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Mapping Convergent and Divergent Cortical Thinning Patterns in Patients With Deficit and Nondeficit Schizophrenia

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Deficit schizophrenia (DS) is a homogeneous subtype of schizophrenia characterized by primary and enduring negative symptoms. However, the underlying neuroanatomical substrate of DS remains poorly understood. Here, we collected high-resolution structural magnetic resonance images of 115 participants, including 33 DS patients, 41 nondeficit schizophrenia (NDS) patients, and 41 healthy controls (HCs), and calculated the cortical thickness and surface area for statistical comparisons among the 3 groups. Relative to the control group, both the DS and NDS groups exhibited convergent cortical thinning in the bilateral inferior frontal gyri and the left superior temporal gyrus. The cortical thinning in the right inferior frontal cortex in the patient group was significantly positively correlated with declines of cognitive flexibility and visuospatial memory. Importantly, compared to the NDS group, the DS group exhibited a more widespread cortical thinning pattern, with the most significant differences in the left temporo-parietal junction area. For the surface area measurement, no significant group differences were observed. Collectively, these results highlight the convergent and divergent cortical thinning patterns between patients with DS and NDS, which provide critical insights into the neuroanatomical substrate of DS and improve our understanding of the biological mechanism that contributes to the negative symptoms and cognitive impairments in DS.

Keywords: deficit schizophrenia/MRI/cortical thickness/surface area/temporo-parietal junction

Introduction

Deficit schizophrenia (DS) is a homogeneous subtype of schizophrenia, which is characterized by primary and enduring negative symptoms and impaired social function and emotional processing.[1] Elucidating whether neuroanatomical substrates in DS differ from those in nondeficit schizophrenia (NDS) is critical for the facilitation of biomarker discovery in this disease.

Structural MRI provides a promising avenue to quantitatively describe the neuroanatomical features of the brain. For example, several cross-sectional studies have documented that the negative symptoms in schizophrenia are associated with volumetric measures in specific parts of the brain, including the gray matter (GM) in the entire frontal cortex,[2] the ventro-medial prefrontal cortex,[3] and the temporal lobe[4] and the white matter in the prefrontal cortex.[5] Longitudinal studies have revealed that an accelerating reduction in frontal lobe GM and white matter volumes, an increase in the frontal lobe cerebrospinal fluid (CSF) volume,[6,7] and progressive reduction in temporal lobe GM volume[6] are correlated with greater negative symptom severity. There is also evidence of a relationship between negative symptoms and the GM thickness of the left orbitofrontal cortex in schizophrenia.[8] These findings regarding the relationship between negative symptoms and morphological measurements raise the possibility that DS patients who exhibit higher levels of negative symptoms are likely to suffer

more severe neuroanatomical abnormalities than NDS patients without the predominant features of lasting negative symptoms.

To date, several structural MRI studies have directly examined the neuroanatomical differences between DS and NDS, primarily focusing on volumetric analyses and producing discordant findings. For example, nonsignificant differences were observed between the DS and NDS groups in several global measures such as the total brain volume, the total volume of the ventricles,[9] the total GM volume, the total white matter volume and the total CSF volume.[10] However, significant volumetric differences in specific GM regions were observed. For example, DS patients exhibited significant volumetric reductions in the superior frontal gyrus,[11,12] superior and middle temporal gyrus,[11–13] the left anterior cingulate and the right putamen[11] compared with the volumes in the NDS patients. Conversely, NDS patients showed a greater volumetric reduction in the dorsal lateral prefrontal cortex than DS patients.[14] These conflicting findings could be associated with insensitive GM volumetric measurements, leading to an imprecise understanding of the neuroanatomical characteristics of DS and NDS.

It is worth noting that the cortical GM volume is the product of two morphological indices: cortical thickness and surface area. Beyond the abovementioned volume-based analyses, these 2 surface-based measurements allow us to obtain more detailed information regarding the alterations of cortical structures observed in schizophrenia. Specifically, it is assumed that the cortical thickness has greater etiological relevance for schizophrenia than that of GM volume or density.[15] While the cortical thickness reveals the number, size, and arrangement of the cells within a column, the surface area is more related to the number of columns within a certain cortical region.[16–18] Previous structural imaging studies have shown that these 2 surface-based characteristics of the brain were associated with schizophrenia[19] and negative symptoms.[8,20] To date, only 2 studies have explored the patterns of cortical thickness and surface area in DS and NDS patients.[21,22] Neither of these studies reported significant differences in surface area between 2 patient groups, or between either patient group and the healthy controls (HCs). With regard to the cortical thickness, Takayanagi et al[21] exclusively examined the mean thickness of the anterior cingulate gyrus using a region of interest (ROI) approach and observed significant thinning in this region in the DS group as compared with that in the NDS groups. Voineskos and colleagues[22] reported that compared with HCs, both DS and NDS patients showed cortical thinning in the several frontal and temporal regions, but no significant differences between the 2 patient groups. They speculated that cortical thinning might serve as a common neuroanatomical feature in patient with schizophrenia, regardless of the 2 clinical subtypes. Thus, it remains to be elucidated whether patients with DS differ from patients with NDS in neuroanatomical measures of cortical morphology such as surface area and cortical thickness.

To address this issue, we examined cortical thickness and surface area measures in a large structural MRI dataset that included 115 participants (33 DS, 41 NDS, and 41 HCs). Given the aforementioned substantial clinical heterogeneity and morphological differences between DS and NDS, we hypothesized that patients with the 2 subtypes of schizophrenia would exhibit convergent and divergent neuroanatomical abnormalities in the frontal and temporal regions and that these structural abnormalities would correlate with cognitive performance. These comparisons might help to clarify the commonalities and differences between the neurobiological characteristics of DS and NDS patients.

Methods

Subjects

A total of 128 males participated in this study, including 84 clinically stable schizophrenia patients (40 DS and 44 NDS) and 44 HCs. The patients were recruited from the psychiatric rehabilitation unit of Yangzhou Wutaishan Hospital, Jiangsu Province, China. The patients' eligibility criteria included: (1) a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and confirmed by the Chinese version of the Structured Clinical Interview for DSM-IV (SCID-I)[23]; (2) right-handed Chinese Han patients between the ages of 20 and 65 years; and (3) having stable psychiatric symptoms and treatment with antipsychotic medications for at least 12 months based on their medical records. The exclusion criteria for the patients included severe comorbid conditions, such as neurological disorders, head trauma, mental retardation, alcoholism or substance abuse, and a history of previous electroconvulsive therapy. The diagnoses of DS and NDS were determined according to the Chinese version of the schedule for the deficit syndrome (SDS).[24] The SDS rates the deficit syndrome as present if 2 of the following symptoms are at least moderately severe, persistent over 12 months and not attributable to secondary sources (eg, medication side effects, depression, paranoia, and anxiety): restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive. The SDS scale is also organized into 2 factors (factor 1, avolition and factor 2, poor emotional expression) based on previous studies.[25,26] The HCs were matched for age and handedness with the patients, were recruited from the local community, and met the following criteria: (1) no lifetime history of psychotic, mood, or substance abuse or dependence, as ascertained by the Structured Clinical Interview for DSM-IV Non-Patient version (SCID-NP) [27]; (2) no history of organic brain disorders, mental retardation, or severe head trauma; and (3) no family history of psychiatric disorders. The data

from 13 subjects were excluded due to head motion during the scan (7 DS, 2 NDS, and 1 HC) and imaging processing failures (1 NDS and 2 HC). Lastly, the data from the remaining 115 participants (33 DS, 41 NDS, and 41 HCs) were included in the final analysis. The study was approved by the Institutional Ethical Committee for clinical research of Zhongda Hospital Affiliated to Southeast University. Written informed consent was obtained from each participant.

Clinical Evaluation

The severity of the schizophrenic symptoms was evaluated by the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), and the Scale for the Assessment of Positive Symptoms (SAPS). The BPRS scale is organized into positive, negative, disorganized, and affect syndromes based on the findings of the most comprehensive factor analysis of the 18-item BPRS.[28,29] Table 1 illustrates the clinical and demographic data of all participants.

Neurocognitive Assessments

For each participant, we performed a battery of classical neuropsychological tests, including the Digit Vigilance Test (DVT), the Animal Naming Test (ANT), the Controlled Oral Word Association Test (COWAT), the Block Design Test in Wechsler Adult Intelligence Scale-Chinese Revision (WAIS-RC), the Trail Making Test-A, B (TMT-A,B), the Stroop Color-Word Test (SCWT), and the Spatial Processing Test (Block Design). Based on previous reports regarding the cognitive processes assessed by each test,[30–34] these variables were further grouped into 4 rationally motivated domains: sustained vigilance/attention (hereinafter labeled sustained attention with 4 tests: DVT, TMT-A, Stroop colors, and Stroop words), cognitive flexibility (2 tests: TMT-B and Stroop interference), ideation fluency (2 tests: ANT and COWAT), and visuospatial memory (2 tests: Spatial Processing, Block Design and WAIS-RC). For each cognitive domain, a composite score analysis was conducted as follows.[30,34,35] Briefly, for each patient the standardized Z score of each cognitive test was calculated based on the corresponding neurocognitive data of the control group. The composite scores in the cognitive domain were then calculated by summing the Z-transformed scores of all of the neuropsychological tests within the domain. The data reduction of the neurocognitive measures avoids multiple comparisons and corrects the interdependency between the neuropsychological measures.[30,34,35] Notably, some variables (eg, TMT), in which low values indicated good performance, were adjusted for sign to ensure that higher Z-scores represented better performance for all variables. Thus, for each patient, we obtained 4 composite scores representing performance in the 4 cognitive domains. Finally, Cronbach's alpha and Cohen's d effect sizes[36,37] were computed for each cognitive domain. Table 2 presented the neurocognitive data of the 3 groups.

Image Acquisition and Processing

Structural MRI data were acquired with a high-resolution 3D magnetization prepared rapid acquisition gradient echo sequences (for details, see supplementary information). We used the CIVET pipeline (version 1.1.9.[38]) to measure the cortical thickness and surface area in the brain. Briefly, the native MR images were first registered into stereotaxic

Table 1. Demographics and Clinical Characteristics for DS, NDS, and HC Groups

	DS ($n = 33$)	NDS ($n = 41$)	HC ($n = 41$)	$F/\chi^2/t$	*P-Value*
Age (years)	49.03 ± 7.67	45.71 ± 6.64	45.78 ± 9.48	1.97	.145
Education (years)	8.82 ± 2.02△	9.12 ± 1.82△	10.54 ± 2.72	6.51	.002
Age at onset (years)	22.03 ± 2.81	22.39 ± 2.66		−0.56	.575
Duration of illness (years)	27.00 ± 6.92*	23.32 ± 6.88		2.28	.025
BPRS total	31.67 ± 2.97**	27.56 ± 2.65		6.29	<.001
Positive syndrome	6.00 ± 1.06	6.41 ± 1.05		−1.68	.097
Negative syndrome	12.33 ± 1.67**	7.46 ± 1.00		14.74	<.001
Disorganized syndrome	6.55 ± 1.37	6.46 ± 0.84		0.32	.752
Affect	6.79 ± 1.19	7.22 ± 1.31		−1.46	.148
SANS total	56.97 ± 8.47**	31.98 ± 6.11		14.73	<.001
SAPS total	8.67 ± 3.76	10.17 ± 4.24		−1.60	.115
SDS total score	11.06 ± 2.52**	4.07 ± 2.42		12.11	<.001
Avolition	5.94 ± 1.56**	2.54 ± 1.52		9.47	<.001
Poor emotional expression	5.12 ± 1.27**	1.54 ± 1.12		12.90	<.001
Smoking ratio (%)	63.60	75.60		1.26	.263
CPZ-equivalent daily dosage (mg/day)	467.73 ± 234.98	527.80 ± 208.14		−1.17	.248

Note: DS, deficit schizophrenia; NDS, nondeficit schizophrenia; HC, healthy controls; BPRS, Brief Psychiatric Rating Scale; SANS, the Scale for the Assessment of Negative Symptoms; SAPS, the Scale for the Assessment of Positive Symptoms; SDS: the Schedule for the Deficit Syndrome; CPZ, chlorpromazine; *Vs NDS, $P < .05$; **Vs NDS, $P < .001$; △Vs HC, $P < .05$.

Table 2. Comparisons of Neurocognitive Domains and Raw Neuropsychological Performance Among DS, NDS, and HC Groups

	DS (n = 33)	NDS (n = 41)	HC (n = 41)	F	P-Value	Cronbach's Alpha
Sustained vigilance/attention	−11.02 ± 6.86	−4.04 ± 3.28	—	—	—	0.789
Digit vigilance test (s)	312.36 ± 161.02**△△	178.31 ± 66.76	137.82 ± 42.34	24.54	<.001	—
TMT-A (seconds)	132.95 ± 67.68**△△	81.80 ± 30.95△	49.31 ± 22.87	27.52	<.001	—
Stroop words only	42.70 ± 18.93**△△	59.07 ± 16.09△△	79.15 ± 16.79	33.66	<.001	—
Stroop colors only	26.79 ± 12.63*△△	35.20 ± 11.14△△	49.32 ± 13.26	22.92	<0.001	—
Ideation fluency	−3.44 ± 1.82	−2.03 ± 2.09	—	—	—	0.669
COWAT	4.88 ± 3.16*△△	6.76 ± 3.51△	9.17 ± 2.33	14.20	<.001	—
Animal naming test	9.73 ± 3.47*△△	12.46 ± 4.46△△	18.41 ± 4.60	33.15	<.001	—
Cognitive flexibility	−4.12 ± 2.59	−2.08 ± 1.37	—	—	—	0.725
TMT-B (s)	304.05 ± 119.44**△△	199.09 ± 53.33△△	123.57 ± 63.47	35.97	<.001	—
Stroop interference	17.42 ± 11.08△△	21.34 ± 8.81△△	32.32 ± 10.58	15.92	<.001	—
Visuospatial memory	−3.72 ± 2.00	−2.11 ± 1.42	—	—	—	0.681
Spatial processing (block design)	11.24 ± 4.39*△△	13.41 ± 3.35 △△	18.02 ± 3.46	24.16	<.001	—
WAIS-RC (block design)	13.55 ± 8.87**△△	21.41 ± 6.55△	27.73 ± 8.27	21.98	<.001	—

Note: Patients' neuropsychological test scores were standardized using the healthy control (HC) group data. Sustained vigilance/attention domain includes Stroop words only and colors only, Trail making test part A and Digit vigilance test. Ideation fluency domain includes Controlled Oral Word Association test and Animal Naming Test. Cognitive flexibility includes Stroop color/word interference test and Trail making test part B. Visuospatial memory domain includes Spatial processing test and Wechsler adult intelligence scale (Block Design, Chinese version). DS, deficit schizophrenia; NDS, non-deficit schizophrenia.*Vs NDS, $P < .05$;**Vs NDS, $P < .001$; △Vs HC, $P < .05$; △△Vs HC, $P < .001$.

space[39] using a 9-parameter linear transformation.[40] Simultaneously, the images were corrected for nonuniformity artifacts using the N3 algorithms.[41] The registered and corrected images were further segmented into GM, white matter, CSF, and background using an advanced neural net classifier.[38] The inner and outer GM surfaces were then automatically extracted from each MR volume using the constrained Laplacian-based automated segmentation with proximities algorithm[42,43] and the cortical thickness was measured in native space using the linked distance between the 2 surfaces at 81 924 vertices (40 962 on each hemisphere) throughout the cortex. The measurement in native space provided an unadjusted estimate of the absolute cortical thickness.[44] Smoothing with 20 mm kernel was then applied to improve sensitivity.[45] The cortical thickness algorithm was validated using both manual measurements[46] and simulation approaches.[47,48] The surface area was evaluated on a mid-surface, represented as a polyhedral mesh lying right in the middle of the inner and outer GM surfaces. The surface area on each vertex was defined as a third of the total area of all the triangles adjoining to it, then smoothed with a 20 mm kernel. The surface area of a brain region was the sum of all the vertices belonging to it.

Statistics

The continuous and categorical variables were analyzed using the general linear model (GLM) and the chi-square test, respectively. Comparisons of clinical symptoms between the DS and NDS groups were conducted using 2 sample t-tests. The differences of composite scores of each cognitive domain between the 2 patient subgroups were evaluated using effect size estimation (Cohen's d). For all analyses, the significance level was set to $P < .05$.

To detect cortical thickness differences among the 3 groups, we performed the GLM analysis with age and education as covariates at 3 scales: the mean thickness, vertex-based, and an ROI-based thickness analysis based on the automated anatomical labeling atlas. For the group main effects from either the vertex-based or ROI-based GLM analyses, a false discovery rate (FDR) correction was implemented to correct for multiple comparisons.[49] Three contrast tests (DS vs HC, NDS vs HC, and DS vs NDS) based on the same model were performed to determine between-group differences. An FDR correction was applied in which the P-values from all 3 comparisons were pooled together. The q-value was set to .05. A cluster size threshold of 30 vertices was then applied to further reduce false positive clusters. To remove the effects of illness duration and medication dose in the patient groups, we applied another GLM to the DS and NDS groups with illness duration and medication dose as additional covariates, followed with an FDR correction at q-value = .05. All the cortical thickness comparisons were conducted using SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/, Accessed November 12, 2017) and the results were visualized using the BrainNet Viewer toolbox.[50] For the surface area measurements, the statistical comparisons were the same as those for the cortical thickness analysis.

To determine brain-cognitive/clinical relationship, we performed the GLM analyses using the GRETNA toolbox.[51] For the overlapping regions with significant

abnormalities shared by the 2 patient groups, we estimated the relationship across all patients. For the regions that differed between the DS and NDS groups, we separately estimated the brain-cognition/clinical (including 2 factors of the SANS: diminished expression and social amotivation) relationships in each group. Age, education, illness duration, and medication dose were taken as covariates. For details, see supplementary materials.

Results

Demographic and Clinical Characteristics

Among the 3 groups, the differences in education (P = .002), but not age (P = .145), were significant (Table 1). Least-significant difference post hoc comparisons revealed lower education levels in both the DS (P = .001) and NDS (P = .005) patients relative to the HCs, whereas the 2 patient subgroups did not differ significantly (P = .562). The DS patients exhibited a longer illness duration (P = .025) and more severe psychopathological total symptoms and negative symptoms (all P < .001) than the NDS patients. For the types of antipsychotic drugs, there was no significant difference between the DS and NDS groups ($\chi^2[2] = 1.163$, P = .559) (conventional antipsychotics: 48.5% [n = 16] and 36.6% [n = 15]; novel antipsychotics: 30.3% [n = 10] and 34.1% [n = 14]; combination: 21.2% [n = 7] and 29.3% [n = 12], respectively). The mean age of onset, smoking, antipsychotic medication dose (chlorpromazine equivalents), the positive, affect, and disorganized syndromes did not differ significantly between the 2 patient subgroups.

Cognitive Characteristics

For each neuropsychological test, we observed significant differences among the 3 groups with age and education as covariates (all P < .001, table 2). Least-significant difference post hoc comparisons indicated that both of the patient groups performed significantly worse than the control group on most of the neuropsychological tests (all P < .05, except the DVT for NDS vs HC, P = .129). Moreover, the DS group performed significantly worse than the NDS group on most neuropsychological measures (all P < .05, except the Stroop interference for DS vs NDS, P = .346). Cronbach's alpha ranged from 0.669 to 0.789 in the 4 cognitive domains, indicating relatively high internal consistency among the measures. The Cohen's d effect size ranged from 0.720 to 1.298 in the 4 cognitive domains, indicating that the DS–NDS differences in cognitive performance achieved moderate to large effect sizes.

Cortical Thickness Comparisons

The mean cortical thickness in the whole cortex differed significantly among the 3 groups (P = .02), with significantly thinner cortices in the DS group than the HC group (P < .005) and nonsignificant differences between the NDS and HC groups or between the DS and NDS groups (P = .16 and .10, respectively). The total surface area did not differ significantly among the 3 groups (P = .26).

The vertex-based analyses revealed the main effects of group (q = .05, FDR-corrected, figure 1A), which was primarily distributed in the bilateral superior temporal gyri, the bilateral middle temporal gyri, the bilateral inferior frontal gyri, the left Heschl gyrus, the left supramarginal gyrus, and the left angular gyrus. Further post hoc analyses revealed that, compared with the HC group, the DS group exhibited widespread cortical thinning, with patterns similar to those observed for the main effects of group and the NDS patients had thinner cortices in the bilateral inferior frontal gyri and the left superior temporal areas (supplementary figure S1). Thus, compared to the HC group, the 2 schizophrenia subgroups exhibited shared cortical thinning in the bilateral inferior frontal gyrus and the left anterior superior temporal gyrus (figure 2, middle row). Notably, the DS group showed significant cortical thinning in the left temporo-parietal junction (TPJ) (including the angular gyrus, the supramarginal gyrus, and the posterior superior temporal gyrus[52]) as compared to the NDS group (Figure 3). The differences of the TPJ area remained significant after removing the effects of 4 cognitive domain scores and clinical evaluations (SAPS, BPRS total score or the positive syndrome, disorganized syndrome, and affect subscales of BPRS). Finally, the ROI-based analyses results were approximately the same as the vertex-analyses results (Figure 1B; supplementary figure S2 and table S1).

Surface Area Comparisons

The surface area analysis did not reveal any significant difference among the 3 groups after FDR correction.

Correlation Between Cognitive/Clinical Variables and the Morphological Measurements

We observed that the mean cortical thickness of the largest overlapping cluster, which was located in the right inferior frontal gyrus, was positively correlated with cognitive flexibility (P = .0018) and visuospatial memory performance (P = .00006) (figure 2, bottom row). For the SANS, we only found a trend toward negative correlation between the TPJ thickness and the social amotivation factor (P = .09) in the DS group.

Discussion

The present study explored the cortical abnormalities of patients with DS and NDS as well as the relationship between cortical thickness and cognitive performance. Relative to HCs, both patient groups demonstrated common cortical thinning in the bilateral inferior frontal and the left superior temporal regions. We also provided the

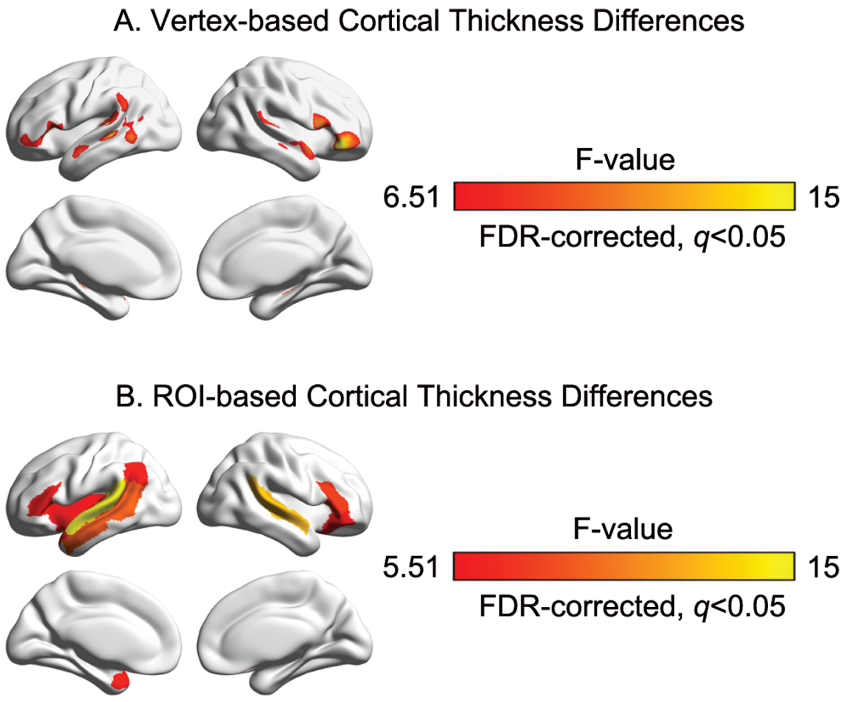

Fig. 1. Main effects of group on the cortical thickness (FDR corrected, $q < .05$). (**A**) Regions differed among the 3 groups on the vertex level. **(B)** Regions differed among the 3 groups on the region of interest level.

first evidence illustrating that the cortical thinning in the left TPJ is a salient feature in DS as compared with NDS.

We observed that the bilateral inferior frontal and left superior temporal areas were overlapped regions showing significant cortical thinning in both of the DS and NDS subgroups relative to the HC subjects. Our findings are in agreement with previous morphological studies revealing cortical thinning in the orbitofrontal, inferior frontal,[8,53–61] and the superior temporal regions[17,53,56–58,62–64] in schizophrenia. A previous study of cortical thickness in DS and NDS found that the patient groups shared nearly the same cortical thinning pattern, involving the bilateral temporal and inferior frontal areas, which is similar to our results.[22] Volumetric studies of DS and NDS patients also identified the frontal and temporal lobes as regions preferentially affected by the 2 subtypes of schizophrenia.[10–14,65] Considering that the current study and other surface-based studies comparing patients with DS and NDS and HCs[21,22] did not find any significant difference in surface area, cortical thickness measurement may play a vital role in describing neuroanatomical signatures in schizophrenia of different subtypes. Rimol and colleagues also demonstrated that cortical thinning rather than surface contraction mainly drives the volume reductions in schizophrenia.[19] Cortical thickness and surface area reveal different neurophysiological information,[16–18] have distinct genetic origins[66,67] and different developmental trajectories.[68–70] These 2 relatively independent structural features of the cortex may respond differently to the undergoing pathological process of schizophrenia, which might account for their different capabilities in revealing the structural changes related to the disease. In this study, the thickness in the right orbital frontal region positively correlated with cognitive flexibility and visuospatial memory performance. Intriguingly, a previous study found correlation between the GM density in the right inferior frontal region and the cognitive flexibility.[71] Another study demonstrated an activation in the right orbitofrontal area in the process of memory formation.[72] Our findings implied that the cortical thinning in the inferior frontal and the superior temporal regions are a common feature of the clinical syndrome of schizophrenia and may contribute to the cognitive impairments, regardless of different subtypes of the disease.

Importantly, we showed distinct cortical thinning patterns in the left TPJ between DS and NDS patients. Different from our findings, Voineskos et al[22] did not report significant differences when they directly compared the cortical thickness between DS and NDS patients. This result discrepancy between the previous work and our study might be due to several methodological differences: the magnetic field strength of the MRI scanning (1.5T vs 3.0T), the criteria classifying DS/NDS patients (PDS [the proxy for the deficit syndrome] vs SDS) and the composition of subjects (gender [14 males and 4 females for each group vs all male participants] and ethnicities [both Caucasians and non-Caucasians vs Chinese]). Although still controversial, it has been previously reported that DS patients exhibit decreased temporal GM volumes[11,12] and an increased left temporal CSF volume,[4] compared with NDS patients. Previous studies also demonstrated that schizophrenia patients with more severe negative

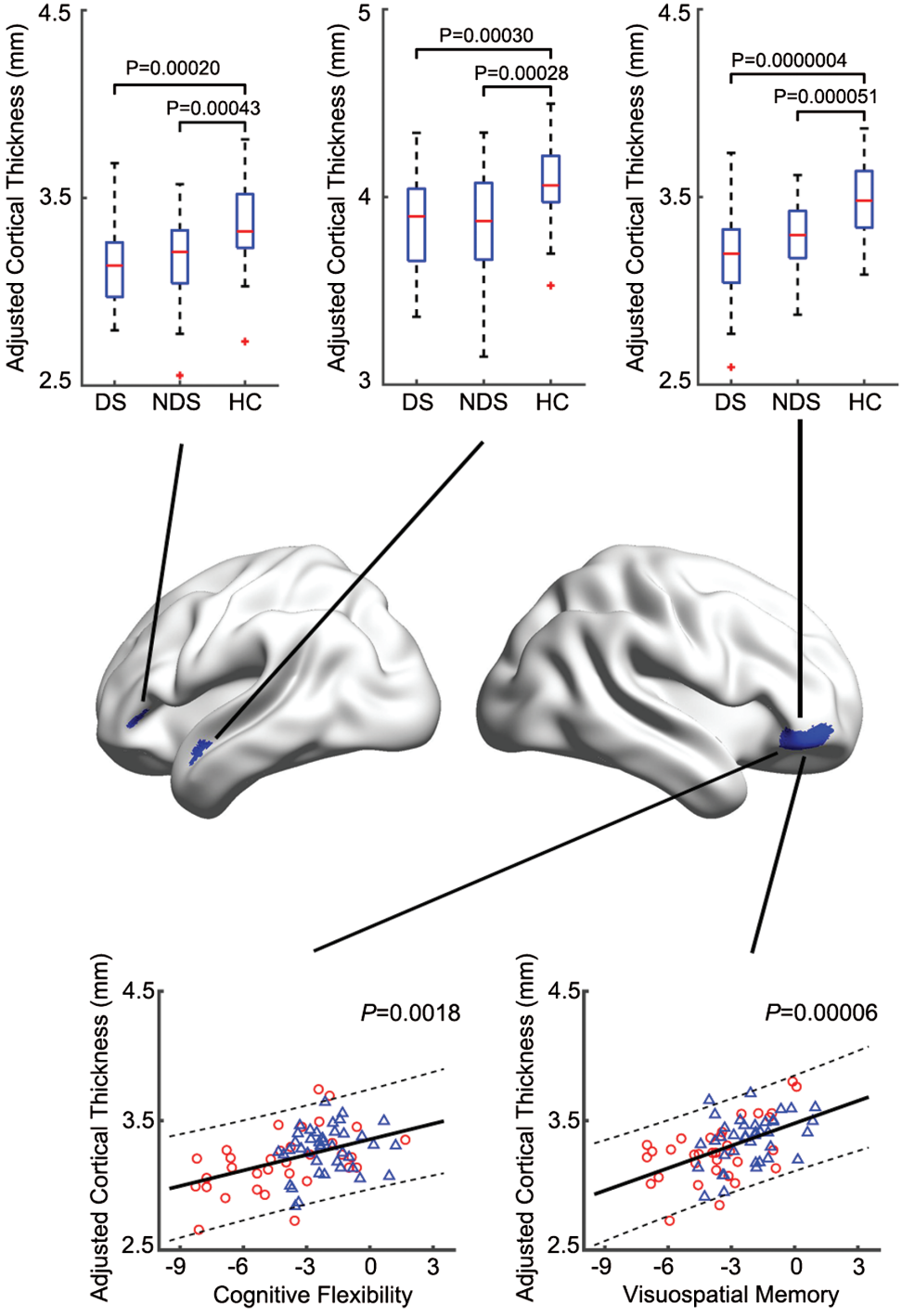

Fig. 2. Regions showing common cortical thinning in the 2 patient groups comparing with the healthy control on the vertex level (false discovery rate corrected, $q < .05$). Box-plots on the top showed the distribution of mean thickness within corresponding cluster. The bottom shows the correlation between the mean thickness of the right inferior frontal region and cognitive flexibility and visuospatial memory scores. Red circles and blue triangles referred to deficit schizophrenia and nondeficit schizophrenia patients, respectively.

symptoms suffered more severe brain atrophy in the left temporal lobe,[4,6] which provided further support for our result. One particularly interesting finding here was that the cortical reduction was apparent predominantly in the left TPJ. Notably, the TPJ is a critical region of the theory of mind (ToM), a social cognitive construct referring to "the ability to make inference upon one's own and other persons' mental states."[73] It has been shown previously that compared to HCs, activation in left TPJ is abnormal in schizophrenia patients during various ToM tasks.[74–83] Previous studies have also demonstrated an association between performance in ToM tasks and the severity of negative symptoms.[84–89] These findings implied that the dysfunction of the left TPJ may be more related to the

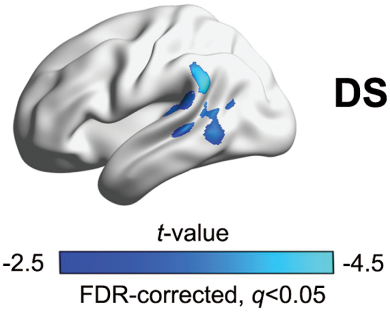

Fig. 3. Regions showing cortical thinning in deficit schizophrenia than nondeficit schizophrenia groups on the vertex level (false discovery rate corrected, $q < .05$).

deficit type of schizophrenia. There are also evidences showing the involvement of the left TPJ in various processes such as eye gaze perception and representation[90] and affective prosody perception.[91] Cortical thickness abnormalities in the left TPJ might interfere these functions and result in difficulties in social activities, which was supported by our finding of a negative association trend between the TPJ thickness and the social amotivation factor of SANS in the DS group. Furthermore, a more severe TPJ (the angular gyrus and the supramarginal gyrus) hypometabolism was also observed in DS than in NDS patients.[92] Finally, transcranial magnetic stimulation on the left TPJ area could alleviate negative symptoms of schizophrenia patients.[93] In summary, our results suggest that the cortical thickness abnormalities in TPJ were related to the negative symptoms but not to the cognitive impairments in DS patients. The biological mechanisms underlying these structural abnormalities remain to be further explored.

The present study has several methodological limitations. First, the patients were all chronic male inpatients. Thus, our results might be contaminated by the influences of antipsychotic medication exposure and limited living environment. Nonetheless, this patient cohort is highly homogenous regarding aspects such as gender and social environment, thus might facilitate the finding of reliable cortical alterations between the 2 patient groups by restricting the variance due to confounders. Future studies should consider collecting larger dataset including female subjects and outpatients. Second, cortical thickness and surface area were selected as morphological measurements, eliminating the possibility of investigating subcortical regions. Volume reductions in the hippocampus and the thalamus have been found in DS patients relative to the HCs and NDS patients,[11,65] implying an association between subcortical regions and negative symptoms. Taking measurements of the subcortical cortex into consideration may help us understand the emergence of negative symptoms, particularly those related to emotional and motivational features. Furthermore, it has been found that fractional anisotropy is reduced in the left uncinate fasciculus of DS patients but not NDS patients.[22,94] These findings indicate that DS patients with the primary negative symptoms might show abnormal brain connectivity, which needs to be explored in the future. Finally, the current study lacked social cognitive tests. Future studies with more comprehensive cognitive evaluations would help understanding the brain–cognition relationship in patients with DS and NDS.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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