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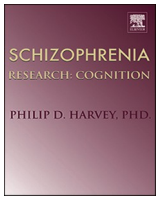

The altered volume of striatum: A neuroimaging marker of treatment in first-episode and drug-naïve schizophrenia

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ABSTRACT

Although schizophrenia patients exhibit structural abnormalities in the striatum, it remains largely unknown for the role of the striatum subregions in the treatment response of antipsychotic drugs. The purpose of this study was to investigate the associations between the striatal subregions and improved clinical symptoms in first-episode drug-naïve (FEDN) schizophrenia. Forty-two FEDN schizophrenia patients and 29 healthy controls (HCs) were recruited. At baseline, the Positive and Negative Syndrome Scale (PANSS) was used to assess the clinical symptoms of patients, MRI scanner was used to obtain anatomical images of patients and HCs. After 12-week stable doses of risperidone treatment, clinical symptoms were obtained in 38 patients and anatomical images in 26 patients. After 12 weeks of treatment, the left nucleus accumbens volume decreased, whereas the left pallidum volume increased in schizophrenia patients. The decreased left nucleus accumbens volume was positively correlated with cognitive factor improvement measured by PANSS. Intriguingly, greater left nucleus accumbens volume at baseline predicted greater cognitive improvements. Furthermore, the responders who had >50 % improvement in cognitive symptoms exhibited significantly greater baseline left nucleus accumbens volume compared to non-responders. The left striatum volume at baseline and after treatment predicted the cognitive improvements in FEDN schizophrenia, which could be a potential biomarker for the development of precision medicine approaches targeting cognitive function.

1. Introduction

The striatum is an important subcortical structure consistently implicated in the pathophysiology of psychosis, which harbors the largest density of dopamine D2 receptors (Mikell et al., 2009). The abnormalities of the striatum were related to psychotic symptoms and cognitive impairments in schizophrenia. A study including 170 patients with first-episode drug-naïve (FEDN) schizophrenia observed that the volume of the nucleus accumbens (part of the ventral striatum) was positively correlated with positive symptoms (Fengmei et al., 2019). Another investigation involving FEDN schizophrenia revealed that the functional connectivity between the striatum and superior frontal gyrus was associated with psychiatric symptoms (Zhang et al., 2022). Additionally, volumes in the striatum, thalamus, hippocampus, and mid-occipital region were correlated with cognitive performance (Sui et al., 2015).

The striatum is also thought to play a fundamental role in the current antipsychotic medications since striatal dopamine D2 receptors are involved in both positive and negative symptoms of schizophrenia (Simpson et al., 2022). Risperidone as a second-generation antipsychotic medication shows a higher affinity for D2 receptors, which is a safe and effective antipsychotic for psychiatry symptoms, which could reorganize the striatal networks by inducing neuroplastic changes (Fusar-Poli et al., 2013; Angelucci et al., 2008). For example, a neuroimaging review identified the striatum as the core target region of risperidone treatment in schizophrenia (Yang et al., 2021). An 8-week course of risperidone

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treatment has been shown to enhance the functional connectivity between schizophrenia patients' striatum subregions and salience network, which was associated with improved clinical symptoms (Han et al., 2020). Additionally, in unmedicated schizophrenia patients, alterations in striatum activation following a 6-week risperidone treatment were linked to improvements in cognitive control (Cadena et al., 2018).

It should be noted that the incomplete responses to antipsychotics in some schizophrenia patients are not readily predicted. Nearly one-third of patients with schizophrenia are resistant to antipsychotic medications, which may lead to long-term untreated disease and cortical progression and functional deterioration of the patient (Harvey and Rosenthal, 2016; Sarpal et al., 2016). Recently, brain imaging techniques may provide effective tools to assess differential responses to antipsychotic treatment by detecting cortical organization and function in schizophrenia before receiving medication (Seeman, 2020, Cao et al., 2018). Few studies have indicated the predicting role of the striatum on antipsychotic treatment. One study found that baseline striatal functional connectivity predicted antipsychotic treatment response in patients with psychotic disorders (Sarpal et al., 2016). A recent study indicated that baseline nucleus accumbens was negatively associated with improvement in positive symptoms in antipsychotic-naive patients with psychosis (Bojesen et al., 2023). However, this study was limited because types of antipsychotics and diseases were not controlled.

Therefore, the current results are inconsistent regarding the role of specific brain regions in predicting the effect of antipsychotic treatment in schizophrenia. One of the reasons might be the involvement of patients with chronic schizophrenia, which may be confounded by potential factors including medication effects, duration of disease, and psychiatric and medical comorbidities associated with chronic illness. Given this, FEDN schizophrenia patients are an ideal population model to investigate the effects of atypical antipsychotics on brain structure (Buckley et al., 2007). Regarding the crucial role of the striatum in the efficacy of antipsychotic medication, the present study aimed to investigate whether structural characteristics of the striatum in FEDN schizophrenia patients are associated with treatment response to risperidone. It was hypothesized that 1) FEDN schizophrenia patients may have significant volume changes, particularly in the striatum, after 12 weeks of risperidone treatment, which are associated with improvements in psychotic symptoms and cognitive function, and 2) baseline volume of the striatum may predict the therapeutic effect of risperidone on improvements in psychotic symptoms and cognitive function.

2. Methods

2.1. Participants

A total of 42 schizophrenia patients (23 males and 19 females) were recruited from Beijing Hui-long-guan Hospital. All participants were diagnosed with FEDN schizophrenia, and the age of the first episode was 25.6 ± 9.8 years. In this study, the first episode was defined as the first symptom onset. Diagnosis and clinical characteristics were evaluated by trained psychiatrists with at least 5 years of clinical practice using the Structured Clinical Interview for DSM-IV (SCID). Inclusion criteria included: 1) meeting DSM-IV diagnostic criteria for schizophrenia; 2) duration of illness not exceeding 5 years; 3) no previous antipsychotic drugs (Breitborde et al., 2009; Pillinger et al., 2017). Patients were excluded if they had a history of head trauma, neurological disorders, and uncontrolled major medical conditions. Participants could withdraw from the study at any time.

Twenty-nine healthy controls (13 males and 16 females) were recruited from the local community by advertisement and were matched to the patients in terms of age, gender, and education. They were excluded if they had any history of mental disorder or any major medical illness.

The study was approved by the Institutional Review Board (IRB) of Beijing Huilongguan Hospital and was conducted following the Declaration of Helsinki. The ethics approval number is SCH-A01 and the clinical trial registration number is NCT00686140. Written informed consent was obtained from all participants before the study.

2.2. Clinical assessments and treatment

Demographic information and clinical data were collected for all participants. Psychiatric symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) at baseline and at the end of 12 weeks of treatment. The PANSS is divided into three subscales: positive symptoms, negative symptoms, and general psychopathology. In addition to these three subscales, the 5-factor model of the PANSS includes cognitive components (Wallwork et al., 2012). The cognitive subscale measures cognitive functioning and is comprised of three items from the PANSS: " Conceptual Confusion" (P2), "Difficulty with Abstract Thinking" (N5), and "Poor Attention" (G11). Higher cognitive factor score indicates greater cognitive impairment (Fong et al., 2015).

Prior to the start of this study, two clinical psychiatrists attended a training session on the use of the PANSS. After the training, their inter-rater correlation coefficients for the PANSS total scores were maintained at >0.8 by repeated assessments.

All patients were treated with a stable dose of risperidone for 12 weeks. During the first week of dosing, it was increased from 1 mg/day to 3–6 mg/day and maintained at these levels until the end of the clinical study. The permitted combination drugs included chloral hydrate or lorazepam for insomnia and the anti-parkinsonian drug benzhexol hydrochloride for extrapyramidal symptoms. No other combination antipsychotics were used during the study period. Due to personal reasons, 4 patients voluntarily withdrew from the study, so 38 patients were evaluated for treatment response (Fig. 1).

2.3. Imaging acquisition and processing

High-resolution anatomical images of the whole brain were acquired on a GE 3 Tesla MRI scanner (GE Healthcare, Buckinghamshire, United Kingdom). T1-weighted scans were performed using spoiled gradient echo (SPGR) with the following parameters: repetition time (TR) = 6.2 ms, echo time (TE) = 2.8 ms, flip angle = 8°, field of view (FOV) = 240 mm, slice thickness = 1.2 mm, matrix size = 256 × 256, total number of slices = 142, and voxel size = 0.94 × 0.94 × 1.2 mm. Patients were fitted with earplugs and foam pads to reduce scanner noise and limit head movement. Each patient was asked to remain stationary during the scanning process. All 42 participants were scanned at baseline, and 26 of them completed a second scan after treatment. Four patients withdrew from the study, with 3 being uncooperative during MRI scanning, and 9 citing personal reasons for withdrawal. There were no significant differences in clinical symptoms at baseline and after treatment between patients who received the second scan and those who did not (all $p > 0.05$) (Fig. 1).

All scans were visually checked for validity and then cortical and subcortical reconstruction and volume segmentation were performed using the Freesurfer pipeline (software version 5.3, http://surfer.nmr.mgh.harvard.edu). The entire procedure included motion correction, intensity normalization, automatic topology correction, automatic segmentation in the Desikan-Killiany Atlas (Desikan et al., 2006), and smooth.

2.4. Statistical analyses

All data were analyzed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA). First, a two-sample *t*-test or chi-square test was used to examine group differences between patients and healthy controls in terms of demographic characteristics and clinical variables. Then, paired-sample *t*-tests were performed to compare changes in clinical symptoms within patient groups at baseline and after treatment.

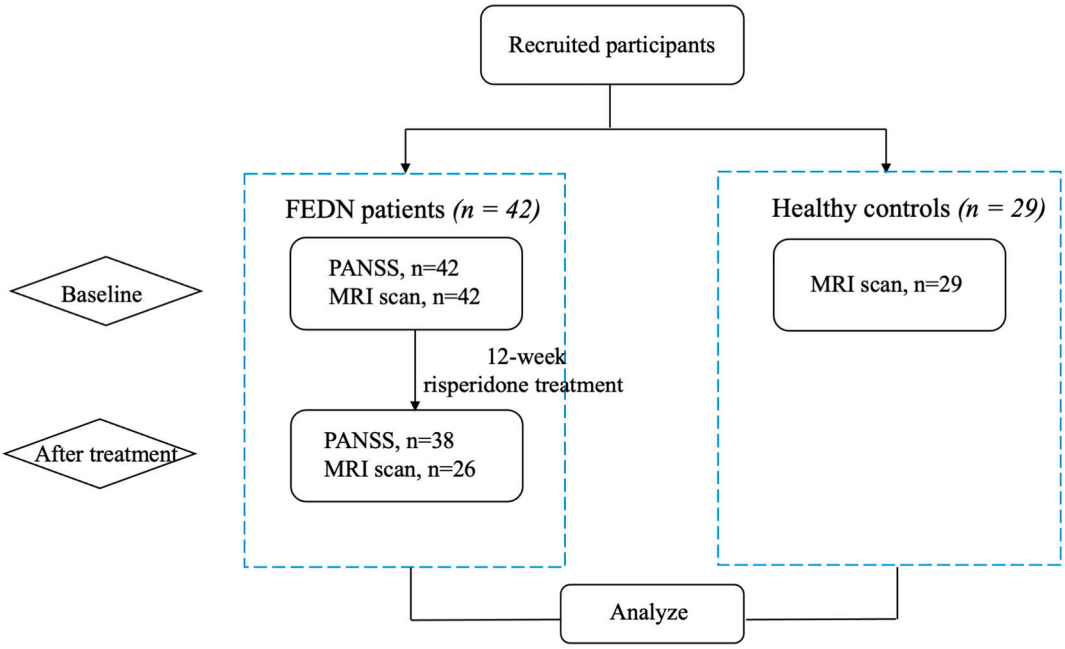

Fig. 1. Flow chart of the study.

As for volume differences, a one-way analysis of covariance was used to compare the differences in brain volumes between FEDN schizophrenia patients and healthy controls after controlling for age, sex, education, and intracranial volume. As for changes in volume, regional changes in brain volume were assessed by paired-sample *t*-tests in schizophrenia patients before and after treatment. False discovery rate (FDR) was applied to these results as a multiple comparison correction (Benjamini & Hochberg, 1995).

Partial correlations were performed to calculate the relationship between volume change (subsequent minus baseline) and clinical symptoms change (subsequent minus baseline) after controlling for age, sex, education, intracranial volume, and baseline clinical symptoms scores. A multiple linear regression model with age, sex, education, intracranial volume, and baseline clinical symptoms score as covariates was used to predict the role of baseline volume in clinical symptom change. In addition, we used the criteria of a 50 % or more improvement in PANSS to define "responders" or "non-responders". We examined the group differences in baseline volume between responders and non-responders.

3. Results

3.1. Volume differences between schizophrenia patients and controls at baseline

There were no significant differences between patients ($n = 42$) and healthy controls ($n = 29$) in terms of gender, age, and education (all $p > 0.05$) (Table 1). Compared to healthy controls, patients with schizophrenia had significantly lower volume of the left lateral occipital cortex ($F_{(1, 70)} = 7.30, p < 0.01$) and the left superior frontal cortex volume ($F_{(1, 70)} = 4.30, p < 0.05$), but significantly higher right temporal pole volume ($F_{(1, 70)} = 6.13, p < 0.05$) (Fig. 2). After FDR, there were no significant volume differences between schizophrenia and healthy controls ($p > 0.05$).

3.2. Changes in clinical symptoms and volumes after treatment

After 12 weeks of risperidone treatment, 38 patients finished the second evaluation. Results showed that PANSS positive ($t_{(37)} = 7.55$, $p < 0.001$), negative ($t_{(37)} = 2.89$, $p < 0.01$), general psychopathology ($t_{(37)} = 6.18, p < 0.001$) and total scores ($t_{(37)} = 7.10, p < 0.001$), PANSS cognitive factor score ($t_{(37)} = 5.79$, $p < 0.001$) were significantly decreased (Table 1).

Table 1
Demographic and clinical characteristics in patients at baseline and follow-up and matched healthy controls.

	Patients		Controls
	Baseline ($n = 42$)	Follow-up ($n = 38$)	$n = 29$
Sex (M:F)	19:23	18:20	13:16
Age	28.62 ± 10.18	28.82 ± 10.15	27.72 ± 7.83
Education	12.31 ± 3.14	12.21 ± 3.05	12.29 ± 3.96
PANSS			
Total	90.74 ± 25.07	64.05 ± 24.43***	
Positive	24.76 ± 6.71	15.95 ± 7.29***	
Negative	21.55 ± 9.19	17.72 ± 8.04**	
General	43.95 ± 14.11	30.38 ± 11.98***	
Cognition	9.33 ± 4.09	6.26 ± 3.56***	

In the first patients' column, significance of demographic information difference between patients and healthy controls were indicated; in the second patients' column, significance of changes in clinical scores between baseline and after treatment were indicated.
Abbreviations: PANSS, Positive and Negative Syndrome Scale.
*** $p < 0.001$.
** $p < 0.01$.

After risperidone treatment, 26 patients finished the second scan. There were no significant differences in age ($t_{(40)} = 0.95$, $p > 0.05$), gender ($\chi^2_{(40)} = 0.61$, $p > 0.05$), education ($t_{(40)} = -0.24$, $p > 0.05$), baseline PANSS total scores ($t_{(40)} = -1.01, p > 0.05$) and subscale scores (all $p > 0.05$) between patients who participated in the second scan and those who were lost to the second scan. Results showed that after risperidone treatment, patients exhibited a decrease in the right supramarginal gyrus ($t_{(25)} = -2.11, p < 0.05$) and the left nucleus accumbens volume ($t_{(25)} = -2.38$, $p < 0.05$), while the left middle temporal lobe ($t_{(25)} = 2.03$, $p < 0.05$) and the left pallidum volume ($t_{(25)} = 2.71$, $p = 0.01$) increased (Fig. 3, Table S1). After FDR, there were no significant volume alterations after 12 weeks of treatment ($p > 0.05$).

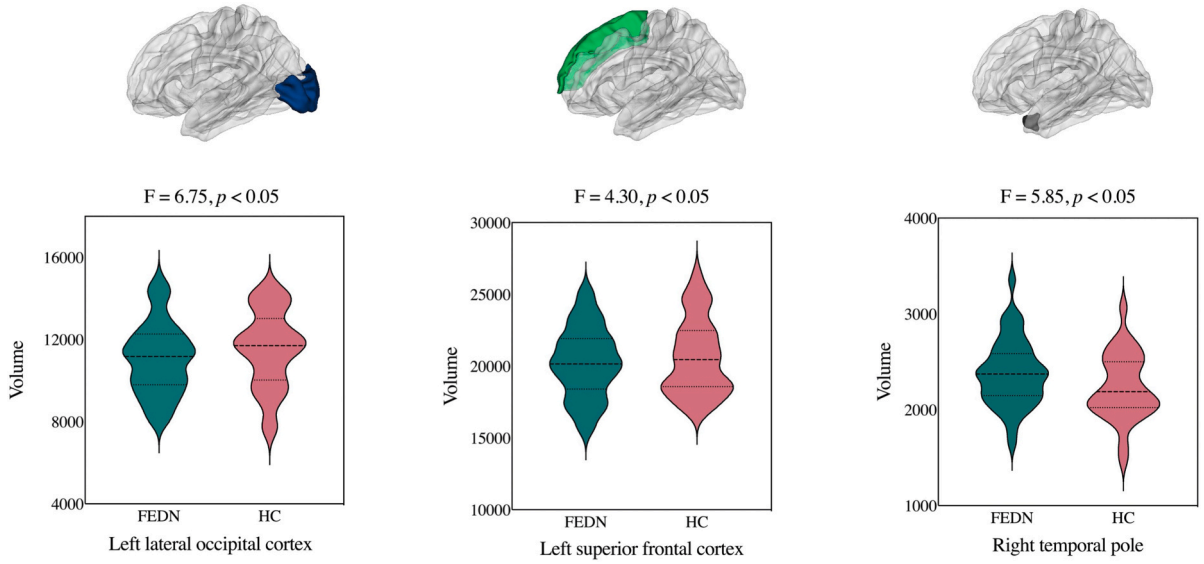

Fig. 2. Baseline volume differences in FEDN schizophrenia patients and healthy controls (HC). Compared with HC, patients showed decreased volume in the left lateral occipital cortex, left superior frontal cortex, and increased volume in the right temporal pole.

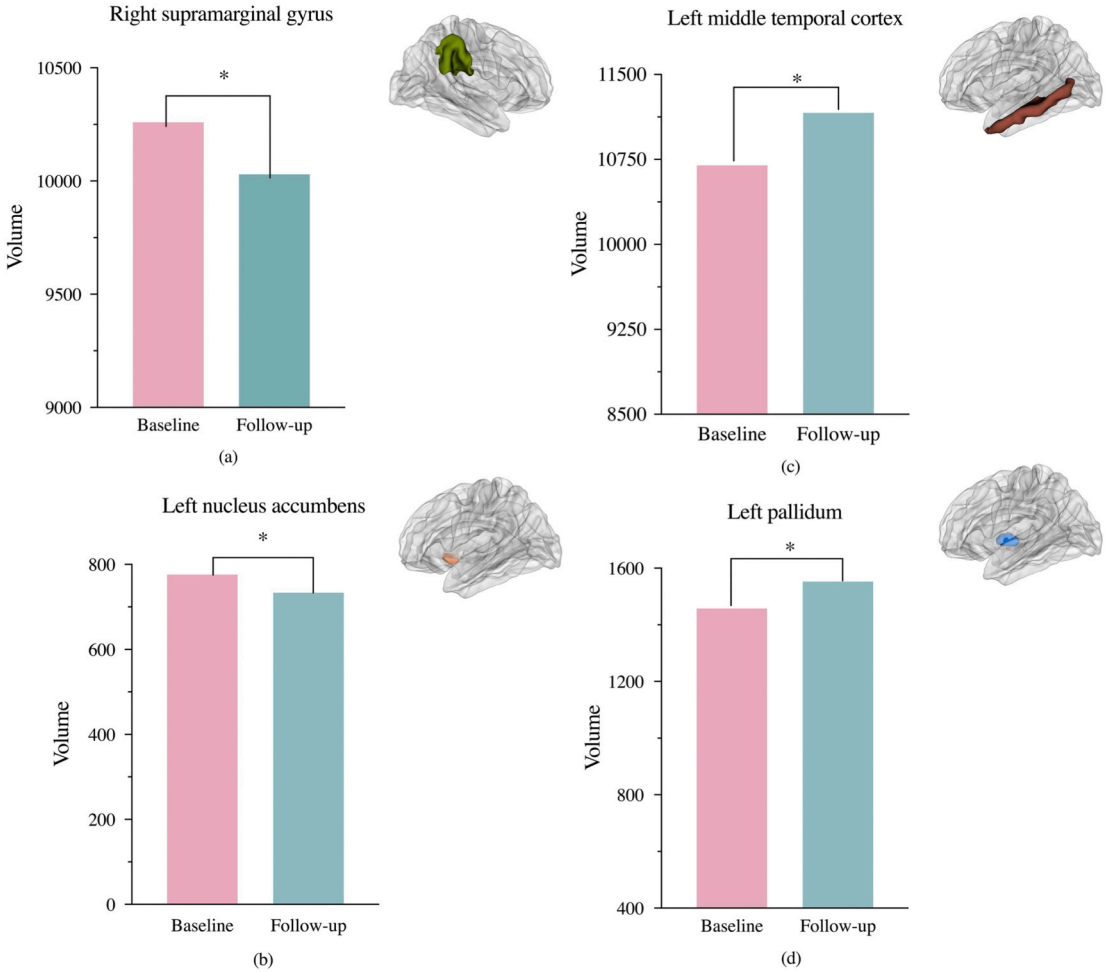

Fig. 3. Volume alterations after 12-week risperidone treatment. After treatment, volume in right supramarginal gyrus and left nucleus accumbens decreased, while volume in left middle temporal cortex and left pallidum increased.

3.3. Relationship between volume changes and changes in clinical symptoms

Partial correlation showed that volume changes in the left nucleus accumbens were positively correlated with cognitive factor changes ($r_{(26)} = 0.45$, $p < 0.05$) after controlling for sex, age, education, intracranial volume, and baseline PANSS total score. Volume changes in the left middle temporal lobe were negatively correlated with the changes in the subscale of general psychopathology ($r_{(26)} = -0.44$, $p < 0.05$). Volume changes in the right supramarginal gyrus were negatively correlated with the changes in positive ($r_{(26)} = -0.56$, $p < 0.01$), negative ($r_{(26)} = -0.54$, $p < 0.01$) and cognitive subscales ($r_{(26)} = -0.74$, $p < 0.001$) (Table S2).

3.4. Baseline volume as a predictor of clinical symptom improvement

General linear regression analysis showed that baseline volume of the left nucleus accumbens negatively predicted improvement in cognitive subscale score ($F_{(1, 37)} = 2.59$, $p < 0.05$), accounting for 35 % of the variance (Fig. 4). Greater volume of the left nucleus accumbens predicted better improvement in positive symptoms and cognitive function.

We used the criteria of a 50 % or more improvement in cognition score to define "responders" ($n = 22$) or "non-responders" ($n = 16$). After controlling for the confounding factors, one-way analysis of covariance analysis showed that responders had a greater volume of the baseline left nucleus accumbens than non-responders ($F_{(1, 37)} = 5.27$, df = $p <$ 0.05). Also, correlations showed that at baseline, left nucleus accumbens volume was positively correlated with cognitive function ($r_{(42)} = 0.43$, $p < 0.05$), while there were no significant correlations after 12-week treatment ($p > 0.05$).

4. Discussion

To our knowledge, this was the first whole-brain structure-based study to simultaneously explore the role of both pretreatment and posttreatment regional brain in psychiatric symptoms improvement during antipsychotic treatment in a unique cohort of FEDN schizophrenia patients. Consistent with our hypothesis, we observed that the volume of the striatum before and after the treatment played a predictive role in clinical symptoms. Specifically, the volume of the left nucleus accumbens at baseline was positively correlated with cognitive function, also it significantly predicted 38 % of cognitive symptom improvement. Second, patients with FEDN treated with 12 weeks of risperidone had reduced volume of the left nucleus accumbens, which is associated with cognitive improvement. These consistent findings in the left nucleus accumbens provide new evidence of the dissociated effects of antipsychotic medications on altering the subregions of the striatum in schizophrenia patients.

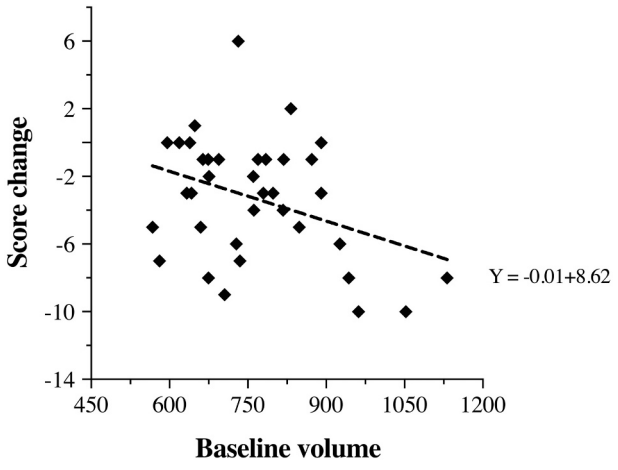

Fig. 4. Relationships between baseline left accumbens volume and cognitive change. The Y axis represents change in cognitive scores (after treatment minus baseline). The patients with larger left nucleus accumbens volume responded better to risperidone treatment.

The most intriguing finding was the consistent result in the left nucleus accumbens before and after treatment. After 12 weeks of risperidone treatment, we observed that in FEDN schizophrenia patients, a reduction in the volume of the nucleus accumbens was associated with improved cognitive performance, which was consistent with previous studies (Carriere et al., 2014; Eslinger et al., 2012; Roth et al., 2016). These results suggest the mechanism by which risperidone may have a beneficial effect on cognition through the nucleus accumbens. The increase in the volume of the nucleus accumbens reflects the reduction in cell death that naturally occurs following disruption of limbic and prefrontal cortical-striatal-pallidal thalamic circuits (Lauer et al., 2001), it is reasonable to suggest that the more the volume of the nucleus accumbens is reduced, the better the cognitive function.

We also found that FEDN patients with larger baseline nucleus accumbens volume responded better to risperidone treatment, suggesting that the more severely impaired baseline nucleus accumbens volume is, the better the response to risperidone treatment. Previous studies indicated that in unmedicated schizophrenia patients, greater baseline activation in the striatum and midbrain predicted subsequent better risperidone treatment response (Cadena et al., 2018). Also, Fei et al. proposed that the main mechanisms of antipsychotic medication could be executed through the orbitofrontal-striate-parietal loop. As a central part of this loop, the nucleus accumbens may be a promising predictor of response to risperidone treatment (Fei et al., 2016). Notably, previous studies have addressed the importance of striatal abnormalities in the pathophysiology of psychotic patients and the role of the striatum as the primary target of all effective antipsychotic drugs (Sarpal et al., 2015). However, the striatum consists of a group of contiguous subcortical structures, including the caudate, putamen, and nucleus accumbens. The anatomy of each structure independently serves a wide range of anatomical and functional connections to cortical structures and other subcortical regions (Alexander et al., 1986; Carlsson, 1999; Haber and Knutson, 2009). The findings in this result consistently show the importance of the nucleus accumbens at baseline and after treatment, which extends current knowledge about the regulatory effects of pharmacological interventions on the striatum to more specific subregions of the brain.

Regarding the volume changes induced by risperidone treatment, molecular mechanisms based on pathophysiology, i.e. the role of neurotransmitter systems associated with schizophrenia, should be fully considered. Most studies have shown that current antipsychotic drugs act mainly by blocking dopamine receptors within the therapeutic window (Kaar et al., 2020). Increased dopamine synthesis and release capacity in the dorsal striatal region underscores the positive symptom of psychosis and suggests that reduced dopamine release in cortical regions contributes to cognitive and negative symptom (Miyamoto et al., 2005; Kaar et al., 2020). Intriguingly, although most studies have focused on cortical dopamine and cognition, recent clinical evidence suggests that alterations in dopaminergic function in schizophrenia are primarily driven by changes in the associative striatum (Conn et al., 2020). Subcortical areas also have a major role in complex cognitive preprocessing (Moore et al., 2013). Thus, we observed an important contribution of baseline volume of the accumbens to cognitive improvement after 12 weeks of risperidone treatment.

Despite the potential significance of this study, its main limitations should be acknowledged. First, although the sample size of FEDN schizophrenia patients in this study was relatively adequate, the results were not significant at the time of completion of the FDR, requiring a larger sample size. In addition, caution should be needed in interpreting these results as subjects in this study were lost in the second MRI scans.

Second, the present study failed to collect the duration of the illness and maintenance dosage of risperidone, which may influence the predicting role of baseline structural features on cognitive improvements. Caution should be needed in interpreting these results. Third, results showed consistent relationships between left nucleus accumbens and cognitive factors of PANSS. Future studies should use more specific cognitive measures, such as the Montreal Cognitive Assessment, and the Brief Assessment of Cognition in Schizophrenia, in schizophrenia to further verify these relationships. Fourth, due to the heterogeneous combination of symptoms and the complexity of pathophysiology in schizophrenia, the actual drug mechanisms and individual differences in clinical practice remain unclear. For example, the effects of antipsychotic drugs on psychotic symptoms vary with sex, and baseline depressive symptoms (Shen et al., 2023; Haack et al., 2009). Future research should consider the influence of patients' baseline characteristics and individual differences on the treatment outcomes.

5. Conclusion

In summary, the present study investigated for the first time the changes in whole brain-based anatomy induced by short-term antipsychotic treatment in patients with FEDN schizophrenia, suggesting that baseline structural features can significantly influence the efficacy of antipsychotic treatment. Consistent findings of nucleus accumbens volume at baseline and after treatment suggest that this subregion, as part of the striatum, is important in predicting the efficacy of antipsychotic treatment in cognitive function. Taken together, this study will undoubtedly contribute to a better understanding of the mechanisms underlying the effects of antipsychotic drugs on the striatum.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of Beijing Huilongguan Hospital and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to the study.

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CRediT authorship contribution statement

Gao-Xia Wei: Writing – review & editing, Writing – original draft, Funding acquisition, Data curation. **Haoran Shen:** Writing – original draft, Visualization, Formal analysis. **Li-Kun Ge:** Methodology, Formal analysis. **Bo Cao:** Visualization, Methodology, Data curation. **Roja Manohar:** Writing – review & editing. **Xiangyang Zhang:** Writing – review & editing, Resources, Project administration, Conceptualization.

Declaration of competing interest

All authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scog.2024.100308.

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