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Gray matter volume changes following antipsychotic therapy in first-episode schizophrenia patients: A longitudinal voxel-based morphometric study

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A R T I C L E I N F O

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A B S T R A C T

Despite evidence of structural brain abnormalities in schizophrenia, the current study aimed to explore the effects of antipsychotic treatment on gray matter (GM) volume using structural magnetic resonance imaging (MRI) and investigate the relationship between brain structure and treatment response. The GM volumes of 33 patients with first-episode schizophrenia were calculated with voxel-based morphometry (VBM), with 33 matched healthy controls. Longitudinal volume changes within subjects after 4-month antipsychotic treatment were also evaluated. Correlation between volumetric changes and clinical symptoms derived from the Positive and Negative Syndrome Scale (PANSS) were further investigated. Compared with healthy controls, decreased GM volumes in the frontal gyrus were observed in schizophrenia patients. After 4-month treatment, patients showed significantly decreased GM volume primarily in the bilateral frontal, temporal and left parietal brain regions. In addition, the GM volume changes of the left postcentral gyrus was positively correlated with negative symptoms improvement, and the correlation analysis revealed the total PANSS scores changes were associated with GM volume changes in the right inferior frontal gyrus and the right superior temporal gyrus. Besides, non-responders had reduced GM volume in the bilateral middle frontal gyrus and the right superior frontal gyrus compared with responders and healthy controls. Our results suggest that the abnormality in the right frontal gyrus exists in the early stage of schizophrenia. Moreover, the relationship between antipsychotics and structural changes was identified. The GM volume might have the potential to reflect the symptom improvement in schizophrenia patients. And MRI may assist in predicting the antipsychotic treatment response in first-episode schizophrenia patients.

1. Introduction

Schizophrenia is a complex psychotic disorder characterized by abnormal behavior, confused thinking and auditory verbal hallucination. The presence of gray matter (GM) volume abnormalities in schizophrenia patients, primarily the reductions in the frontal and temporal cortex, insula, etc, have been reported in numerous imaging studies (Honea et al., 2005; Shepherd et al., 2012; Wright et al., 2000). However, some studies reported increased GM volume or no structural differences in schizophrenic patients (Bruder et al., 1999; Knochel et al., 2016). Therefore, studying first-episode patient is helpful for understanding the pathophysiology of schizophrenia, especially in the early stage of the disease.

Progressive reductions in brain volume have been reported in long-term studies after onset of first psychotic symptoms (Haijma et al., 2013; Olabi et al., 2011). It was assumed that besides the disease progression, antipsychotic treatment could at least in part be related to the GM loss (Emsley et al., 2017; Fusar-Poli et al., 2013). Thus longitudinal design study is crucial to evaluate the treatment effect for schizophrenia patients. A few studies investigating structural brain abnormalities in first-episode schizophrenia patients have reported inconsistent results. For example, Yue et al. reported increased GM volume in the bilateral

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prefrontal cortex, insula, thalamus and left superior occipital cortex (Yue et al., 2016). A meta-analysis reported a reduction of GM volume after antipsychotic treatments (Fusar-Poli et al., 2013). Moreover, previous studies have mostly focused on the long-term progression in GM changes at least for years (Emsley et al., 2017; Ho et al., 2011; Veijola et al., 2014). Short term study is still lacking for understanding whether the progressive changes in GM was related to antipsychotic treatment.

The controversial results from those longitudinal studies might be explained as follows: First, typical and atypical antipsychotics could lead to different pharmacological actions and thus induce brain structures changes differently (Dazzan et al., 2005; Yue et al., 2016). Second, the dose of antipsychotics, the observation intervals and symptom severity could all affect the nature of the pathophysiologic process of schizophrenia thus make the progressive brain changes a matter of speculation (Haijma et al., 2013; Ho et al., 2011; Vita et al., 2015; Zhang et al., 2018). Moreover, how the patients react to the antipsychotics is also worth discussing. Therefore, considering the above mentioned factors, especially the patients' responses to antipsychotics, could help us better identify the important brain structures during the treatment.

To enhance our understanding of structural brain alterations in patients with schizophrenia, the current study was to investigate the effects of illness and antipsychotic treatment on morphologic changes in first-episode schizophrenia patients using whole-brain voxel-based morphometry (VBM). We first investigated whole brain structural changes by comparing first-episode schizophrenia with healthy controls. The influence of atypical antipsychotics on changes in GM volume after 16 weeks of atypical antipsychotic treatment were further examined. Finally, we hypothesized that VBM factors could predict treatment response. We aimed to ascertain which structural brain changes would reflect the clinical moderators including antipsychotics responses and illness severity.

2. Material and methods

2.1. Subjects

Thirty-three subjects diagnosed with first-episode schizophrenia were recruited from the Department of Psychiatry for the present study. All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and were at the first-episode of schizophrenia with exposure to antipsychotic treatment within 2 weeks. All patients had received a Positive and Negative Syndrome Scale (PANSS) total score to evaluate psychopathological symptoms at baseline and 4-month follow-up by two senior clinical psychiatrists from the Department of Psychiatry. Individuals with any history of the following were excluded: (1) serious somatic disorders; (2) central nervous system diseases; (3) alcohol or substance abuse; (4) extreme agitation; or (5) a restricted MRI examination. 33 healthy controls were also recruited and entered into the healthy group. None has any lifetime history of neurological or medical illness, head injury or substance abuse. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the local Research Ethics Committee. Written informed consent was obtained from all subjects/patients.

2.2. Antipsychotic and response criteria

All patients received a follow-up examination and brain scan after 16 weeks of treatment. The patients were treated with atypical antipsychotic at an average of 12.80 mg/day of olanzapine equivalents (Leucht et al., 2014). During the follow-up, all patients received second generation antipsychotic drugs, including risperidone, olanzapine, paliperidone, amisulpride and aripiprazole. For the present study, treatment response was operationally defined using criteria described previously (Andreasen et al., 2005). In brief, specific items from PANSS were chosen including the positive symptoms of delusions (P1), conceptual disorganization (P2) and hallucinatory behavior (P3), the negative symptoms of blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6), the general psychopathology of mannerisms/posturing (G5) and unusual thought content (G9). And any of the above mentioned item with a score > 3 was considered as non-response. Based on the response criteria, 22 patients were classified as responders and 11 patients were classified as non-responders.

2.3. Image acquisition

Brain imaging data were acquired with a 3.0-Teslaa GE MRI scanner equipped with an eight-channel receiver head coil. Contiguous axial images using a 3D Bravo T1-weighted sequence across the entire brain were acquired with the following parameters: repetition time = 8.2 ms, echo time = 3.2 ms, flip angle = 12°, matrix size = 256 × 256, slice thickness = 1 mm, field of view = 256 × 256 mm^2, and voxel size = 1 × 1 × 1 mm^3.

2.4. Image processing and analysis

All of the T1-weighed MRI images were processed using the voxel-based morphometry (VBM) toolbox in the FMRIB Software Library (FSL), as one reliable measurement for evaluating GM volume (Schnack et al., 2010; Xing and Zuo, 2018). In Detail, structural data was processed with FSL 5.0.10 software. First, brain extracting tool (BET) was employed to cut the skull from all T1 MRI structural images (Smith, 2010); Next, FSL Automated Segmentation Tool (FAST) was adopted to carry out tissue-type segmentation (Zhang et al., 2001); the segmented GM parietal volume images were then aligned to the MNI standard space (MNI152) by applying linear image registration tool FLIRT and nonlinear registration FNIRT methods. A study-specific template was created by averaging the registered images, to which the native GM images were then non-linearly re-registered. The registered GM parietal volume images were modulated for the contraction/enlargement due to the nonlinear component of the transformation by dividing them by the Jacobian of the warp field. Finally, the segmented and modulated images were then smoothed with isotropic Gaussian kernels with a standard deviation (sigma = 3 mm).

2.5. Statistical analysis

Student's t-test and chi-square test were utilized to examine group differences in demographic characteristics and clinical data at baseline between patients and healthy controls with SPSS (IBM SPSS Statistics for Windows, version 17.0, IBM Corp.). For detection of between-group differences in GM volume, a paired *t*-test (baseline vs follow-up) or two-sample *t*-test (healthy controls vs patients from baseline; healthy controls vs patients at follow-up) was used to identify regional GM changes. General linear model (GLM) was employed to assess regional changes in GM volume using permutation-based non-parametric testing with 5000 random permutations (Zhu et al., 2017). The threshold for significance was $P < 0.05$, using threshold-free cluster enhancement (TFCE) method with family wise-error (FWE) correction for multiple comparisons (Smith and Nichols, 2008).

Values of GM volumes of the brain regions showing abnormal morphological differences were extracted and Pearson correlation coefficients were used to examine the associations between the changes in regional GM volume and changes of PANSS scores using SPSS. Correction for multiple comparisons was accomplished using the false discovery rate (FDR) method, with the "mafdr" script implemented in MATLAB. The change in PANSS from baseline to follow-up was

Table 1
Demographic characteristics and clinical measures of schizophrenia patients and healthy controls.

(a)	Patients (n = 33)	Controls (n = 33)	*p*-value
Demographic characteristics			
Age (years)	15-59 (24.3 ± 8.8)	16-58 (23.8 ± 8.4)	0.82
Sex (male/female)	16/17	16/17	1
Education (years)	4-19 (12.0 ± 3.0)	7-20 (13.7 ± 3.2)	0.01*
Clinical characteristics			
Family history (Y/N)	4/29	–	–
Follow-up interval (m)	2-12 (4.6 ± 1.9)	–	–
Olanzapine equivalence (mg/d)	2–33.25 (12.80 ± 7.20)		
PANSS baseline(n = 33)			
Positive Score	7-34 (22.4 ± 5.1)	–	–
Negative Score	7-33 (20.8 ± 6.6)	–	–
General Score	30-64 (44.5 ± 8.9)	–	–
Total Score	63-126 (88.1 ± 14.1)	–	–
PANSS 4-month *(n = 33)*			
Positive Score	7-21 (10.2 ± 3.6)	–	–
Negative Score	7-28 (14.4 ± 5.1)	–	–
General Score	18-46 (26.8 ± 6.5)	–	–
Total Score	33-92 (53.0 ± 13.1)	–	–

(b)	Responders (n = 22)	Non-responders (n = 11)	*p*-value
Demographic characteristics			
Age (years)	16-40 (23.1 ± 6.5)	15-59 (26.8 ± 12.2)	0.12
Sex (male/female)	8/14	8/3	0.07
Education (years)	4-19 (11.9 ± 3.2)	7-20 (13.7 ± 3.2)	0.96
Clinical characteristics			
Family history (Y/N)	3/19	1/10	–
Follow-up interval (m)	2-12 (4.9 ± 2.1)	2–6.5 (4.2 ± 1.6)	0.92
Olanzapine equivalence (mg/d)	5–29.88 (12.29 ± 6.72)	2–33.25 (13.84 ± 8.31)	0.95
PANSS baseline (n = 33)			
Positive Score	17-31 (23.5 ± 3.3)	7-34 (20.3 ± 7.2)	0.03*
Negative Score	7-29 (20.3 ± 6.4)	7-33 (21.7 ± 7.1)	0.76
General Score	35-64 (45.2 ± 8.8)	30-63 (43.2 ± 9.5)	0.94
Total Score	63-111 (89.0 ± 14.0)	72-126 (86.3 ± 15.0)	0.73
PANSS 4-month *(n = 33)*			
Positive Score	7-12 (8.7 ± 1.7)	7-21 (13.1 ± 4.7)	< 0.01*
Negative Score	7-21 (12.1 ± 3.4)	12-28 (19.0 ± 4.9)	0.12
General Score	18-31 (23.4 ± 3.5)	25-46 (33.4 ± 6.1)	0.06
Total Score	33-60 (46.3 ± 7.4)	48-92 (66.5 ± 11.6)	0.32

Data were presented as mean ± SD. Abbreviation: SD, Standard deviation; PANSS, Positive and negative syndrome scale; **P*: T-test with $P < 0.05$.

examined using paired *t*-test.

To compare the responders with non-responders, the demographic characteristics were compared using student's t-test and chi-square test. The comparisons of GM volume among healthy controls, responders and non-responders from baseline were conducted using one-way analysis of variance (ANOVA). The threshold for significance was $P < 0.05$, using TFCE method with FWE correction for multiple comparisons. Post hoc unpaired *t*-tests were computed between the groups where appropriate.

3. Results

3.1. Demographic characteristics and clinical information

The demographic characteristics and clinical information of the participants are shown in Table 1a. There were no significant differences between patients and healthy subjects in age ($t = 0.23$, $P = 0.82$) or sex ($\chi^2 = 33.00$, $P = 1.00$), between patients and controls. Fewer education years ($t = -2.80$, $P = 0.01$) in schizophrenia patients were observed compared to controls.

3.2. Baseline analysis

Compared to the healthy controls, patients before 16-week treatment showed significantly reduced GM volume in the right middle frontal gyrus, right medial frontal gyrus and bilateral superior frontal gyrus (Fig. 1, Table 2, TFCE corrected, $P < 0.05$).

3.3. Longitudinal analysis

After 16 weeks of treatment, pronounced GM decreasing were noted mainly in the left precentral gyrus, left middle frontal gyrus, bilateral inferior frontal gyrus, left insula, left postcentral gyrus and left temporal gyrus (Fig. 1, Table 2, TFCE corrected, $P < 0.05$). Significant decreases in the total scores of the PANSS and its subscores were also observed in the treated patient group (Supplementary Table 2).

In addition, a positive correlation was observed between the GM volume changes of the left postcentral gyrus with the reduction of PANSS negative symptoms scales, and the GM volume changes of the right inferior frontal gyrus and the right superior temporal gyrus were positively correlated with the clinical improvement, reflecting with the change of total PANSS scores, respectively (Fig. 2).

3.4. Antipsychotics response

There were no significant differences in distributions of age, sex, education, follow-up interval and olanzapine equivalence between responders and non-responders (Table 1b).

Both responders and non-responders had relatively decreased GM volumes compared with healthy controls (TFCE corrected, $P < 0.05$, $F = 11.2$). Non-responders had decreased GM volumes in the bilateral middle frontal gyrus and the right superior frontal gyrus compared with responders and healthy controls (Fig. 3). However, no significant group difference was found with post-hoc *t*-test between responders and non-responders ($P = 0.15$).

4. Discussion

Our study first indicates that, compared with healthy controls, first-episode schizophrenia patients showed reduced GM volume in the right middle frontal gyrus, right medial frontal gyrus and bilateral superior frontal gyrus at baseline. We then examined the effect of antipsychotics on brain structures after 16 weeks of treatment in patients with schizophrenia. Specifically, the cortical volume changes in the left postcentral gyrus, the right inferior frontal and superior temporal gyrus was positively associated with the negative symptoms and total PANSS scores, respectively. Moreover, MR imaging measures showed GM volume differences among responders, non-responders and healthy controls in the bilateral middle frontal gyrus and the right superior frontal gyrus. Few investigations to our knowledge have performed such a comprehensive study using first-episode patients to investigate disease-related changes in brain structure and then further performed a longitudinal study to examine the effects of atypical antipsychotics (Yue et al., 2016). This longitudinal study might hopefully be helpful in identifying small structural changes in schizophrenia patients receiving antipsychotic treatment in the early stage of disease.

The presence of structural brain abnormalities has been established before in chronic (Rimol et al., 2010; van Haren et al., 2011) and first-episode schizophrenia (Crespo-Facorro et al., 2011; Narr et al., 2005; Schultz et al., 2010). Temporal and frontal lobes have been reported as common locations of pathological brain aberrations affected by

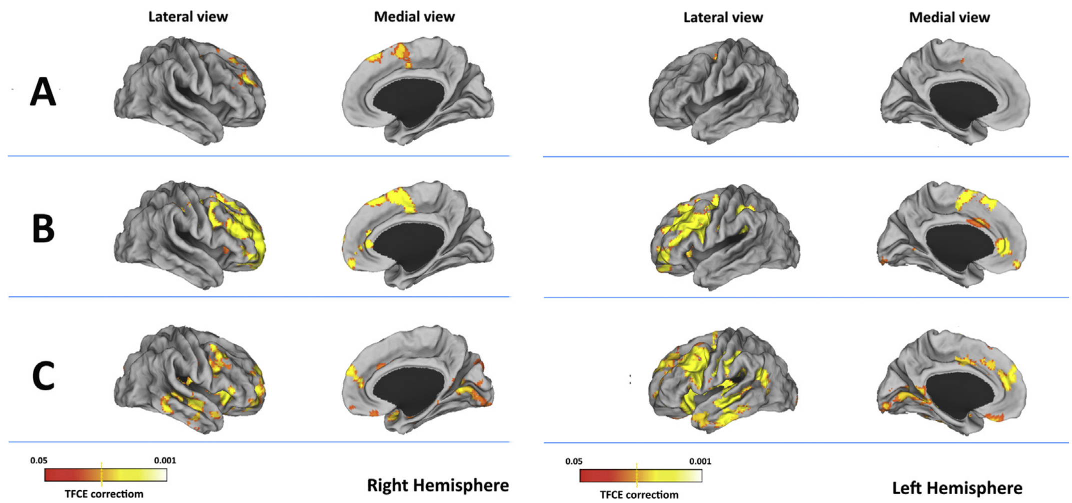

Fig. 1. Differential changes in gray matter volume in first-episode schizophrenia patients (n = 33) and controls (n = 33). (A) Regions of decreased gray matter volume at baseline in first-episode schizophrenia patients compared to healthy controls using Student's t-test. (B) Regions of decreased gray matter volume in schizophrenia patients after 4-month antipsychotic treatment compared to healthy controls using Student's t-test. (C) Regions of decreased gray matter volume from baseline to follow-up in patients with schizophrenia using paired *t*-test.

Table 2
Results from whole-brain analysis of covariance on voxel-based morphometry volume.

Anatomical region	Voxels	Coordinate (MNI)			P value
		x	*y*	*z*	
HC vs. SZ Baseline					
Right Middle Frontal gyrus	522	28	46	26	0.0064
Right Medial Frontal gyrus	236	8	30	59	0.0092
Left Superior Frontal gyrus	139	−25	−9	51	0.0064
Right Superior Frontal gyrus	457	24	−5	54	0.006
SZ baseline vs. SZ follow-up					
Left Precentral gyrus	1033	−47	−11	30	0.0004
Left Superior Frontal gyrus	123	−29	25	33	0.0008
Right Superior Frontal gyrus	196	15	58	15	0.0056
Left Middle Frontal gyrus	1087	−40	16	35	0.0004
Right Middle Frontal gyrus	143	25	48	−13	0.0066
Left Inferior Frontal gyrus	1576	−40	9	9	0.0002
Right Inferior Frontal gyrus	535	39	17	5	0.0016
Left Rolandic operculum	615	−52	0	7	0.0006
Right Rolandic operculum	107	43	10	13	0.0048
Right Medial Frontal gyrus	151	12	56	15	0.005
Left Insula	927	−39	10	2	0.0002
Right Insula	372	38	4	6	0.0014
Left Postcentral gyrus	1001	−47	−12	30	0.0004
Left Inferior Parietal gyrus	456	−46	−28	36	0.0004
Left SupraMarginal	348	−51	−28	30	0.0004
Left Putamen	463	−29	14	3	0.0004
Right Putamen	351	29	4	14	0.0012
Left Superior Temporal gyrus	544	−44	−11	−13	0.0004
Left Middle Temporal gyrus	1106	−56	−22	−10	0.0002
Right Middle Temporal gyrus	114	49	−40	−14	0.0062
Left Inferior Temporal gyrus	632	−59	−26	−21	0.001
Right Inferior Temporal gyrus	100	53	−42	−17	0.0056

Abbreviation: HC: Healthy controls; SZ: Schizophrenia; MNI: Montreal Neurological Institute.

schizophrenia (Shenton et al., 2001, 2010). Reduced volume of superior temporal gyrus, thalamus and cerebellum deficits in first-episode schizophrenia patients were also observed (Gur et al., 1998; Ichimiya et al., 2001; Keshavan et al., 1998; Narayanaswamy et al., 2015). We observed no increased but only decreased GM volume mainly in the frontal gyrus in first-episode schizophrenia patients which were partially consistent with previous studies (Zhang et al., 2001; Zhu et al., 2017). However, we did not observe the temporal gyrus GM changes between schizophrenia patients and healthy controls at baseline. The possible reason may be the auditory function of the patients recruited in the current study, as the temporal gyrus was proved to be involved in auditory processing (Narayanaswamy et al., 2015). Moreover, several meta-analysis have shown that the abnormalities in schizophrenia are progressive (Andrade, 2016; Olabi et al., 2011). Thus the duration of the disease may also affect our current results.

Accumulating evidence has indicated that antipsychotic medication could also modulate brain morphology. The neuroanatomical alterations in schizophrenia may be associated with antipsychotic treatment besides the disease itself (Fusar-Poli et al., 2013). We observed excessive reductions in cortical GM volume in first-episode schizophrenia patients after 4 months of antipsychotic treatment. Our results were inconsistent with some of the previous study. Dazzan et al. demonstrated that reduced cortical volume was associated with typical antipsychotics, while enlargement of the thalami was associated with atypical antipsychotics (Dazzan et al., 2005). Deng et al. investigated the effects of antipsychotics on brain structures in drug-naïve patients with schizophrenia and observed increased GM volume in the thalamus, frontal cortex, occipital cortex (Deng et al., 2009). Gur et al. reported higher volumes in the putamen of schizophrenia patients than the healthy subjects (Gur et al., 1998). It was also indicated increased cortical thickness in the prefrontal cortex over 8 weeks of atypical antipsychotic treatment in first-episode schizophrenia (Goghari et al., 2013) and an enlarged prefrontal volume after 4 weeks of antipsychotic treatment for schizophrenia (Garver et al., 2005). Conversely, our study was consistent with some other studies showing cortical volume increasing in first-episode schizophrenia after receiving antipsychotics (Fusar-Poli et al., 2013; Ho et al., 2011; Lesh et al., 2015). We considered the possible inconsistence might partially be related to the type and term of the antipsychotics. Firstly, typical and atypical antipsychotics might affect brain structures differently due to their different pharmacological actions (Gur et al., 1998). Therefore, studies of schizophrenia patients treated with only one type of antipsychotic could eliminate the confounding effects of mixed antipsychotics, and thus, identifying the brain structures related to the corresponding antipsychotic treatment. Secondly, the term of treatment could affect the result as well. Different study included the observation time from 3 weeks to years (Deng et al., 2009; Ho et al., 2011). Our study only focused on the effect of short-term treatment with atypical antipsychotics. Additional data regarding the longer-term effects of antipsychotics on brain structure is further needed.

To explain the mechanisms for antipsychotic treatment effects on

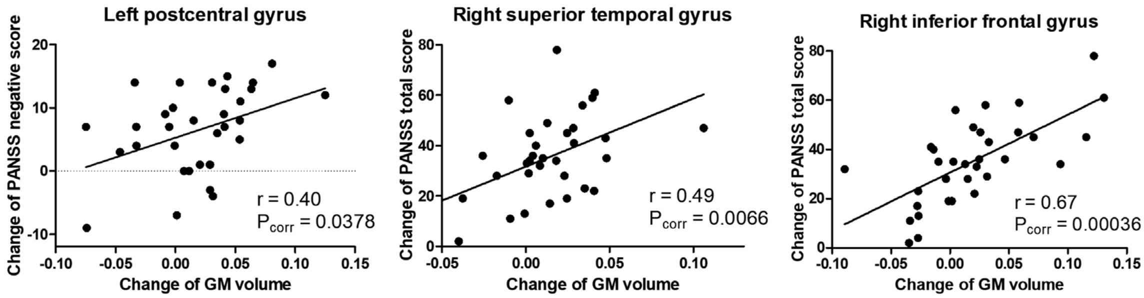

Fig. 2. Gray matter volume abnormalities and its correlation with clinical symptom changes in patients with schizophrenia. The gray matter volume changes of the left postcentral gyrus was positively correlated with the changes of PANSS negative symptoms (A), and the gray matter volume changes of the right superior temporal gyrus (B) and the right inferior frontal gyrus (C) were positively correlated with the changes of the total PANSS scores, respectively. The gray matter volume changes present the Pre minus the Post. P_{corr}: false discovery rate (FDR) corrected P values.

brain structure, macaque monkeys and rodents' exposure to antipsychotics has been linked to GM loss (Dorph-Petersen et al., 2005; Vernon et al., 2012). The GM changes could be explained by fewer glial cells and higher densities of neurons (Konopaske et al., 2007). The mechanism for antipsychotic treatment on structural changes was also explained with neuroinflammatory models. As evidence implicates increased extracellular volume in GM in the feature of schizophrenia and anti-inflammatory effect of antipsychotic treatment (Andrade, 2016; Carter et al., 2014), decreases in extracellular volume and reduction of GM volume after antipsychotic treatment could address our findings. There were some patients had increased GM volume in the brain regions after treatment. We considered it to be individual difference and the heterogeneous features of every single SZ patient at baseline and during follow-up. More patients included in the future study might strengthen our indication.

Correlational analyses demonstrated some associations between the degree of GM reduction and clinical symptoms. We found association between cortical volume reduction in left postcentral gyrus and the improvement of negative PANSS. The postcentral gyrus contains the primary somatosensory cortex and is the main sensory receptive area for the sense of touch and kinesthesia (Asami et al., 2012). The structural abnormality in the postcentral gyrus was observed in schizophrenia patients in previous study (Ferro et al., 2015; Zhang et al., 2017). The GM reductions of right inferior frontal gyrus and right superior temporal gyrus were also positively correlated with the total PANSS scores. The frontal cortex, playing important roles in regulating, controlling and carrying out executive functions, has been observed with abnormal GM volume or thickness in many previous studies of schizophrenia (Ellison-Wright et al., 2008; Nakamura et al., 2007; Narr et al., 2005). Superior temporal gyrus is functionally substrated of auditory and language processing (Galaburda et al., 1978). Some studies have indicated that GM loss in temporal regions was related to positive symptoms and GM loss in the frontal regions was related to negative symptoms (Bachmann et al., 2004; Horacek et al., 2006). Therefore, the decreasing of GM volume in the frontal and temporal cortex that we found might represent a benefit from antipsychotic treatment. The

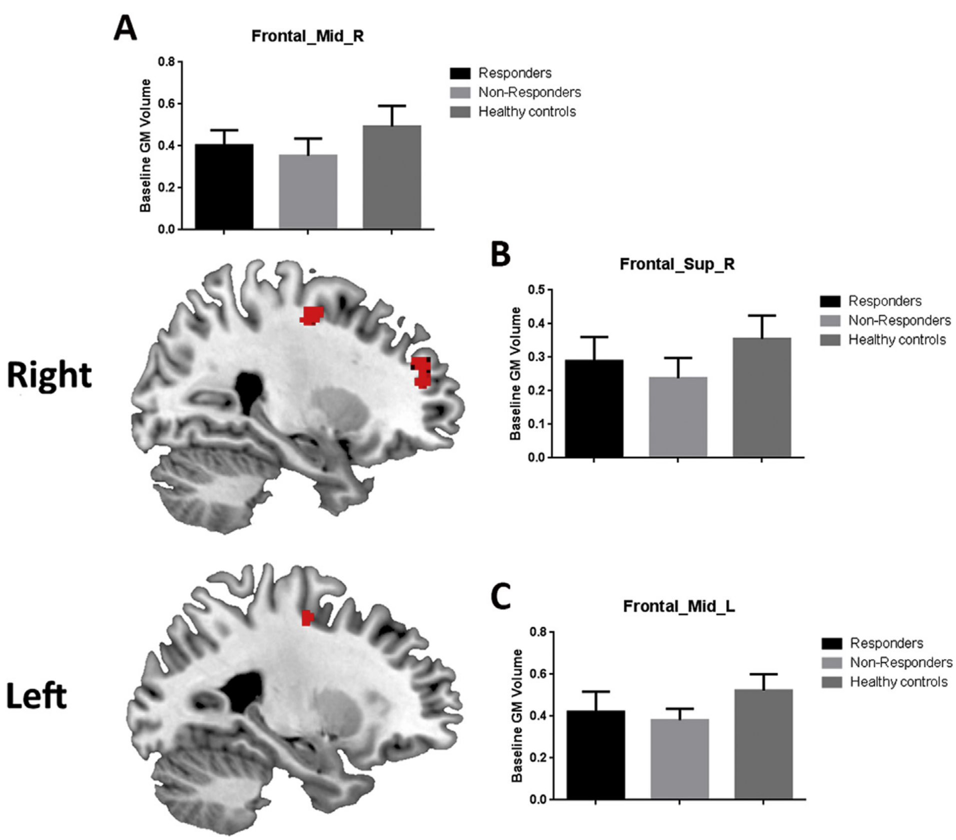

Fig. 3. Areas of significant gray matter differences across the three groups (healthy controls, responders and non-responder schizophrenia patients) with one-way ANOVA. Statistically significantly different areas of gray matter volumes among three groups were shown in red. Abbreviations: Frontal_Mid_R, right middle frontal gyrus; Frontal_Sup_R, right superior frontal gyrus; Frontal_Mid_L, left middle frontal gyrus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

association between brain volume reduction and symptom improvement was observed, indicating antipsychotic treatment may be related to the efficacy of medication. Using dosage as one potential mediator of the correlation analysis, we observed that the correlation still existed. There is certain support from previous published paper (Zhang et al., 2018), suggesting the anatomical changes are related to the PANSS improvement, while Veijola et al. declared the opposite (Veijola et al., 2014). Emsley et al. also suggested opposite results but pro to the idea that antipsychotics are effective in treating symptoms of psychosis in short term (Emsley et al., 2017). The dosage dependent effect would be further study with more patients included.

The relationship between the changes of cortical GM in schizophrenia and the response of patients to the pharmacological intervention is one important issue for clinical practice. It could be argued the patients' response as the indirect index of severity of patients' psychopathology, since a higher daily dose of antipsychotics is expected to be related to more severe illness. A dose-response effect could reflect volume reductions rather than a direct effect of treatment (Emsley et al., 2017). There could be considerable heterogeneity in how patients respond to antipsychotic treatment (Robinson et al., 2006), leading to previous debate and controversial results, even though we observed association between the improvement of the symptom and the changes of GM volume. Previous studies suggested that MRI morphometry could be used to prediction of treatment response (Garner et al., 2009; Seeley et al., 2002; Szeszko et al., 2012). But multiple factors that could affect the results have not been taken into consideration, including the prior exposure to antipsychotic medications, method limitations, lack of definition of response criteria (Szeszko et al., 2012). We proved that comparing healthy controls, responders and non-responders to atypical antipsychotics had reduced brain GM volume in the bilateral middle frontal gyrus and the right superior frontal gyrus. However, we failed to find statistically significant GM differences when compared between patients who responded to treatment and non-responders. Our result indicated the brain GM volume might be predictors of treatment response given that these measures may inform intervention to potentially alter the course of illness. The correlation of regional abnormalities and treatment resistance may need further exploration.

Our study has some limitations. Firstly, the sample size is still limited, especially considering the comparison between responders and non-responders, thus possibly, having contributed to no significantly statistical differences with post-hoc *t*-test. Moreover, the choice of medicine is clinical-led. A prospective, within-subject, counterbalanced drug/placebo design would be preferable to the naturalistic design of the present study, but such a study would not be feasible or ethically justified (Lesh et al., 2015). Thirdly, adipogenic effects of antipsychotics were not considered in the current study, as first-episode schizophrenia patients are particularly susceptible to the weight-gain effects of antipsychotics (Emsley et al., 2017).

5. Conclusion

Our study revealed that the frontal gyrus may represent the core region of pathological change in first-episode schizophrenia patients. The effects of atypical antipsychotics could involve multiple brain regions, and examination of GM volume abnormalities in the left postcentral gyrus, right inferior frontal gyrus and the right superior temporal gyrus may be particularly effective in evaluating the improvement of schizophrenia symptoms after exposure to atypical antipsychotics. Our study also suggested that MRI might be useful in identifying a subgroup of patients who response to antipsychotic medications early in the course of schizophrenia. The present study provides a new perspective for the debate of the effects of antipsychotics on cortical GM.

Conflicts of interest

All authors declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.009.

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