severe negative symptoms [34]. Furthermore, negative symptoms in schizophrenia spectrum disorders have been found to be associated with reduced orbitofrontal cortex thickness [35]. We found a significant negative correlation between negative symptoms and right temporal cortical thickness (*rh_G_temporal_inf_thickness* and *rh_G_temporal_middle_thickness*), even after Bonferroni correction. In other words, the thinner the right temporal cortex is (rh_G_temporal_inf_thickness and rh_G_temporal_middle_thickness), the more severe the negative symptoms. Moreover, the positive findings above were noted to be present only in DS patients.

We conducted a neurocognitive battery on all the subjects and found that the schizophrenia patients performed significantly worse than the HCs did on all the cognitive tests and that the DS group had significantly worse cognitive test results than did the NDS group. Rampino et al. [36] reported that cognitive deficits are core features of schizophrenia and affect the ability of patients to process even very simple stimuli, thus dramatically lowering their quality of life and overall functioning. The DCT is primarily used to assess various aspects of prefrontal cortex function, including information processing speed, the ability to focus attention, and executive function [37]. Executive deficits mediated by slow processing speed are a core feature of *schizophrenia* [38]. Compared with NDS patients, cognitive deficits in DS patients are characterized by slow processing speed and impaired attention [39]. We found a significant negative correlation between *lh_S_circular_insula_ant_thickness* and the DCT score in DS patients only. In other words, the thinner the left insular cortex *(lh_S_circular_insula_ant_thickness*) of DS patients is, the higher the DCT score, which represents impaired processing speed and attention. This finding is consistent with previous findings that the insula plays a crucial role in various cognitive functions [31].

A near-infrared spectroscopy (NIRS) study revealed that intervention programs focused on enhancing frontotemporal function may have a greater impact on social and occupational outcomes in patients with *schizophrenia* [40]. A study revealed that language complexity and cohesion are reduced in the subgroup with cortical thinning in first-episode schizophrenia patients [16]. Verbal memory (VM) is one of the most affected cognitive domains in *schizophrenia* patients, and studies have shown that patients with significant VM impairment experience cortical thinning in the left frontal lobe and parahippocampal gyri [41].

Negative symptoms are important symptoms that affect the social functioning of patients with *schizophrenia* [42]. This study revealed that temporal cortical thinning (*rh_G_temporal_inf_thickness* and *rh_G_temporal_middle_thickness*) in patients with DS was associated with negative symptoms.

Previous animal, lesion, and imaging studies have shown that the insular cortex is involved in several cognitive functions, such as language fluency, decision-making, declarative memory, and working memory [43–46]. Studies have reported thinning of the insula in first-episode *schizophrenia* patients, but no associations have been found between insula thickness and cognitive function or clinical symptoms. We found that both DS and NDS male patients with *schizophrenia* exhibit thinning of the insular cortex (*lh_S_circular_insula_ant_thickness*), which is associated with impaired attention function. The sources of attention can be divided into three functions: alerting, orienting, and executive control [47]. Vigilance refers to the ability to maintain attention over time. Patients with schizophrenia may have difficulty fully participating in daily conversations with others and following important instructions at work [48]. These cognitive deficits appear to be related to functional outcomes, such as community functioning and skill acquisition [48].

The associations between antipsychotic drugs (APMs) and cortical morphology have been explored in patients with *schizophrenia*. A widespread reduction in cortical thickness was observed in patients who were antipsychotic-naive. After taking APM, the cortical thickness of patients decreases further, even in the frontal and temporal regions without baseline reduction [49]. The short-term and long-term (medium- to long-term) effects of APMs on cortical structure may differ. For example, clinical trial reports examining changes in cortical structure during short-term (less than 3 months) antipsychotic treatment have shown that the cortical thickness remains stable or even increases after 6–12 weeks of antipsychotic treatment [50], whereas long-term (over 3 months) studies have shown cortical structure loss compared with healthy control (HC) groups [51]. In the largest randomized longitudinal study to date, the effects of different antipsychotic drug types on brain volume were compared. Olanzapine can reduce brain volume within one year [52]. Owing to the challenges of conducting clinical trials with atypical antipsychotic effects for over a year,

most observational results come from cross-sectional and longitudinal studies with naturalistic designs. For example, cross-sectional studies of SZ patients receiving current or chronic (over 5 years) treatment have shown cortical loss [53]. In this study, the use of APMs in both DS and NDS patients exceeded one year. Compared with that in normal individuals, cortical thickness was reduced in multiple brain regions (left superior temporal, right insula, and left supramarginal).

This study employed Freesurfer, whereas prior research [15] utilized CIVET. Compared to healthy controls, both the DS and NDS patient groups exhibited cortical thinning in specific brain regions. Furthermore, the DS group demonstrated additional cortical thinning relative to the NDS group. Methodologically, Freesurfer utilizes 163,842 vertices per hemisphere, in contrast to CIVET's 81,924 vertices per hemisphere. Both pipelines applied generalized linear model (GLM) analyses, but diverged in their approaches to multiple comparison correction: Freesurfer employed permutation testing, while CIVET adopted false discovery rate (FDR) correction. Consequently, this work validates cortical thinning in DS patients at a higher spatial resolution, advancing our understanding of the neurobiological mechanisms underlying DS-associated negative symptoms and cognitive impairments.

Limitations

First, there are concerns about the accuracy of machine-automated segmentation; however, it has advantages in that it is standardized, unbiased, and easy to *reproduce*. Second, since the patients in this study were taking *antipsychotics*, we could not rule out an effect of these antipsychotics on brain morphology. Future research will include *drug-naive* individuals to exclude the effects of antipsychotics. Third, the normal sexual dimorphism of the brain has been shown to be disrupted or even reversed by *schizophrenia* [54]. The clinical process and prognosis of male and female mental illnesses are different [55], and *schizophrenia* may exhibit sex-specific neurobiological differences [56]. This study focused on the comparison of cortical thickness between male patients and healthy *men*. In future studies, we will include female patients to explore the impact of *sex differences*. Fourth, since the subjects were all hospitalized, they were all affected by a *limited living environment*. Nonetheless, this patient cohort is highly homogenous with respect to aspects such as sex and the social environment, thus facilitating the identification of reliable cortical alterations between the *two patient groups* by restricting the variance due to confounders. The results of this study were derived from a highly homogeneous inpatient cohort, which may affect its universality in *outpatient* or *community patient populations*. Future research should include outpatient patients and conduct follow-ups to exclude the influence of a *limited living environment*, providing data support for trend analysis and prediction. Fifth, in line with the increasing attention given to the ecological validity of the neuropsychological assessment, the low *ecological validity* of the executive function test is one of the limitations of this research.

Conclusion

The present study adds to the evidence for cortical thinning in people with *deficit schizophrenia (DS)* obtained from the few existing studies on cortical thickness in this subtype of schizophrenia. These findings provide insight into the relationships between cortical thinning and the *negative symptoms* and *attention deficits* found in DS patients. We found that *temporal cortex* (rh_G_temporal_inf_thickness and rh_G_temporal_middle_thickness) thinning in the DS group was associated with negative symptoms, whereas *insular cortex* (lh_S_circular_insula_ant_thickness) thinning was associated with attention deficits. Studying cortical thinning patterns has important implications for gaining a deeper understanding of the pathophysiology of the *negative symptoms* and *cognitive deficits* associated with DS. This study may provide targeted biomarkers for the cognitive remediation of schizophrenia patients with *deficit schizophrenia (DS)*, which will facilitate improvements in cognitive remediation and may lead to the exploration of new cognitive remediation methods to improve the cognitive and psychosocial outcomes, such as quality of life, employment outcomes, and academic and social functioning, of these patients.

Prospective statement

This study revealed a significant relationship between cortical thinning, *negative symptoms*, and *attention deficit* in *deficit schizophrenia (DS)* patients, providing valuable insights for future research and clinical practice. First, the correlation between the weakness of the *right temporal lobe* and *left prefrontal cortex* and specific cognitive impairments has been clarified, enabling us to more accurately identify potential biomarkers for early screening and intervention in the future. Second, the research results lay the foundation for developing *personalized treatment plans* for *deficit schizophrenia (DS)* patients, especially for improving cognitive function and social adaptability. By further exploring the relationship between changes in cortical thickness and *drug efficacy*, future research can promote the optimization and use of antipsychotic drugs. In summary, these findings not only enhance the understanding of the pathological mechanisms of *deficit schizophrenia (DS)* but also provide new research directions for improving patients' quality of life and cognitive repair. This study contributes to a

comprehensive understanding of the pathophysiology of schizophrenia, promoting more detailed and personalized clinical practice.

Abbreviations

DS	deficit schizophrenia
NDS	nondeficit schizophrenia
HC	healthy controls
PANSS	Positive and Negative Syndrome Scale
CPZ	chlorpromazine
BMI	body mass index

Author contributions

Jin Li and Xiaobin Zhang recruited the subjects, collected the clinical data, performed the schizophrenia symptom assessment, analysed the data, and wrote the manuscript. Junjie Wang, Haidong Yang, Man Yang and Ju Gao conducted the clinical and cognitive symptom assessments. Xiangdong Du designed the study and prepared the manuscript. All the authors participated in the preparation of the manuscript and approved its final version.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Human ethics and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the WuTaiShan Hospital Ethics Committee for clinical research (approval No. 2018-056). Written informed consent was obtained from all participants.

Consent to publish

Declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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