

Depressive symptom in the first-episode schizophrenic patients is related to the reduction of grey matter volume in the subgenual anterior cingulate cortex - a pilot study

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ABSTRACT

Approximately 25–75% of patients with schizophrenia also present major depressive systems. Investigations into the pathological features associated with depressive symptoms in patients with schizophrenia would provide important information for the development of treatments for depressive symptoms in patients with schizophrenia. In present study, we enrolled 17 first-episode schizophrenic patients with depressive symptoms and 17 well-matched first-episode schizophrenic patients without depressive symptoms and compared differences in their grey matter volume (GMV) using voxel-based morphometry (VBM). We observed significantly decreased GMV in the subgenual anterior cingulate cortex (sgACC) in the first episode schizophrenic patients with depressive symptoms compared to the first episode schizophrenic patients without depressive symptoms. However, we did not observe a correlation between the severity of the decreased GMV and the severity of depressive symptoms. Although convincing evidence supporting this postulation is lacking and requires further study for confirmation, to some extent, our findings provide indirect evidence for the suggestion that the reduction of the GMV in the sgACC may play a key role in the depressive symptoms in the first episode schizophrenic patients.

INTRODUCTION

According to several previous studies, depressive symptoms are usually accompanied with psychotic disorders, particularly schizophrenia [1, 2]. Most notably, depressive symptoms could occur in every stage of schizophrenia, including the prodromal stage, acute episode stage and remission stage. Many previous studies have confirmed that approximately 25–75% of patients with schizophrenia also demonstrate with different levels of depressive symptoms [3, 4]. Depressive symptoms in patients with schizophrenia are usually induced by detrimental consequences, including

suicidal ideations, an increased relapse rate and poor quality of life. The above-mentioned detrimental consequences directly increase mortality of patients with schizophrenia [5, 6]. Hence, explorations of the brain-related pathological features of depressive symptoms in patients with schizophrenia and the specific treatment targets have become the key issues in developing effective treatment strategies for depressive symptoms in the schizophrenic patients, especially in the first episode schizophrenic patients with depressive symptoms [8].

Based on the advances in neuroimaging techniques in the last two decades, many studies have adopted magnetic resonance imaging (MRI) and functional MRI

(fMRI) techniques to explore the pathological features of major depression disorder (MDD) and schizophrenia. These studies have acquired important and useful information that has improved our understanding of the biological basis of schizophrenia and have provided many indices to aid psychiatrists in improving the rates of accurate diagnoses and treatment efficacies [9–17]. However, most of these previous studies have focused on exploring the common brain features shared by patients with schizophrenia and depression, these previous studies have provided evidence that structural or functional impairments in some brain regions in patients with schizophrenia overlap with impairments observed in patients with MDD to some extent, The temporal lobe and anterior cingulate are the main affected regions [7, 18–31].

Although previous studies have provided important and useful information that has improved our understanding of the association of depressive symptoms with pathological characteristics in the brains of patients with schizophrenia, to the best of our knowledge, few studies have reported the association of depressive symptoms with structural alterations in the brains of patients with first-episode schizophrenia. In the present study, our aims were to compare the alterations in grey matter volume (GMV) between patients with first-episode schizophrenia patients who accompanied with and without depressive symptoms. We assumed that the first-episode schizophrenic patients with depressive symptoms probably had specific structural alterations compared to the first episode schizophrenic patients without depressive symptoms.

RESULTS

Demographics and clinical characteristics

The demographic and clinical characteristics of the participants are presented in Table 1. No significant group differences were observed in gender ($X^2 = -0.806$, $P = 0.426$), age ($t = -0.497$, $P = 0.623$), educational level ($t = 0.539$, $P = 0.534$), illness duration ($t = -0.331$, $P = 0.743$), antipsychotic drug dosages ($t = 0.484$, $P = 0.631$), or PANSS scores ($t = 0.094$, $P = 0.926$). The mean antipsychotic dosages (chlorpromazine equivalents) were 533.0 ± 78.7 mg/d in the patients with depressive symptoms and 526.6 ± 79.8 mg/d in the patients without depressive symptoms. Fourteen patients with depressive symptoms were administered five antidepressants, including venlafaxine, mirtazapine, citalopram, sertraline, and fluoxetine, and three patients were simultaneously treated with mirtazapine and venlafaxine (i.e., the “California rocket treatment method”) for very severe depression. Detailed information about the demographic and clinical characteristics is listed in Table 1.

GMV alterations in first episode schizophrenic patients with moderate to severe depressive symptoms

Compared to first-episode schizophrenic patients without depressive symptoms, decreased GMV were observed in the subgenual anterior cingulate cortex (sgACC) and bilateral occipital lobe in the first-episode schizophrenic patients with moderate to severe depressive symptoms. However, after the false discovery rate (FDR) correction, only the reduced GMV in the sgACC was significant (Figure 1). The difference in the GMV in the bilateral occipital lobe disappeared (Figure 2). Additionally, the partial correlation analysis did not find any correlations between the severity of the GMV reduction and the severity of the CDSS scores.

DISCUSSION

In the present study, we initially compared the differences in GMV between the first-episode schizophrenic patients who accompanied with and without depressive symptoms. GMV was decreased in the sgACC in the first-episode schizophrenic patients who accompanied with depressive symptoms. Thus, the decreased GMV in the sgACC might be a specific pathological feature of depressive symptoms in patients with first-episode schizophrenia. Many previous studies have focused on investigating the pathological features of depression and confirmed that structural and functional alterations in the sgACC are pathological features of patients with depression. Moreover, these alterations are also related to the treatment response, particularly in patients with treatment-refractory depression [32–36]. Simultaneously, according to some previous studies, structural and functional alterations in the temporal lobe and sgACC overlap in patients with major depression and schizophrenia [8, 9, 10, 37]. Our findings converged with the previous findings to support the hypothesis that the sgACC is a pathological centre in patients with MDD and the hypothesis that the sgACC is a common pathological feature in patients with schizophrenia and depression [32–37]. To some extent, our findings provide indirect evidence for the postulation that the sgACC may be one of the specific pathological features of depressive symptoms in patients with schizophrenia, although conclusive evidence supporting this postulate is lacking and requires further study for confirmation.

The severity of depressive symptoms in patients with schizophrenia differs in different illness stages, and more severe depressive symptoms usually occur in the first-episode stage [38]. The psychological explanation for this phenomenon is that it may be a natural reaction to the development of psychotic symptoms [39]. According to this postulate, psychotic symptoms cause psychological stress, which may be the reason for the

severe depressive symptoms. Chronic stress has been shown to cause depressive reactions and reduced GMV in some but not all patients. The patients in the present study experienced illness at a mean of 7.5 months, which is sufficient period to cause GMV reductions. Our findings support the hypothesis that the psychiatric symptoms induced psychological stress, subsequently induced the GMV reduction in some key brain regions, such as sgACC. [40, 41].

A counterintuitive phenomenon observed in this study is the lack of correlation between the severity of the GMV reduction and the severity of depressive symptoms. However, this counterintuitive phenomenon is not incredible; in several of our previous studies, we did not observe correlations between the GMV alterations and PANSS scores, illness duration, or dosage of antipsychotics. Some other previous studies have also reported this counterintuitive phenomenon. Previous studies have proposed that the severity of structural or functional alterations does not correlate with the severity of clinical symptoms, possibly indicating that the structural or functional alterations should only be used as a quality index to assist in the disease diagnosis and not as a quantity index to assess the severity of the disease [41–44].

Limitations

The present study has several limitations. The first limitation is that limited by the previous designed cohort study's deficit, we did not find well-matched healthy controls for enrolment in the study; hence, we could not adopt one-way analysis of covariance (ANCOVA)

methods to compare the differences in GMV between the two patient groups and healthy controls. Hence, our current conclusion is not convincing. Second, in the present study, patients with first episode schizophrenia patients who accompanied with depressive symptoms were administered antidepressants, and patients without depressive symptoms did not receive antidepressant treatment; thus, the antidepressants may have influenced the findings. Due to a lack of a uniform equation to convert the dosages of antidepressants to a standard similar to the antipsychotics, we could not regress out the influences of the antidepressants using the same method as for the antipsychotics. These influences were not examined under these conditions. Fortunately, in many previous studies, antidepressant dosages were normalized to GMV impairment. These reports provide indirect support for our hypothesis.

MATERIALS AND METHODS

Sample

The present study included 17 first-episode schizophrenic patients who accompanied with moderate to severe depressive symptoms and 17 well-matched first-episode schizophrenic patients who did not accompany with depressive symptoms. The entire sample was derived from our research database of hospitalized patients at Tianjin Mental Health Center, and healthy volunteers were recruited through advertisements. The diagnoses of patients with first-episode schizophrenia patients who accompanied with and without depressive symptoms were determined by two professional psychiatrists who

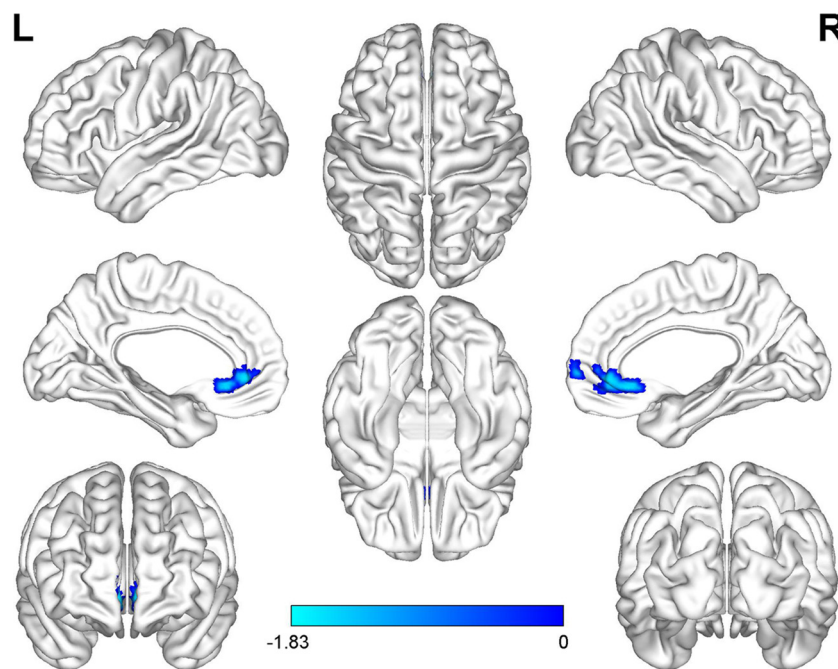


Figure 1: Decreased GMV in the sgACC (after the FDR correction).

Table 1: Demographic and clinical characteristics

Characteristics	FSC + D	FSC	T/X ²	P value
Age	27.1 ± 5.3	27.6 ± 5.1	-0.497	0.623
Gender (male/female)	10/7	8/9	-0.806	0.426
Education level	12.3 ± 2.7	12.0 ± 2.6	0.539	0.534
PANSS scores	140 ± 21.6	139.7 ± 21.0	0.094	0.926
Illness duration (months)	3.3 ± 1.5	3.3 ± 1.6	-0.331	0.743
Chlorpromazine equivalent dosage	533.0 ± 78.7	526.6 ± 79.8	0.484	0.631
CDSS score	16.8 ± 3.0	NA		

Abbreviations: FSC + D: First-episode schizophrenic patients accompanied with depressive symptoms; FSC: First-episode schizophrenic patients without depressive symptoms.

adopted the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) Disorders (SCID) [45]. In the present study, the first episode was referred as that the illness duration of the schizophrenic patients did not exceed 6 months. The exclusion criteria for all samples were: 1) a history of consciousness disturbances lasting more than 5 min; 2) a history of substance abuse; 3) female patients who were pregnant and lactating; 4) a history of any physical and neurological illnesses, such as cardiovascular disease and epilepsy; and 5) any contraindications for MRI scanning. Schizophrenic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) [46]. Depressive symptoms were assessed with the Calgary Depression Rating Scale (CDSS) [47], which is usually adopted to assess the severity of depressive symptoms in patients with schizophrenia. For each patient, the chlorpromazine equivalent dose was calculated according to the

antipsychotic drugs and dosages used in the last week before the MRI scan, according to uniform criteria [48]. However, due to the lack of uniform criteria for calculating the equivalent dosages of antidepressants, a uniform dosage of the antidepressants used by the patients was not calculated. The Medical Research Ethics Committee of Tianjin Anding Mental Health Center approved our study. The patients' guardians and healthy participants all completely understood the risks and benefits of the study, and written informed consent was obtained from each of the subjects.

MRI data acquisition

MRI images were acquired with a 3.0-Tesla MR system (Discovery MR750, General Electric, Milwaukee, WI, USA). Foam padding was used to minimize head motion, and earplugs were used to minimize scanner

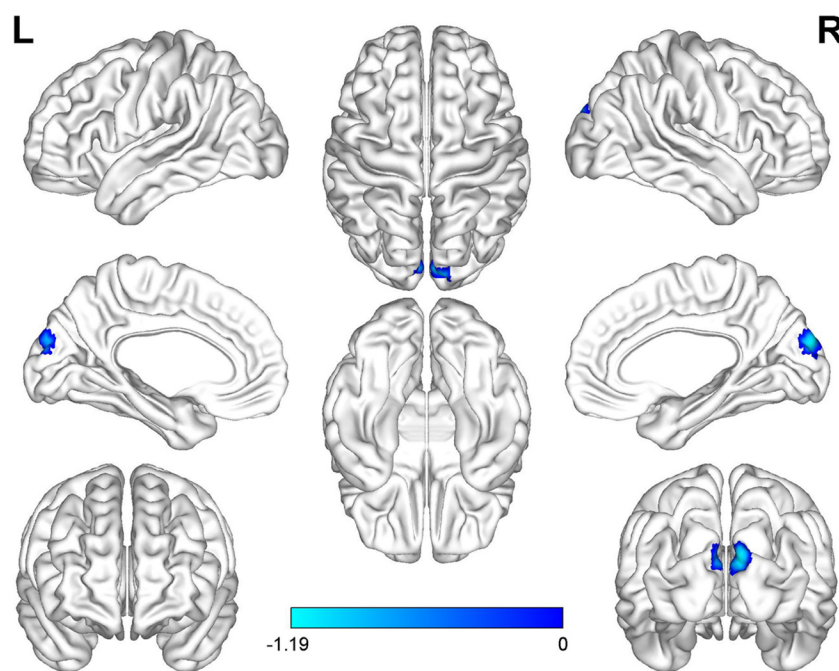


Figure 2: Decreased GMV in the occipital lobe (before the FDR correction).

noise. Sagittal 3D T1-weighted images were obtained with a brain volume sequence using the following parameters: repetition time (TR) = 8.2 ms; echo time (TE)=3.2 ms; inversion time (TI)=450 ms; flip angle (FA)=12°; matrix=256×256; field of view (FOV)=256 mm×256 mm; slice thickness=1 mm; no gap; and 188 sagittal slices. During the scanning period, all subjects were asked to keep their eyes closed, relax, control their head movement, and think of nothing while not falling asleep.

GMV calculation

SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) software was adopted to calculate the GMV of each voxel. According to the operational manual, the structural MR images were segmented into grey matter (GM), white matter and cerebrospinal fluid (CSF) using the standard unified segmentation model. When an initial affine registration of the GM concentration map into the Montreal Neurological Institute (MNI) space was performed, the GM concentration images were nonlinearly warped by diffeomorphic anatomical registration using the exponentiated lie algebra technique, and the results were resampled to a voxel size of 3 mm×3 mm×3 mm. The GMV of each voxel was acquired by multiplying the GM concentration map by the non-linear determinants extracted from the spatial normalization step. A full-width at half-maximum Gaussian kernel of 6 mm×6 mm×6 mm was adopted to smooth the GMV images. After spatial preprocessing, the smoothed GMV maps were used for the statistical analyses.

Statistical analysis

Group differences in the GMVs were compared in a voxel-wise manner using a two-sample *t*-test, with age and gender as nuisance variables. Multiple comparisons were corrected using a false discovery rate method with a significant threshold of $P<0.05$. Partial correlation analyses were used to test the relationship between the GMV and the CDSS scores. Age, gender, antipsychotic dosage, duration of illness and PANSS scores were regressed out, and multiple comparisons were corrected using the Bonferroni method ($P<0.05$).

CONCLUSIONS

Our present study is the first to find that the GMV in the sgACC was significantly reduced in the first-episode schizophrenic patients who accompanied with moderate to severe depressive symptoms. This finding provides evidence to support the hypotheses that structural alterations in the sgACC are pathological features of MDD and that the sgACC is a common pathological feature of schizophrenia and depression. To some extent, our findings also provide indirect evidence for the suggestion that the

sgACC impairment may play key role in the depressive symptoms in the first-episode schizophrenic patients, although convincing evidence supporting this postulation is lacking and requires further study for confirmation.

Author contributions

CZ and DM: conceptual design and writing of the draft manuscript; CC, CS,RJ and WZ: conceptual design and writing of the final manuscript; CC,LW, XH and DJ collected and analyzed the data enrolled in this manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

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