

## RESEARCH ARTICLE

# Structural abnormalities of cingulate cortex in patients with first-episode drug-naïve schizophrenia comorbid with depressive symptoms

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## Funding information

Scientific Foundation of Institute of Psychology; Chinese Academy of Sciences, Grant/Award Number: Y9CX402008; Open Research Fund of the CAS Key Laboratory of Behavioral Science, Institute of Psychology; CAS Key Laboratory of Mental Health, Institute of Psychology, Grant/Award Number: KLMH2011ZK07; National Natural Science Foundation of China, Grant/Award Number: 31671163

## Abstract

Depressive symptoms are common in patients with first-episode psychosis. However, the neural mechanisms underlying the comorbid depression in schizophrenia are still unknown. The main purpose of this study was to characterize the structural abnormalities of first-episodes drug-naïve (FEDN) schizophrenia comorbid with depression by utilizing both volume-based and surface-based morphometric measurements. Forty-two patients with FEDN schizophrenia and 29 healthy controls were recruited. The 24-item Hamilton Depression Rating Scale (HAMD-24) was administered to divide all patients into depressive patients (DP) and non-depressive patients (NDP). Compared with NDP, DP had a significantly larger volume and surface area in the left isthmus cingulate cortex and also had a greater volume in the left posterior cingulate cortex. Correlation analysis showed that HAMD total score was positively correlated with the surface area of the left isthmus cingulate and gray matter volume of the left isthmus cingulate cortex. In addition, gray matter volume of the left isthmus cingulate was also correlated with the PANSS general psychopathology or total score. The findings suggest that prominent structural abnormalities of gray matter are mainly concentrated on the cingulate cortex in FEDN schizophrenia patients comorbid with depression, which may contribute to depressive symptoms and psychopathological symptoms.

## KEYWORDS

comorbidity, gray matter, psychiatry, subcortical structures

## 1 | INTRODUCTION

Depressive symptoms are prominent characteristics of schizophrenia, which may represent the core part of the first episode and drug naïve (FEDN) of schizophrenia (D. Addington, Addington, & Patten, 1998). Studies have shown that depression is a major problem in patients with schizophrenia during the acute phase and in the first year of illness (D. Addington et al., 1998; Onwuameze, Uga, & Paradiso, 2016).

A recent meta-analysis showed that at least one-quarter of patients with FEDN schizophrenia experienced depressive symptoms (Herniman et al., 2019). It is worth noting that the prevalence of depressive symptoms in patients with FEDN schizophrenia is as high as around 50% in the Chinese population (Dai et al., 2018; Larson et al., 2006). There is growing evidence that depressive symptoms (DP) in schizophrenia patients are closely associated with severe deficits in psychosocial functioning (D. Addington et al., 1998), higher risk

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of suicide (Duko & Ayano, 2018; Uptegrove et al., 2009), and more relapse and treatment resistance (Higashi et al., 2013). Despite recognizing this clinical burden, the use of depressive symptoms as a unique diagnostic entity for schizophrenia is controversial (D. D. Addington et al., 2002; Dai et al., 2018). Consistently, it is integrated into the treatment because of inadequate description in current classification systems (Castle & Bosanac, 2012).

Compared with schizophrenia patients without depressive symptoms (NDP), the schizophrenia patients with DP may exhibit typical morphometrical characteristics (Kohler, Swanson, Gur, Mozley, & Gur, 1998). However, there is no study examining structural abnormalities in FEDN schizophrenia patients with DP. At present, more and more evidences show that there are structural changes in limbic system in patients with FEDN schizophrenia, which may provide meaningful insight for further investigation of FEDN patients with DP. A brain imaging meta-analysis of 1,424 patients indicated that the hippocampal volume of patients with FEDN schizophrenia was significantly smaller than that of healthy controls (Steen, Mull, McClure, Hamer, & Lieberman, 2006). Moreover, a recent meta-analysis study showed widespread abnormalities in the cerebellar subregions (Ding et al., 2019). Another MRI study found that the patients had significantly thinner cingulate cortex, which is an important subcortical area associated with clinical symptoms than healthy controls (Narr et al., 2005).

Currently, only one study has explored the brain structure of schizophrenia comorbid with DP. Kohler et al. (1998) reported that larger volumes of bilateral temporal lobes and reduced laterality in the anterior cingulate in schizophrenia comorbid with DP compared to controls. With regard to major depressive disorder (MDD), there is increasing evidence that the cingulate cortex is a crucial region of the brain that is associated with the psychopathological mechanism underlying the clinical symptoms of MDD (McLaren et al., 2016; Ries, Wichmann, Bendlin, & Johnson, 2009). A systematic and meta-analysis review of voxel based morphometric studies in MDD demonstrated that compared with healthy controls, gray matter abnormalities in rostral anterior cingulate cortex were the most consistent findings in MDD (Bora, Fornito, Pantelis, & Yucel, 2012). The cingulate cortex is a functionally heterogeneous region because it is strongly connected to the basal ganglia, insula, orbitofrontal cortex and amygdala. Comprehensive evidence from cellular structure, connection electrophysiology and lesion studies, as well as imaging studies undoubtedly indicates that the cingulate cortex is the neural basis of emotion regulation and processing (Etkin, Egner, & Kalisch, 2011). A large number of neuroimaging studies have found damage to the cingulate cortex in patients with schizophrenia, indicating that the role of this brain region dysfunction in the etiology of schizophrenia may be through its role in the integration of cognition and emotion (Anticevic et al., 2008). It is worth noting that this is a region of particular interest, because there is a considerable overlap of structural brain changes in multiple neuropsychiatric disorders (Amanzio et al., 2011; Hobbs et al., 2011).

The volume of gray matter (GM) is a voxel-based quantitative method used to measure the intensity within each voxel in the entire

brain GM structure (Lemaitre et al., 2012), while surface-based morphometry is used to construct and analyze the surfaces that represent structural boundaries within the brain (Wang et al., 2018), which takes into account the cortical folding patterns (Anticevic et al., 2008) and cytoarchitectural abnormalities (Narr et al., 2005). The use of both voxel-based and surface-based analysis can help researcher better understand the pathophysiology of mental disorders (Palaniyappan et al., 2015). From a comprehensive understanding of GM structure, the combination of two imaging analyses in one study is an ideal approach to completely measure the cortical and subcortical morphometric changes behind the clinical symptoms of schizophrenia.

The study of FEDN with DP is of great significance for understanding the psychopathological symptoms in schizophrenia to minimize the potential impact of confounding factors including medication effects, duration of disease, and the psychiatric and medical comorbidities associated with chronic disease (Buckley, Correll, & Miller, 2007). In the view of the existing evidences, it is speculated that the FEDN patients with DP may exhibit abnormal structural characteristics, especially in the cingulate cortex. In this study, we aim to compare FEDN patients with and without DP through voxel-based and surface-based methods to detect multiple morphological changes. Moreover, we also tried to establish the correlations between gray matter structural brain abnormalities and clinical symptoms, especially the severity of depressive and psychiatric symptoms in FEDN patients with DP, so as to further explore the neural basis of depressive symptoms in FEDN patients.

## 2 | METHODS

### 2.1 | Subjects

Forty-two FEDN patients (23 females and 19 males) were recruited from Beijing Hui-long-guan Hospital, with an age range of 18–45 years old (mean age:  $28.6 \pm 10.2$  years). All FEDN patients were followed up for about 3 months to confirm a DSM-IV diagnosis of schizophrenia. The inclusion criteria included: (a) meeting the criteria for DSM-IV acute schizophrenia; (b) less than 60 months of course of disease; (c) did not receive antipsychotic medication and any other medications. In this study, first episode was defined as first symptom onset. The age of their first episode was  $25.6 \pm 9.9$  years.

We also recruited 29 age, sex and education matched healthy controls (13 males and 16 females) from the community through local advertisement (average age:  $27.7 \pm 7.8$  years). The psychiatrists also evaluated the current mental health status of each healthy volunteer, excluding those with any personal or family history of mental illness.

This study was approved by the Institutional Review Board (IRB) of Beijing Hui-long-guan Hospital and was performed in accordance with the Declaration of Helsinki. All subjects received a full explanation of the study and provided written informed consent to participate in the study.

## 2.2 | Psychopathological assessment in patients

Demographic information for all participants was collected. Two psychiatrists with at least 5 years of experience in clinical practice were blind to the clinical status of the participants and assessed the patients' psychopathology with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). The original PANSS was divided into three subscales: positive, negative and general psychopathology (Kay et al., 1987). The 24-item Hamilton Depression Scale (HAMD) was administered to assess the severity of depressive symptoms (Hamilton, 1960). All items are scored on a 5-point scale, ranging from 0 (not present) to 4 (severe). In this study, a cut-off point of 20 was used to divide subjects into two groups with or without depressive symptoms based on the previous studies:  $<20$  = without depressive symptom and  $\geq 20$  = with depressive symptom (Merkl et al., 2013; Zhou et al., 2005). In the course of the study, the inter-rater correlation coefficient  $> 0.8$  was maintained for the PANSS and HAMD total scores by repeated assessments.

## 2.3 | Imaging acquisition

High-resolution anatomical images of the whole brain were acquired on a GE 3T MRI scanner (GE Healthcare, Buckinghamshire, United Kingdom). T1-weighted scan used a spoiled gradient echo (SPGR) with the following parameters: TR = 6.2 ms, TE = 2.8 ms, flip angle = 8, field of view (FOV) = 240 mm, slice thickness = 1.2 mm, matrix size =  $256 \times 256$  and total slices = 142. During the scanning process, each subject lay on his back on the scanner bed and was asked to remain still during the imaging process.

## 2.4 | Preprocessing of brain imaging data

We adopted both voxel-based morphometry and surface-based cortical reconstruction in the preprocessing of fMRI data. Voxel-based morphometry was performed using FSL-VBM toolbox. All images were processed by using the default parameters of the toolboxes. For FSL-VBM, structural data was processed by FSL 5.0 software. FSL-VBM is a voxel-wise method performed with FNIRT (Douaud et al., 2007) (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>) to analyze GM volume, which is an optimized VBM protocol (Good et al., 2001) implemented using FSL tools (Smith et al., 2004). First, brain-extracted and GM-segmented were performed on the structural image before registering the structural images into the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template in order to transform into a standard space with left-right symmetry. Second, all native GM images were non-linearly registered to this study-specific template and "modulated" to correct local expansion (or contraction) caused by the non-linear component of the spatial transformation. Notably, the GM template was created on equal number of data from each group

according to the protocol. The number was determined by the group with lesser sample. In this study, when we compared the difference of volume between DP ( $n = 11$ ) and NDP ( $n = 31$ ), we selected 11 subjects from each group to create specific GM template. Then, the modulated GM images were smoothed with a 3 mm isotropic Gaussian kernel. Finally, a voxel-wise GLM was applied to correct multiple comparisons across space using permutation-based non-parametric tests. This protocol has been extensively applied to examine structural change in clinical diseases such as schizophrenia (Anderson, Goldstein, Kydd, & Russell, 2015) and generalized anxiety disorder (Hui Li et al., 2020). Moreover, it was used to examine the regional subcortical characteristics among healthy population (Schinazi, Nardi, Newcombe, Shipley, & Epstein, 2013).

Cortical reconstruction was conducted using Freesurfer (version 5.3; <http://surfer.nmr.mgh.harvard.edu/>) based on volume and surface pipelines (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, Tootell, & Dale, 1999). Starting from the segmentation of white matter and the subdivision of the gray/white boundary, the initial surface was obtained after automated topological correction. In order to reconstruct the pial, this initial surface was used as the initial shape of the deformable model. After reconstructing all surfaces, the cortical thickness was computed. Point correspondences across subjects in a standard surface-based coordinate system was also established. Then, the following procedures included the establishment of an average template, cortical surfaces reconstruction (Fischl et al., 1999), and resampling of cortical thickness data. The 20-mm width was used to smooth the cortical thickness map to increase the signal-to-noise ratio and to improve the ability to detect morphometric changes (Chung et al., 2005).

## 2.5 | Statistical analyses

Since sex differs between DP and NDP, the ANCOVA is invalid if we performed ANCOVA controlling for sex, age, education, and intracranial volume (Miller & Chapman, 2001). Therefore, both in volume and surface area analysis, we only consider age, education and total intracranial volume as covariates to perform a two-sample *t* test to compare all morphometric indexes between patients and controls, and between DP and NDP patients.

For group comparisons, the GM volumes of the two groups were entered into a general linear model (GLM). The regional changes of the GM volume were assessed using permutation-based non-parametric tests, with 5,000 random permutations. The significance threshold was  $p < .05$ , using threshold-free cluster enhancement (TFCE) method and family-wise error (FWE) corrections were used for multiple comparisons (Smith & Nichols, 2009). Finally, the GM values of the brain regions that showed abnormal morphological differences were extracted.

Regarding surface-based cortical reconstruction, statistical analyses were performed on each cortex of all subjects. We performed a two-sample *t* test to compare all morphometric indexes between patients and controls, and between DP and NDP patients. The

threshold  $p \leq .001$  was used to define clusters, and only clusters with a minimum of 100 points were reported. Then, a corrected cluster-wise  $p$ -value was obtained by using random field theory (RFT). After multiple comparison correction, the significance level of the cluster was set to  $p < .05$ .

Behavioral data was analyzed using SPSS 20.0 (IBM Corp., Armonk, NY). Kolmogorov–Smirnov one-sample test was utilized to measure the normal distribution of continuous data. If the data conforms to a normal distribution, chi-squared tests and two-sample  $t$ -test (two-tailed) were used to compare the demographic characteristics and clinical symptoms between the two groups. If not, a non-parametric test was conducted. Chi-square test was used to determine the sex difference between the two groups. Partial correlation analysis was performed to calculate the relationship between brain morphometric variables and behavioral performance in patients with DP and NDP, after adjusting for confounding factors. Only those morphometric variables with significant group differences were calculated. In addition, Bonferroni correction was adopted to adjust multiple tests. A two-tailed  $p$  value of less than .05 was considered statistically significant.

### 3 | RESULTS

#### 3.1 | Demographic and symptom data

There were no significant differences in sex, age and education between patients and healthy controls (all  $ps > .05$ ). Further, there was significant difference in sex ( $\chi^2 = 18.041$ ,  $p < .001$ , effect size = 0.655, power: 0.989) between DP and NDP patients, but there was no significant difference in age ( $U = 141.0$ ,  $p > .05$ ), education ( $t = 0.599$ ,  $p > .05$ ) and age of first episode ( $U = 129.5$ ,  $p > .05$ ). Compared with NDP patients, DP patients scored significantly higher in HAMD ( $U = 0$ ,  $p < .001$ ), positive symptom ( $t = -3.450$ ,  $p < .01$ ), general psychopathology ( $U = 39.5$ ,  $p < .001$ ), PANSS total score ( $U = 44.5$ ,  $p < .001$ ) (Table 1).

	NDP (n = 31)	DP (n = 11)	t/U/ $\chi^2$	p	Effect size (r)
Sex (F/M)	23/8	0/11	18.041	<.001	0.655
Age (y)	29.32 ± 10.33	26.64 ± 9.97	141.000	.398	0.130
Education	12.48 ± 3.38	11.82 ± 2.44	0.599	.553	0.111
First episode	26.632 ± 10.38	22.691 ± 6.82	129.500	.240	0.181
Positive	22.87 ± 5.62	30.09 ± 6.89	-3.45	.001	-0.498
Negative	20.32 ± 6.97	25.00 ± 13.51	146.000	.482	0.108
General	38.42 ± 9.40	59.55 ± 13.73	39.500	<.001	0.579
PANSS	82.00 ± 18.67	115.36 ± 25.05	44.500	<.001	0.557
HAMD	8.48 ± 4.69	33.64 ± 13.65	0	<.001	0.754
Cognition	8.68 ± 3.55	11.18 ± 5.08	-1.789	.081	-0.274
Excitement	10.94 ± 5.11	16.00 ± 6.02	83.500	<.001	0.385
Depression	4.81 ± 2.12	9.09 ± 3.75	52.500	<.001	0.533

Abbreviations: DP, depressive patients; NDP, non-depressive patients.

#### 3.2 | Group differences in brain structure between schizophrenia patients and healthy controls

Compared with the healthy controls, schizophrenia patients had significantly lower cortical thickness in the left rostral middle frontal gyrus ( $F = 7.132$ ,  $p < .01$ , Partial  $\eta^2 = 0.095$ ) and the right inferior temporal lobe ( $F = 4.132$ ,  $p < .05$ , Partial  $\eta^2 = 0.057$ ). However, there was no significant difference in other morphometric indicators, including GM volume and surface area between schizophrenia patients and healthy controls. The descriptive result of schizophrenic patients and healthy controls was summarized in Table 2.

#### 3.3 | Group differences in brain structure between DP, NDP and healthy controls

Results of ANCOVA analysis indicated that DP patients had higher GM volume in the left isthmus cingulate ( $F = 10.823$ ,  $p < .01$ , Partial  $\eta^2 = 0.231$ ) and the left posterior cingulate cortex ( $F = 4.735$ ,  $p < .05$ , Partial  $\eta^2 = 0.116$ ) compared with NDP patients (see Table 2). Further, DP patients showed greater surface area in the left isthmus cingulate cortex ( $F = 7.084$ ,  $p < .05$ , Partial  $\eta^2 = 0.164$ ), the left superior parietal gyrus ( $F = 4.836$ ,  $p < .05$ , Partial  $\eta^2 = 0.118$ ) and the right cuneus ( $F = 4.603$ ,  $p < .05$ , Partial  $\eta^2 = 0.113$ ) than NDP patients (Table 2; Figure 1). To investigate the effect of score of PANSS on the morphological measures, we further compared the group difference by taking PANSS as covariate. The results showed that the significant differences still existed in the GM volume and surface area of left isthmus cingulate ( $F = 6.878$ ,  $p < .05$ , Partial  $\eta^2 = 0.157$ ;  $F = 7.767$ ,  $p < .01$ , Partial  $\eta^2 = 0.173$ ), the left superior parietal gyrus ( $F = 5.407$ ,  $p < .05$ , Partial  $\eta^2 = 0.128$ ) as well as the right cuneus ( $F = 5.995$ ,  $p < .05$ , Partial  $\eta^2 = 0.139$ ) between DP and NDP. However, the significant level reached marginal in the GM volume of the left posterior cingulate cortex between these two group ( $F = 3.267$ ,  $p = .079$ , Partial  $\eta^2 = 0.081$ ).

Additionally, we compared the differences of the brain regions with significance between NDP and the controls. As shown in

**TABLE 1** Demographics of patients with DP and NDP in schizophrenia patients

**TABLE 2** Descriptive result of brain structures with significant differences in DP, NDP, all patients in FES and controls

Dependent variable	DP (n = 10)	NDP (n = 29)	FES (n = 41)	Control (n = 29)
lh_isthmuscingulate_volume	2,974.60 ± 352.62	2,385.03 ± 324.24	2,526.73 ± 410.51	2,508.97 ± 475.50
lh_isthmuscingulate_area	1,150.60 ± 137.16	923.59 ± 148.62	975.93 ± 175.51	944.31 ± 180.48
lh_superiorparietal_area	5,725.30 ± 495.59	4,942.90 ± 603.38	5,108.56 ± 669.59	5,062.86 ± 576.28
lh_posteriorcingulate_volume	3,575.40 ± 350.43	2,930.31 ± 507.46	3,067.98 ± 548.62	2,963.97 ± 460.51
rh_cuneus_area	1,622.60 ± 138.36	1,337.72 ± 229.80	1,404.17 ± 239.35	1,445.31 ± 188.89

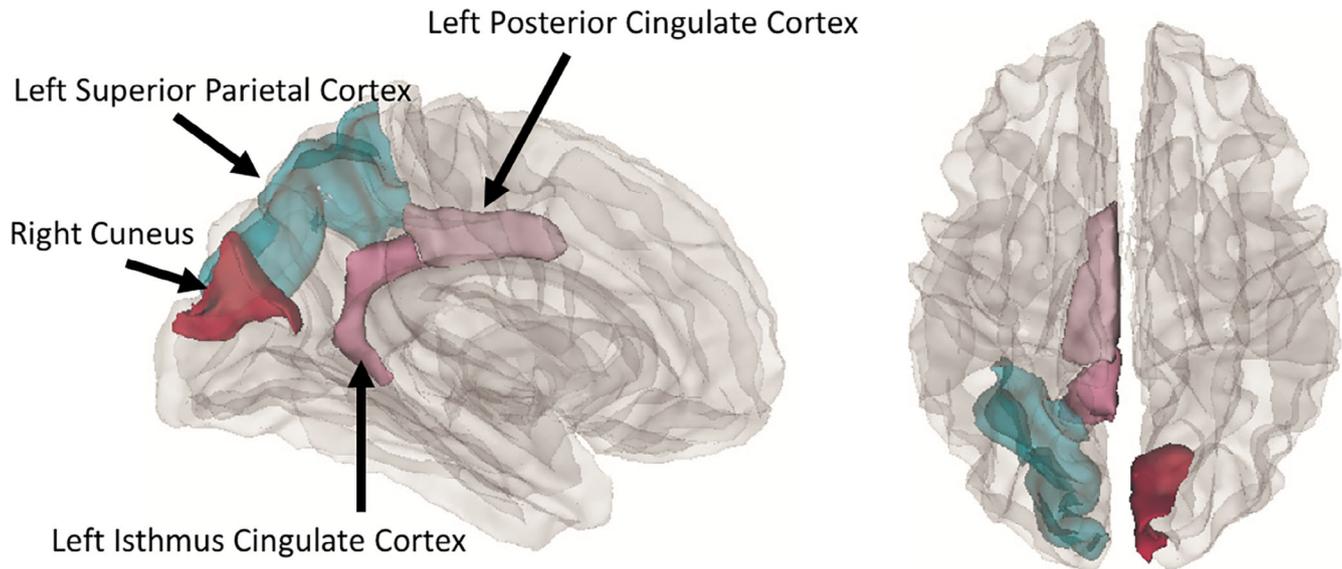
**FIGURE 1** Compared with nondepressive patients (NDP), depressive patients (DP) showed increased volume and surface area in colored brain regions. Purple clusters are those with significance reached  $p < .05$  (corrected) in GM volume, which includes left isthmus cingulate cortex and left posterior cingulate cortex. Red, green and dark purple are clusters with significance reached  $p < .05$  (corrected) in surface area, which are located in right cuneus, left superior parietal cortex and the left isthmus cingulate cortex

Table S1, there were no significant differences in these morphological measures between NDP and controls (all  $ps > .05$ ).

### 3.4 | Relationship between brain structures and psychopathology in DP, NDP and all schizophrenia patients

Considering possible influence of PANSS on depressive symptom-related brain structures, we conducted partial correlation controlling PANSS as covariate, which showed that both the surface area and GM volume of the left isthmus cingulate were significantly correlated with the total score of HAMD in DP ( $r = 0.846$ ,  $p < .01$ ;  $r = 0.696$ ,  $p < .05$ ). There was also a significantly positive correlation between the GM volume in the left isthmus cingulate and the PANSS general psychopathology ( $r = 0.818$ ;  $p < .01$ ) or PANSS total score ( $r = 0.656$ ;  $p < .05$ ) (See Supporting Information: Figure S1).

Additionally, we conducted correlation analysis between PANSS and HAMD both in DP and NDP. However, the results showed that

the score of PANSS was not significantly correlated with HAMD in DP ( $r = -0.178$ ;  $p = .601$ ) and NDP ( $r = -0.151$ ;  $p = .678$ ).

Moreover, we further conducted correlation between brain morphological characteristics and psychopathological measures both in NDP and all schizophrenia patients. For NDP, the results showed that the total score of PANSS was positively correlated the left superior parietal area ( $r = 0.401$ ;  $p < .05$ ) and was negatively correlated with the left posterior cingulate volume ( $r = -0.468$ ;  $p < .05$ ) while no significant correlation was found between the brain structures and scores of HAMD ( $p > 0.05$ ). For all schizophrenia patients, we also observed significant correlations between the brain structures with significance and psychopathology, as summarized in Table S2.

## 4 | DISCUSSION

To the best of our knowledge, this is the first structural study to fully explore the GM abnormalities in the FEDN schizophrenia patients comorbid with DP through the use of whole-brain morphometry. Consistent with our hypothesis, the cingulate cortex, a fundamental part

of the limbic system associated with depression, exhibited significant abnormalities in DP patients. Specifically, compared with NDP patients, DP patients showed larger volume and surface area of the left isthmus cingulate. Interestingly, the structural changes of the left isthmus cingulate cortex were positively associated with depressive symptom evaluated by HAMD and clinical psychiatric symptoms evaluated by PANSS in DP patients. Moreover, compared with NDP patients, DP patients showed greater GM volume in the left posterior cingulate cortex and greater surface area in the left superior parietal gyrus. Regarding the structural alterations in schizophrenia patients, we found that schizophrenia patients showed lower cortical thickness in the left rostral middle frontal gyrus and the right inferior temporal lobe than healthy controls. These results provide direct neuroanatomical evidence for structural changes associated with depressive symptoms in patients with FEDN schizophrenia.

One of the most intriguing results was the consistent findings of neuroanatomical abnormalities in the left isthmus cingulate cortex by using different imaging analysis methods, indicating that the results of neuroanatomical changes in the left isthmus cingulate cortex are highly reliable. Abnormalities in this brain region were also found in structural imaging study of schizophrenia, showing that the patients exhibited lower than normal levels of FA in the fibers connecting the cingulate isthmus with the parahippocampal cortex. Moreover, the changes in anatomical connections were correlated with the severity of patients' clinical symptoms assessed by PANSS (Whitford et al., 2014). This study further showed that such enlargement in the left isthmus cingulate was associated with depressive symptoms. The isthmus cingulate cortex refers to the narrowing of the cingulate cortex connecting the posterior cingulate cortex to the parahippocampal gyrus. Although the function of the isthmus cingulate is not well understood, converging evidence from structural imaging shows the role of the isthmus cingulate cortex in both major and subthreshold depression (H. Li et al., 2015; Ries et al., 2009), indicating that the abnormality of the isthmus cingulate may be closely associated with depression. However, some studies reported that the depression is associated with a reduction in volume, thickness and surface area, while others have demonstrated an increase in morphometry (McLaren et al., 2016). These changes in isthmus cingulate may indirectly reflect the dysfunction of emotional response and impaired ability to handle emotional stimuli that originate from episodic memory (Nielsen, Balslev, & Hansen, 2005). A meta-analysis review demonstrates that patients with schizophrenia have common impairment in using emotion to effectively regulate memory intensity and establish long-term positive experience memory (Herbener, 2008). Notably, the abnormal isthmus cingulate might be related to emotional recognition and expression. Several comparative studies between schizophrenics, depression and the comorbid depression in schizophrenia might provide insights to advance the understanding of the role of isthmus cingulate in processing of emotional stimuli. Herniman, Allott, Killackey, Hester, and Cotton (2017) investigated 82 young people with first-episode psychosis by using adult photographs depicting facial expressions to compare their differences in response to emotional recognition task. The results showed that those with comorbid depression

made fewer errors in recognizing facial expressions of sadness than those without comorbid depression, indicating the patients in DP had a mood congruent negative bias in facial emotional recognition. Recently, a behavioral study examined the differences of emotional experience and expression between the blunted schizophrenics, non-blunted schizophrenics, the major depressive disorders and normal subjects, which showed that the patients with depression were less responsive than the non-blunted schizophrenics to the positive stimuli and also differed in response to sadness from schizophrenics as well as the normal subjects (Berenbaum & Oltmanns, 1992). This study also provided behavioral evidence that individuals with major depressive disorder tend to be less happy and angrier than both schizophrenic and non-psychiatric individuals. Therefore, in view of the role of the isthmus cingulate cortex in processing emotional information, abnormal neural representation of isthmus cingulate cortex may lead to depressive symptoms and the general psychopathological symptoms by destroying specific emotional memory and response such as sadness in FEDN patients with DP. The researchers emphasized the need to focus on the structural and functional changes in the cingulate isthmus in patients with depression to help clarify the mechanisms by which different symptom dimensions may be inversely related to this region (McLaren et al., 2016). These evidences might provide insight for treating patients in FES with DP from emotional processing perspective. It is promising to use structural MRI in the left isthmus cingulate as a possible biomarker of repetitive transcranial magnetic stimulation (rTMS) treatment response if future longitudinal studies support the association between the structural change in this brain region and depressive symptom in schizophrenia with DP (Boes et al., 2018). However, it must be emphasized that this study did not evaluate the patients' ability of emotional processing; therefore, any attempt to generalize the current results should be treated with great caution until the results are replicated.

Another interesting result is that both surface area and GM volume in the left isthmus cingulate cortex were significantly correlated with the score of HAMD while only the GM volume in this brain region was significantly correlated with the score of PANSS. Although it is difficult to infer which brain morphological measurement is more sensitive to depressive symptoms in view of unknown biological implication of volume and surface by different significant level of correlation analysis, it is possible that the surface area of the left isthmus cingulate brain might be anatomical characteristics related to depressive symptom only for DP and is independent of the severity of clinical schizophrenia. It further supports the association between depressive symptom and the change of surface area in the left isthmus cingulate in the schizophrenia with DP. Hopefully, future longitudinal study with a large sample size are needed to demonstrate the difference of morphological measures related to depressive symptom in schizophrenia.

We found a larger volume of the posterior cingulate cortex in FEDN schizophrenia patients with DP. The posterior cingulate cortex is the core part of limbic system, and also has functions related to emotional evaluation. Functional imaging studies have consistently found that emotional stimuli activated the posterior cingulate cortex,

suggesting that this region may mediate the interaction between emotion and memory-related processes (Maddock, Garrett, & Buonocore, 2003). In addition, structural changes in the posterior cingulate cortex have been extensively described in both nonclinical sample and patients with MDD, and the higher score of depression subscale is related to the larger volume of left posterior cingulate (McLaren et al., 2016). However, there is evidence that the volume of the posterior cingulate cortex is decreased in depressed adults (Ries et al., 2009). Therefore, due to the limited number of studies, it is still inconclusive to determine whether the neuroanatomical structures of the posterior cingulate cortex associated with depressive symptoms are enlarged or atrophied. The inconsistent findings may be due to the heterogeneity of the sample size, different measurements of depressive symptoms and the complexity of the pathopsychological mechanism of depression. Nevertheless, in the early stages of depression, greater brain volume is associated with increased metabolic activity and blood flow, while brain volume shows a sustained decline after long-term use of drugs and stress (Frodl et al., 2003). Similarly, we also found that the DP patients had a larger surface area in the superior parietal gyrus than NDP patients. The high-risk participants with depression responded more in the superior parietal cortex than low-risk participants when classifying and memorizing positive and negative self-referential personality trait words, indicating the role of the superior parietal cortex in negative biases in emotional processing (Chan, Harmer, Goodwin, & Norbury, 2008). Therefore, the structural enlargement of the superior parietal gyrus may also reflect the impairment of emotional processing.

Although this study has potential implications, its main limitations should be acknowledged. First, anxiety is another common symptom associated with depression among schizophrenia patients. However, the level of anxiety was not evaluated, which might influence the present findings in brain morphology related to mood and emotions. Therefore, future studies should attach great importance on demonstrating the mediation effect of anxiety on depressive symptom in schizophrenia. Second, after we determined the cut-off point for all patients with a score of more than 20, the sample size of DP patients was relatively small. Thus, caution should be taken when drawing any conclusions about the neural basis of depressive symptoms in FEDN patients. Larger sample size of replication studies are needed from different ethnic populations. Third, only male patients participated in the DP group in this study, which obviously limited the generalizability of the results. To test the main findings of this study, the heterogeneous sex ratios should be included in future investigation. Fourth, the cross-sectional study design of this study cannot clarify causal relationship. A longitudinal study with clear assumption is also required. Fifth, regarding the clinical measurements of depressive symptom, more suitable instruments specifically for schizophrenia comorbid with depressive symptoms should be used, such as Calgary Depression Scale for Schizophrenia (Martín-Reyes et al., 2011).

In summary, this study firstly investigated the structural characteristics of FEDN schizophrenia patients comorbid with depressive symptoms through whole-brain morphometry by recruiting the first-

episode drug-naïve patients, and undoubtedly ruled out the effects of common confounding variables such as illness duration, medication and other clinical comorbidities. We detected an increase in morphometry in the isthmus cingulate and posterior cingulate cortex in FEDN schizophrenia patients with DP, which was also associated with the severity of depressive symptoms. These findings suggest that schizophrenia patients comorbid with depressive symptoms exhibit structural abnormalities concentrating on the cingulate cortex, suggesting that defects in the limbic system may unravel the neural correlates of the psychopathology behind the depressive symptoms of schizophrenia. Moreover, consistent results based on whole-brain morphometric measurements indicate that depression in FEDN patients may have unique neural circuits, so it should be considered as an inseparable symptom domain in clinical diagnosis and treatment.

#### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

#### DATA AVAILABILITY STATEMENT

Our clinical data is not able to be made openly available because of ethics and privacy.

#### ETHICS STATEMENT

This study was approved by the Institutional Review Board (IRB) of Beijing Hui-long-guan Hospital and was performed in accordance with the Declaration of Helsinki.

#### PATIENT CONSENT STATEMENT

All subjects received a full explanation of the study and provided written informed consent to participate in the study.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Wei G-X, Ge L, Chen L-Z, Cao B, Zhang X. Structural abnormalities of cingulate cortex in patients with first-episode drug-naïve schizophrenia comorbid with depressive symptoms. *Hum Brain Mapp*. 2021;42: 1617–1625. <https://doi.org/10.1002/hbm.25315>