A Dissociation in Effects of Risperidone Monotherapy on Functional and Anatomical Connectivity Within the Default Mode Network

Xiaofen Zong1,3,11, Maolin Hu1,3,11, Spiro P. Pantazatos3,4, J. John Mann3,4, Gaohua Wang1, Yanhui Liao1, Zhong-Chun Liu2, Wei Liao5, Tao Yao6, Zongchang Li1, Ying He1, Luxian Lv7, Deen Sang7, Jinsong Tang1,3,9,10,12, Huafu Chen5,12, Junjie Zheng5,12, and Xiaogang Chen*,1,8,9,10,12

1Department of Psychiatry, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China; 2Department of Psychiatry, Renmin Hospital of Wuhan University, Wuhan, Hubei, China; 3Division of Molecular Imaging and Neuropathology, Columbia University and New York State Psychiatric Institute, New York, NY; 4Department of Psychiatry, Columbia University, New York, NY; 5Key Laboratory for Neuroinformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, Sichuan, China; 6Department of Neurology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China; 7Department of Psychiatry, Henan Mental Hospital, The Second Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan, China; 8Mental Health Institute of Central South University, Changsha, Hunan, China; 9National Clinical Research Center on Mental Disorders (Xiangya), National Technology Institute on Mental Disorders, Changsha, Hunan, China; 10Hunan Key Laboratory of Psychiatry and Mental Health, Changsha, Hunan, China

11These authors contributed equally to this work.
12J.T., H.C., J.Z., and X.C. are co-corresponding authors who jointly directed this work.

*To whom correspondence should be addressed; Department of Psychiatry, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China; tel: +86-731-85531571, fax: +86-731-85531571, e-mail: chenxiaogang@csu.edu.cn

Respective changes in functional and anatomical connectivities of default mode network (DMN) after antipsychotic treatment have been reported. However, alterations in structure–function coupling after treatment remain unknown. We performed diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging in 42 drug-naïve first-episode schizophrenia patients (FESP) both at baseline and after 8-weeks risperidone monotherapy, and in 38 healthy volunteers. Independent component analysis was used to assess voxel-wise DMN synchrony. A 3-step procedure was used to trace fiber paths between DMN components. Structure–function couplings were assessed by Pearson’s correlations between mean fractional anisotropy and temporal correlation coefficients in major tracts of DMN. Pretreatment, FESP showed impaired functional connectivity in posterior cingulate cortex/precuneus (PCC/PCUN) and medial prefrontal cortex (mPFC), but no abnormalities in fibers connecting DMN components. After treatment, there were significant increases in functional connectivities of PCC/PCUN. Increases in functional connectivity between PCC/PCUN and mPFC correlated with improvement in positive symptoms. The structure–function coupling in tracts connecting PCC/PCUN and bilateral medial temporal lobes decreased after treatment. No alterations in DMN fiber integrity were detected. This combination of functional and anatomical findings in FESP contributes novel evidence related to neurobehavioral treatment effects. Increased functional connectivities between PCC/PCUN and mPFC may be treatment response biomarkers for positive symptoms. Increases in functional connectivities, no alterations in fiber integrity, combined with decreases in structural–functional coupling, suggest that DMN connectivities may be dissociated by modality after 8-week treatment. Major limitations of this study, however, include lack of repeat scans in healthy volunteers and control group of patients taking placebo or comparator antipsychotics.

Key words: default mode network/functional magnetic resonance imaging/diffusion tensor imaging/risperidone/schizophrenia

Introduction

Schizophrenia has been hypothesized to be associated with disrupted connectivities across multiple systems or regions of the brain, but not in the overall brain.1,2 Our previous studies, taking a whole-brain approach, identified abnormalities in functional activity and structural connectivity in striatal areas, prefrontal cortex, and limbic system components.3,4 Given that the default mode network (DMN)5 has become a focus of research into the pathophysiology of schizophrenia,6–9 this study focused on multimodal imaging outcomes (and their interrelationships) of the DMN specifically. The DMN is deactivated during task initiation and conversely is active...
during a resting state, displaying a high degree of connectivity across multiple regions including posterior cingulate cortex/precuneus (PCC/PCUN), medial prefrontal cortex (mPFC), and bilateral angular gyri and medial temporal lobes (mTLs). Previous functional magnetic resonance imaging (fMRI) studies have reported functional connectivity and activity abnormalities in the DMN in patients with chronic schizophrenia. However, inconsistent findings such as abnormally decreased or increased connectivity strength have been reported. Several factors may contribute to the inconsistencies, including use of different methods for identifying spatial patterns of coherent blood oxygen level-dependent fluctuations within the DMN. Among these methods, independent component analysis (ICA) is a statistically powerful data-driven technique, and it can yield reliable findings.

Another key issue impacting consistency of findings may be the effect of psychopharmacological intervention with antipsychotics because previous studies were primarily conducted in chronically treated patients. All known antipsychotic agents bind to dopamine (DA) receptors and DA signaling may affect DMN regulation. For instance, systemic administration of dopaminergic agonists, such as levodopa, apomorphine, and modafinil in patients having Parkinson’s disease and in healthy individuals can modulate activities of PCC and mPFC in the DMN. Furthermore, one longitudinal fMRI study has reported that the treatment effect of atypical antipsychotic agent olanzapine is associated with increases of functional connectivity strength in ventromedial PFC in the DMN in 19 patients having schizophrenia (including 13 drug-naive and 6 drug-free patients).

Effects of antipsychotic treatment on anatomical connectivities have also been reported in our and others’ studies. Our previous diffusion tensor imaging (DTI) study suggested that topological properties in limbic areas changed, whereas prefrontal topological characteristics persisted after risperidone treatment. However, our previous study defined regions of interesting (ROIs) based on a whole-brain atlas parcellation. Rather than using predefined anatomical ROIs, in this study we functionally defined seed and target regions using ICA to extract DMN ROIs, and then traced anatomical fibers among these ROIs. The results of tractography analyses depend on how ROIs are defined, and this approach may be more accurate in identifying functionally relevant tracts. We took this approach to investigate anatomical as well as functional connections within the DMN.

Although respective changes in functional and anatomical connectivities of DMN after treatment have been reported, their coupling alterations after antipsychotic therapy remain largely unknown. The coupling patterns between the 2 modalities are thought to capture more subtle neuropathological changes. The simultaneous assessment of anatomical and functional connectivities of the DMN in the same patients may produce more sensitive detections of treatment-related neurologic alterations than any single modality.

This study investigated for the first time the alterations of DMN connectivities using baseline rest-fMRI and DTI scans within 12 months of psychosis onset in first-episode schizophrenia patients (FESP) who had never been treated with any antipsychotic agent, and a second scan after the baseline scan following risperidone monotherapy for 8 weeks, which can therefore not only shed new light on the therapeutic effects on the DMN connectivities as well as coupling patterns between the 2 modalities, but also clarify the degree to which the previously reported connectivity abnormalities in patients with chronic schizophrenia might be due to the effect of antipsychotic medications. We hypothesized that functional and anatomical connectivities in the DMN would be strengthened by antipsychotic treatment; the treatment-related connectivity alterations would correlate with psychotic symptoms remission given previous associations between aberrant DMN connectivity and symptom severity, as well as the correlations between connectivity changes in the DMN and symptom improvement after treatment. Given that treatment-related functional changes are to a large extent different from anatomical alterations with respect to the regional distribution, we hypothesized that treatment-related alterations of the DMN would be dissociated between functional and anatomical modalities, and the coupling patterns between the 2 modalities would be decreased.

**Methods**

**Participants**

A total of 42 drug-naive FESP (average age 24.86 ± 4.80 years, illness duration 8.38 ± 2.61 months) and 38 healthy volunteers (average age 24.76 ± 4.56 years) were recruited from July 1, 2010 through January 31, 2014 from the Henan Mental Hospital, China. This dataset was previously used in other recent studies by our group. Detailed sample characteristics were shown in supplementary methods and supplementary table S1.

**Therapy and Clinical Assessments**

All patients were stabilized on risperidone monotherapy at a dosage of 4–6 mg/day for 8 weeks. Mood stabilizers and antidepressants were not used. Details regarding allowed concomitant medications taken by patients are shown in the Therapy and Clinical Assessments section of supplementary methods. The efficacy and safety of risperidone was assessed weekly by clinical interviews. During the 8-week treatment, no serious adverse effects occurred. Symptoms severity of all patients (n = 42) was evaluated at baseline and follow-up on the day of scanning with the 30-item Positive and Negative Syndrome Scale (PANSS).

**Imaging Data Acquisition and Data Pre-processing**

This section is shown in supplementary methods.

**ROI Extraction and Functional Connectivity Analysis Within the DMN**

To examine the DMN in patients...
(both at baseline and follow-up) and healthy volunteers groups, we used ICA to decompose the fMRI dataset of each individual in the 3 groups into independent spatial components (ISCs) with the Infomax algorithm using GIFT, version 1.3e (http://icatb.sourceforge.net). More details about the ROI extraction and group-level comparison are shown in supplementary methods.

Structural Connectivity in the DMN  A 3-step procedure for fibers extraction from DMN regions (figure 1A), which was previously used by our group and others, is described in supplementary methods.

Coupling of Functional and Anatomical Connectivity in the DMN  The process for measuring coupling between functional and anatomical connectivity in the DMN is shown in figure 2. Mean fractional anisotropy (FA) values of the 3 tracts connecting PCC/PCUN to mPFC and PCC/PCUN to bilateral mTLs were extracted to produce a vector of structural connectivity values. We then conducted a ROI-wise analysis to measure the functional connectivity strength between PCC/PCUN and mPFC, and between PCC/PCUN and bilateral mTLs. Spherical ROI masks with 5 mm radius were centered on the peak Montreal Neurological Institute (MNI) coordinate from DMN ISC one sample t test maps from the healthy control group. Temporal correlation coefficient between ROIs was computed followed by Fisher’s Z transform. Subsequently, the Pearson correlations between functional connectivity and structural connectivity values for each of the 3 DMN tracts were calculated for each group separately. The resulting Pearson correlation coefficient was used to quantify the functional and structural coupling values. Fisher’s Z transform was then applied to the coupling correlations. The between-group differences in the r-to-z values were normalized by the appropriate degrees of freedom to yield a z score that tested the null hypothesis of no difference in coupling values between groups. The Z-test was performed with \( P < .05 \) FDR corrected as significance level. The FDR was conducted in 3 (3 tracts ie, PCC to mPFC, and PCC to bilateral mTLs) \( \times 2 \) (between case and control, and before and after treatment within FESP) multiple tests.

Results  

Demographic and Clinical Variables  

As shown in supplementary table S1, FESP and healthy volunteer groups were age-, education-, gender-, and handedness-matched (\( P_s > .05 \)). Risperidone treatment in FESP resulted in decreases in total symptom severity from the healthy control group. Temporal correlation coefficient between ROIs was computed followed by Fisher’s Z transform. Subsequently, the Pearson correlations between functional connectivity and structural connectivity values for each of the 3 DMN tracts were calculated for each group separately. The resulting Pearson correlation coefficient was used to quantify the functional and structural coupling values. Fisher’s Z transform was then applied to the coupling correlations. The between-group differences in the r-to-z values were normalized by the appropriate degrees of freedom to yield a z score that tested the null hypothesis of no difference in coupling values between groups. The Z-test was performed with \( P < .05 \) FDR corrected as significance level. The FDR was conducted in 3 (3 tracts ie, PCC to mPFC, and PCC to bilateral mTLs) \( \times 2 \) (between case and control, and before and after treatment within FESP) multiple tests.

Fig. 1.  Schematic overview of fibers extraction from default mode network (DMN) regions. (A) The 3-step procedure of fibers extraction from DMN regions. First, whole-brain fibers were traced by using the interactive software Trackvis with the fiber assignment by an interpolated streamline propagation algorithm in the diffusion tensor imaging (DTI) native space for each individual. Second, an initial ROI after the inverse transformation (\( T^{-1} \)) of spatial normalization into the native DTI space was chosen; the fiber tracts that reached the ROI1 were picked from the whole collection of fibers. Third, a second ROI after \( T^{-1} \) was chosen from the remaining DMN ROIs. Only the tracts reaching the ROI2 were retrieved from the rest of tracts. (B) Three examples of fiber tractography for 1 patient at baseline, 1 patient at follow-up, and 1 healthy volunteer. The 3 tracts connecting medial prefrontal cortex (mPFC) to posterior cingulate cortex/precuneus (PCC/PCUN), and PCC/PCUN to bilateral medial temporal lobes (mTLs) were detected in almost all subjects of the 3 groups. Red demonstrates the medio-lateral orientation. Blue demonstrates the rostro-caudal plane. Green demonstrates the dorso-ventral direction. For color, see the figure online.
Independent Spatial Maps of the DMN in Each Group

The DMN mask generated by 1-sample t test ($P < .05$ voxel-wise FDR corrected) over the voxel loading values in each of the 3 groups (figure 3A–C) revealed clusters in PCC/PCUN, mPFC, and bilateral mTLs, angular gyri, and inferior temporal gyri (iTGs) (see details in supplementary tables S2–S4).

Impaired Functional Connectivity in PCC/PCUN and mPFC in DMN Maps and Correlations With Symptom Severity at Baseline

At baseline, patients had lower functional connectivity strength in the PCC/PCUN as well as the mPFC with the rest regions of the DMN compared with controls ($Ps < .05$, voxel-wise FDR correction; figure 3D; table 1).
We performed multiple regression analyses in the FESP group at baseline to compare the PANSS scores with the functional connectivity (FC) maps for the PCC/PCUN seed as well as the mPFC seed. Functional connectivity between the left PCC/PCUN and a cluster of voxels located in right ANG, and between right PCC/PCUN and a cluster of voxels located in right ANG was decreased in patients relative to healthy volunteers and was negatively correlated with PANSS-N scores (\( P \leq .05 \) with AlphaSim correction, cluster-defining \( P \leq .001 \); figure 4A; supplementary table S5; minimum cluster size > 18), and right PCC/PCUN to a cluster of voxels located in right angular gyri (ANG) (\( P \leq .05 \) with AlphaSim correction, cluster-defining \( P \leq .001 \); figure 4A; supplementary table S5; minimum cluster size > 18) showed significantly negative correlations with PANSS-N scores, although no voxels can exist after voxel-wise FDR correction. In addition, no significant correlations were detected between PANSS scores and FC maps of the mPFC (\( P > .05 \)). There are no significant correlations between symptoms and ISC loading values (\( Ps > .05 \)).

**Longitudinal Increase in PCC/PCUN Functional Connectivity in DMN Maps and Correlations With Treatment Response**

After 8-weeks treatment, there was an increase in connectivity strength between PCC/PCUN and the rest of the
regions of DMN ($P < .05$, voxel-wise FDR correction; figure 3E; table 1), but not in the mPFC.

Multiple regression analyses were performed in the FESP group to determine the relationship of the decreases in PANSS scores with alterations in FC
maps of the PCC/PCUN. Increases of functional connectivity between PCC/PCUN and a cluster of voxels located in mPFC were positively correlated with decreases in positive symptom scores (figure 4B; supplementary table S6) \( (P < .05 \) with AlphaSim correction, cluster-defining \( P < .001 \), minimum cluster size > 20), although this result did not survive voxel-wise FDR correction.

**Structural Connectivity Within the DMN in Each Group**

Figure 1B shows 3 examples of 3 connections for each of the 3 groups. The 3 fiber bundles were detected in all the 38 healthy volunteers (see more details in supplementary figure S1), 40 of 41 FESP at baseline (supplementary figure S2) and 37 of 38 patients at follow-up (supplementary figure S2).

The superior frontal–occipital association bundles connecting mPFC to both left and right ANG were detected in 14/7 (left/right) of 38 healthy controls, 9/10 (left/right) of 41 FESP at baseline and 14/9 (left/right) of 38 patients at follow-up. The tracts connecting the left and right iTGs, respectively, to PCC/PCUN were detected in 16/23 (left/right) of 38 volunteers, in 21/20 (left/right) of 41 untreated FESP, and in 16/20 (left/right) of 38 treated FESP.

**Between-group Comparisons and Post-treatment Changes in Structural Connectivity Within the DMN**

At baseline, no differences were detected between groups \( (Ps > .05) \) in mean FA of all the 3 tracts. After 8-weeks treatment, no alterations in mean FA of all the 3 tracts were found \( (Ps > .05) \).

**Coupling of Anatomical and Functional Connectivity Within the DMN in Each Group**

As shown in supplementary table S7, there were no significant between-group differences \( (Ps > .05) \) in coupling values of all the 3 tracts at baseline. After treatment, there was significant decrease in FESP coupling values of the 2 tracts connecting the left \( (P = .03, \) FDR corrected) and right \( (P = .03, \) FDR corrected) mTL, respectively, to PCC/PCUN.

**Discussion**

This study aimed to investigate antipsychotic treatment-related alterations of multimodal connectivity patterns within the DMN in schizophrenia and their relationship to clinical behaviors. We integrated fMRI and DTI to investigate both functional and anatomical connectivity organizations in drug-naive FESP at baseline and then after 8-weeks risperidone monotherapy. As hypothesized, patients’ positive symptoms improved and functional connectivity strength (ISC loading values) within the DMN in PCC/PCUN increased after treatment. Increases of functional connectivity strength between PCC/PCUN and mPFC were positively correlated with the improvement of patients’ positive symptom scores after treatment. Neither connectivity strength in the mPFC nor negative symptoms changed after treatment. As for anatomical connections within the DMN, we found no significant alterations in the integrity of the 3 bundles. However, patients’ structural–functional coupling patterns of the tracts connecting bilateral mTLs to PCC/PCUN at follow-up revealed decreased coupling compared with that of baseline. These findings confirmed our hypothesis that changes of anatomical and functional connectivity after treatment within the DMN were dissociated by modality.

Our results demonstrating decreased functional connectivity strength in the DMN with the anterior (mPFC) and posterior (PCC) components as particular loci of dysfunction are in accordance with previous imaging studies, and confirm the functional disconnectivity of DMN in schizophrenia. After 8 weeks of antipsychotic treatment, patients had significantly increased functional connectivity in the PCC/PCUN with the remaining components within DMN. Contrary to our results, a study conducted by Sambataro et al in FESP found that the decreased functional connectivity in PCC within the DMN was not significantly modulated after 8 weeks of olanzapine treatment. This discrepancy is probably due to the inconsistent time point of the first MRI data acquisition. In the study by Sambataro et al, the first MRI scans of patients were collected at 4 weeks of treatment but not at baseline. Therefore, it is difficult to exclude the possibility that the deficits of functional connectivity in PCC may have already improved during the first 4 weeks of treatment. Despite the alterations of PCC connectivity, neither connectivity strength in the mPFC nor negative symptoms altered after treatment, which is consistent with our and others’ reports. Data from relatives of patients with schizophrenia demonstrated that abnormal functional connectivities in mPFC exist in both patients and their first-degree relatives. This evidence leads us to propose that the dysconnectivity of mPFC within the DMN observed in this study might be a “trait-dependent” biomarker affected primarily by genetic factors and unresponsive to risperidone treatment. However, the lack of changes in negative symptoms as well as mPFC connectivity may be also due to a limited effect of antipsychotic treatment on DA signals in mPFC.

After finding the increase of functional connectivity strength of PCC/PCUN with the remaining DMN components after treatment, we then applied voxel-wise analyses using PCC as a seed ROI to detect DMN FC alterations that were correlated with patients’ symptom improvement. We found that alterations of connectivity...
between mPFC and PCC were associated with patients’ positive symptoms improvement, which is consistent with another study. Several studies demonstrated correlations between treatment response and alterations of functional connectivities. Sarpal et al. reported that changes in cortico-striatal functional connectivity after treatment of risperidone and aripiprazole correlated with decreases in ratings of psychotic symptoms. Moreover, Kraguljac et al. assessed functional connectivity with hippocampal seeds and found significant changes that correlated with treatment response in a cohort of previously unmedicated subjects who were all treated with risperidone. Interestingly, our current study also found a relationship between negative symptoms severity and connectivity of PCC to angular gyri at baseline. It is known that PCC is a particularly important hub within the DMN, and it may play an important role in both negative and positive symptoms.9,37

Rather unexpectedly, there was no change in the integrity of 3 bundles within the DMN after treatment, even though these findings combined with the results of increases in the functional connectivity in the DMN can confirm our hypothesis that treatment-related changes of connectivity in the DMN were dissociated between the 2 modalities. The relative stability of anatomical connectivity measures after treatment in this study stands in contrast to other reports that demonstrated moderate alterations in the integrity (mean FA) of tracts within the DMN in patients with schizophrenia after treatment.18–21 The inconsistency may be partially due to the differences in methodologies. This study traced anatomical fibers among DMN ROIs extracted by ICA, which estimates anatomical connectivity properties more reliably than those based on a whole-brain atlas parcellation. Inappropriate definition of these ROIs, ie, seeds and targets not localized correctly may include either irrelevant structural subnetworks or erroneously exclude relevant ones.22

Our results suggest that abnormalities of functional connectivities are not necessarily accompanied by impaired anatomical connectivities. In contrast to this, some studies proposed that the anatomical connectivity may serve as a material substrate for functional connectivity, and functional connectivity abnormalities within the DMN were suggested to be induced by anatomical impairments. Conversely, a recent report contends that functional connectivities impacts fiber connectivities through neuroplasticity. Thus, we speculate that the relatively stable structural connectivities of DMN after treatment in this study may imply the treatment-induced changes in functional connectivities were insufficient to change fiber integrity.

Previous research has demonstrated that structural–functional connectivity coupling can be disrupted in pathological states including schizophrenia. However, given that the patients were older in at least one of these studies, the finding of altered coupling could be due to progressive changes of the disease over time. This interpretation is consistent with our current study, which found no significant baseline abnormalities of coupling values in the very early phase of schizophrenia. The coupling values of the tracts connecting bilateral mTLs to PCC/PCUN were decreased after treatment, consistent with our current findings that changes of DMN connectivity strength occurred in functional patterns but not in the anatomical modality after treatment. Notably, the structural–functional coupling between 2 midline nodes, ie, PCC/PCUN and mPFC, which are neuroanatomically linked by the cingulum tract was preserved following treatment. The connection between PCC/PCUN and mPFC is a long-distance connection that is vital for central neural systems.41 We propose that long-range tracts are relatively less vulnerable to neurotoxicity of short-term psychopharmacological intervention during the early stage of schizophrenia to ensure the relative stability of the overall dynamics between functional and structural connectivities in the DMN.

Several limitations of our current study need to be noted. First, structural networks constructed using tractography and functional networks defined using ICA have high or moderate test–retest reliability. However, the lack of repeat scans with DTI and fMRI in the healthy volunteer group is a limitation of our current study as we cannot completely exclude the possibility that the observed functional connectivity and coupling pattern changes in the DMN after treatment might be due to, ie, regression to the mean or acclimation to the scanning environment instead of purely an effect of 8-weeks risperidone treatment. Second, the absence of a patient control group receiving placebo prevents confidence in excluding other causes of changes in imaging indices, but such a design is clinically unethical as known effective antipsychotic treatments cannot be withheld from patients for 8 weeks. Third, there is no other control group of patients receiving other type of antipsychotics, and we therefore cannot determine whether the effects observed in this study are specific to risperidone. Fourth, anatomical connectivity analyses were limited to the 3 fiber tracts that were identified in almost all the subjects in this study. Although it has been inferred that fiber bundles might not exist between every pair of DMN components, we still cannot completely exclude the possibility that other important fiber tracts within the DMN may also exist. More sensitive fiber tractography methods are needed to further detect such fiber tracts. Fifth, although the detected associations between clinical symptoms and FC maps of DMN regions survived cluster-extent multiple comparisons correction, they should be considered as exploratory as they did not survive voxel-wise FDR correction. Sixth, although patients in this study (disease duration 8.38 ± 2.61 months) are in the early phase of disease, the potential influence of schizophrenia disease...
Dissociation in Effects of Risperidone Monotherapy

progression on DMN connectivities is improbable but cannot be ruled out.

In summary, this study investigated antipsychotic treatment effects on both functional and anatomical connectivities, and structure–function coupling patterns in the DMN. Increased functional connectivities between PCC/PCUN and mPFC may be treatment response biomarkers for positive symptoms. Increases in functional connectivities, no alterations in the fiber integrity, combined with decreases in structural–functional coupling, suggest that antipsychotic treatment effects on the DMN may be dissociated by modality. These findings only apply to acute phase treatment. It remains to be seen whether meaningful structural reorganization in the brain can occur later with a longer course of treatment. Major limitations of this study, however, include lack of repeat scans in the healthy volunteer group and no control group of patients taking placebo or other type of antipsychotics.

Supplementary Material

Supplementary data are available at Schizophrenia Bulletin online.

Funding

This study was supported by grants from Wuhan Science and Technology Bureau grant (2017060201010169), China Scholarship Council Program (201506370095), Natural Science Foundation of Hubei Province (132795), Teachers funding project of Wuhan University (2042018k0126), the National Key R&D Program of China (2018YFC1314600), the National Natural Science Foundation of China (81271484, 81471361, 61533006, 81871057, and 81371480), the National Basic Research Program (973) (2012CB517904), the National Institute of Mental Health (K01MH108721), and the 863 project (2015AA020505). The authors declare no conflict of interest.

Acknowledgments

The authors declare no conflicts of interest.

References


34. Agid O, Mamo D, Ginovart N, et al. Striatal vs extrastriatal dopamine D2 receptors in antipsychotic response—a double-blind PET study in schizophrenia. Neuropsychopharmacology. 2007;32:1209–1215.


