Changes in Brain Structure, Function, and Network Properties in Patients With First-Episode Schizophrenia Treated With Antipsychotics

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Purpose: Comprehensive and longitudinal brain analysis is of great significance for understanding the pathological changes of antipsychotic drug treatment in patients with schizophrenia. This study aimed to investigate the changes of structure, function, and network properties in patients with first-episode schizophrenia (FES) after antipsychotic therapy and their relationship with clinical symptoms.

Materials and Methods: A total of 30 patients diagnosed with FES and 30 healthy subjects matched for sex and age were enrolled in our study. Patients at baseline were labeled as antipsychotic-naive first-episode schizophrenia (AN-FES), and patients after antipsychotic treatment were labeled as antipsychotic treatment first-episode schizophrenia (AT-FES). The severity of illness was measured by using the PANSS and CGI score. Structural and functional MRI data were also performed. Differences in GMV, ALFF, and ReHo between the FES group and healthy control group were tested using a voxel-wise two-sample t-test, and the comparison of AN-FES group and AT-FES group was evaluated by paired-sample t-test.

Results: After the 1-year follow-up, the FES patients showed increased GMV in the right cerebellum, right inferior temporal gyrus, left middle frontal gyrus, parahippocampal gyrus, bilateral inferior parietal lobule, and reduced GMV in the left occipital lobe, gyrus rectus, right orbital frontal cortex. The patients also showed increased ALFF in the medial superior frontal gyrus and right precentral gyrus. For network properties, the patients showed reduced characteristic path length and increased global efficiency. The GMV of the right inferior parietal lobule was negatively correlated with the clinical symptoms.

Conclusions: Our study showed that the antipsychotic treatment contributed to the structural alteration and functional improvement, and the GMV alteration may be associated with the improvement of clinical symptoms.

Keywords: schizophrenia, first-episode, antipsychotics, neuroimaging, functional magnetic resonance imaging
INTRODUCTION

Schizophrenia is a complex disease of the central nervous system, and a great deal of health care resources are devoted to these patients (1, 2). The genetic and environmental factors play an important role in the occurrence and development of schizophrenia. However, its pathogenic mechanism has not been fully defined, and further research is still needed. Functional magnetic resonance imaging (fMRI) has been widely used in the study of schizophrenia (3). The voxel based morphometry analysis is a common method to evaluate the change of gray matter volume (GMV). Resting-state fMRI is more stable and relatively easier to perform than task state fMRI, and is mainly used for brain functional connectivity and brain network analysis. Previous studies have shown structural and functional deficits in patients with schizophrenia, which may provide useful information for understanding the pathophysiology of schizophrenia (4).

Typical antipsychotics control symptoms by reducing the function of dopaminergic neurons (5). In addition to disease progression, many studies have confirmed that antipsychotics may affect the structure, function, and network characteristics of patients with schizophrenia to a certain extent (6, 7). However, previous studies have used a relatively single brain analysis method for cross-sectional design, which may not provide a comprehensive understanding of the effects of antipsychotics on patients with schizophrenia. Longitudinal and comprehensive studies on the effects of antipsychotics on patients with schizophrenia to a certain extent (4).

Therefore, in this study, we aimed to analyze the changes in the structure, function, and network properties of FES after antipsychotic therapy and their correlation with clinical symptoms.

MATERIALS AND METHODS

Subjects

A total of 30 subjects diagnosed with FES were enrolled in our study. The FES patients were defined according to the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV) (8). Patients at baseline were labeled as antipsychotic-naive first-episode schizophrenia (AN-FES), and patients after antipsychotic treatment were labeled as antipsychotic treatment first-episode schizophrenia (AT-FES). Patients were selected from our hospital. The exclusion criteria for all subjects were a history of head injury, organic mental disorder, neurological disorder, serious medical or surgical illness, and a history of substance abuse. The healthy control subjects were recruited from the local community by advertisement. They had no history of psychiatric illness, as determined by the non-patient edition of the SCID, and no history of psychotic disorders among their first-degree relatives. This study was approved by our ethics committee, and all subjects provided fully informed written consent to participate in the study.

Treatment and Response Assessment

The severity of illness was measured by senior clinical psychiatrists from the Department of Psychiatry using the Positive and Negative Syndrome Scale (PANSS) (9) and Clinical Global Impression Scales (CGI). CGI includes CGI for severity (CGI-S) and CGI for improvement (CGI-I). Patients received treatment according to the severity of the condition at baseline. During the follow-up, all patients received second generation antipsychotic drugs, including risperidone, aripiprazole and olanzapine. The PANSS and CGI score were assessed again after 1-year follow-up.

Image Acquisition and Preprocessing

MRI data acquisition was performed on a 3.0T scanner (Signa HDx; GE Medical Systems, Milwaukee, WI, USA) equipped with an 8-channel phased-array brain coil at our hospital. Details regarding the image acquisition protocol and fMRI data preprocessing were presented in the Supplemental Material.

GMV Calculation

The VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) was used to estimate GMV. Structural MRI images were segmented into GM, WM, and cerebrospinal fluid using the standard segmentation model. After initial affine registration of the GM concentration map into the Montreal Neurological Institute (MNI) coordinate space, the GM concentration images were non-linearly warped using the DARTEL technique and then resampled to a voxel size of 1.5 × 1.5 × 1.5 mm. The GMV was obtained by multiplying the GM concentration map by the non-linear determinants that were derived from the spatial normalization step. Finally, the GMV images were smoothed using a Gaussian kernel of 6 × 6 × 6 mm full width at half maximum (FWHM).

Amplitude of Low-Frequency Fluctuation (ALFF) and Regional Homogeneity (ReHo) Calculation

ALFF and ReHo were calculated using REST software (http://restfmri.net/forum/rest_v18). For standardization purposes, the ALFF of each voxel were divided by the global mean ALFF value within the whole-brain mask. Prior to the calculation of ReHo, the data were bandpass filtered (0.01–0.08 Hz). Subsequently, ReHo was determined on a voxel-by-voxel basis by calculating Kendall’s coefficient of concordance of the time courses of a given voxel with those of its nearest 26 neighbors. Similar to the ALFF analysis, the ReHo of each voxel was divided by the global mean ReHo value.

Construction of the Functional Brain Network and Properties Analysis

The software Gretna (http://www.nitrc.org/projects/gretna, v1.2.1) was used to reconstruct the functional brain network. The brain was divided into 90 regions by anatomical automatic labeling, and each region was regarded as a node of network. The pearson correlation coefficient between different nodes was calculated and a matrix with 90 × 90 symmetric distribution was established. Then the matrix was transformed into binary connection matrix, and the sparsity of connection matrix was regarded as a set threshold to construct brain functional networks. The whole and local topology parameters were analyzed at each sparsity. The whole topology parameters...
include small-world parameters and network efficiency. The small-world parameters include clustering coefficient ($C_p$), characteristic path length ($L_p$), normalized clustering coefficient ($\gamma$), normalized shortest path length ($\lambda$), and small-world index ($\sigma$). The network efficiency includes local efficiency ($E_{loc}$) and global efficiency ($E_{glob}$). The local topology parameters include knodal, Enodal, Degree centrality, and Betweenness centrality.

### Statistical Analysis

For voxel-based analyses of GMV, ALFF, and ReHo, the parametric test in the SPM8 package was used to test for statistical significance. Statistical inferences were determined with a voxel-level statistical threshold ($P < 0.001$, uncorrected). Differences in GMV, ALFF, and ReHo between the FES group and healthy control group were tested using a voxel-wise two-sample $t$-test, and the comparison of AN-FES group and AT-FES group was evaluated by paired-sample $t$-test.

The network parameters were analyzed by the software Gretna, and took the Sparsity as threshold, the range was $0.05 \leq S \leq 0.5$, the interval value is 0.05, so the network analysis within this scope. In order to clarify the differences among subjects of the topology properties, the FES and healthy control group was tested by two-sample $t$-test, AN-FES group and AT-FES group was evaluated by paired-sample $t$-test. Meanwhile, the edge index of the network was considered qualitatively by using NBS, the threshold was $P < 0.05$, and the result was presented by BrainNet Viewer software.

Correlations among structural, functional abnormalities, global network properties, and severity of illness in AN-FES and AT-FES group were evaluated by partial correlation analysis. The gender and age were regarded as covariate for subsequent analysis. The correlation between the GMV, ALFF, ReHo, and global network properties in different regions in AT-FES group compared with AN-FES group and the difference value of positive, negative, general psychopathology, total scores on the PANSS, and CGI-S score before and after treatment and CGI-I score after treatment was analyzed. The threshold was $P < 0.05$.

### Results

#### Demographic and Clinical Characteristics

Table 1 shows the demographic and clinical characteristics of the FES group and healthy control group. The CGI-I scores of the AN-FES group and the AT-FES group were 0 and 1.6 ± 0.7, respectively, indicating a significant therapeutic effect. The scores of CGI and PANSS in AT-FES group were lower than those in AN-FES group, and the difference was statistically significant (Table 2, $P < 0.05$).

#### Baseline Analysis of GMV, ALFF, and ReHo

Compared with healthy control group, the AN-FES group showed reduced GMV in the midbrain and left superior temporal gyrus (Supplementary Table 1, $P < 0.001$).

ALFF in the medial superior frontal gyrus, left middle frontal gyrus, right superior frontal gyrus, and right insula were all decreased in AN-FES group compared with healthy controls (Supplementary Table 1, $P < 0.001$).

#### Baseline Analysis of Global and Local Network Properties

As $0.05 \leq$ Sparsity $\leq 0.5$, both the AN-FES group and healthy control group had higher $\gamma$ value (all larger than 1) and approximately equal $\lambda$ value. The $\sigma > 1$ of the two groups indicated that the two groups exhibited no difference in the small-world architecture of the functional brain network ($P > 0.05$). Compared with healthy controls, the $C_p$, $E_{glob}$, and $E_{loc}$ of AN-FES were lower, and the $L_p$ was higher, with statistically significant differences (Supplementary Table 2, $P < 0.05$).

There were significant differences in the betweenness centrality and degree centrality between AN-FES and the healthy control group, as shown in Supplementary Table 3.

#### Longitudinal Analysis of GMV, ALFF, and ReHo

The AT-FES group showed increased GM volume in the right cerebellum, right inferior temporal gyrus (ITG), left middle frontal gyrus (MFG), parahippocampal gyrus, bilateral IPL, and reduced GMV in the left occipital lobe, gyrus rectus,
right orbital frontal cortex with that of the AN-FES group (Supplementary Table 4, Figure 1, $P < 0.001$).

The AT-FES patients showed increased ALFF in the medial superior frontal gyrus and right precentral gyrus (Supplementary Table 4, Figure 2, $P < 0.001$).

The ReHo in AT-FES group and AN-FES group showed no difference.

**Longitudinal Analysis of Global and Local Network Properties**

As $0.05 \leq \text{Sparsity} \leq 0.5$, both the AN-FES group and AT-FES group had higher $\gamma$ value (all larger than 1) and approximately equal $\lambda$ value. The $\sigma > 1$ in both groups indicated that the two groups showed no difference in the small-world structure of functional brain networks (Supplementary Table 5).

**The Correlation Analysis of Structural, Functional Abnormalities, Global Network Properties, and Severity of Illness**

Partial correlation analysis showed that GMV of the left parietal lobe was positively correlated with the general psychopathological differences of PANSS before and after...
FIGURE 3 | Comparison of the whole brain attributes between AN-FES group and AT-FES group at different sparsity. AN-FES, antipsychotic-naive first-episode schizophrenia; AT-FES, antipsychotic treatment first-episode schizophrenia.

FIGURE 4 | The abnormal NBS functional connectivity in AN-FES group and AT-FES group. NBS, network-based statistic; AN-FES, antipsychotic-naive first-episode schizophrenia; AT-FES, antipsychotic treatment first-episode schizophrenia.

...treatment \( (r = 0.519, P = 0.016) \). The details were shown in Supplementary Table 7.

**DISCUSSION**

In this study, we analyzed the differences in brain structure, function, and network topological characteristics between the FES group and healthy controls at baseline, and explored the effect of antipsychotics on FES after 1 year of follow-up. Multiple brain regions showed reduced GMV, ALFF, and ReHo at baseline, and the GMV of FES after treatment showed coexisting reduced and increased brain regions. The partial correlation analysis showed the correlation of GMV, network topological properties, and clinical symptoms. Our study provides comprehensive and valuable longitudinal information on FES.

MRI confirmed a decrease in GMV and white matter volume (WMV), with some investigators noting that the decrease in GMV (2%) was more pronounced than the decrease in WMV (1%) \( (10, 11) \). Thus, the study of GMV in schizophrenia patients may help for pathogenesis and pathologic changes research. Our results showed reduced GMV in the midbrain and left superior temporal gyrus at baseline. Most previous studies indicated the reduction of GMV usually existed in the prefrontal cortex, temporal lobe and parietal cortex \( (12–14) \). Nopoulos et al. \( (15) \) also found that the schizophrenia patients had significantly smaller midbrain measures compared with control subjects. Since dopamine disorders are central to the pathophysiology of psychosis, the midbrain contains the extranuclear body of all dopamine neurons in the human brain.

In our study, ALFF and ReHo in some brain regions decreased at baseline, suggesting impaired local brain activity and functional connectivity in FES. The schizophrenia patients showed obvious ALFF reduction in bilateral occipital lobe, motorsensory cortex, and posterior parietal cortex by comparison with healthy subject \( (16) \). Some studies pointed out that the FES had reduced ALFF in prefrontal lobe, and this change was more obvious in early stage of the disease \( (17, 18) \). The increased or reduced ReHo all indicated the abnormality of synchrony of spontaneous neuron activity and coordination mechanism, and evidence abounds that the ReHo abnormality existed in prefrontal lobe, superior temporal gyrus, and posterior cingulate cortex \( (19–21) \). Salvador first used the automated...
showed that antipsychotic drugs ameliorate abnormalities in the control disorders may occur after injury. A previous study indicated that the antipsychotics may improve the reduced superior frontal gyrus decreased at baseline and increased after treatment, suggesting that antipsychotics may have an impact on task state cognition and motor behavior, and also was a part of the default network. In this study, ALFF in the medial superior frontal gyrus decreased at baseline and increased after treatment, suggesting that antipsychotics may have an impact on the local function of this brain region. The anterior central gyrus is involved in the processing of cognitive information related to motor function, and cognitive abnormalities and intentional control disorders may occur after injury. A previous study showed that antipsychotic drugs ameliorate abnormalities in the anterior central gyrus.

There are few studies on the effect of antipsychotics on network properties in patients with schizophrenia. A study indicated that the antipsychotics may improve the reduced $E_{\text{glob}}$ and increased $C_p$ ($p$). In our study, the brain regions with different node properties before and after treatment in FES were the auditory network, which mainly included the insular lobe, transverse gyrus and supramarginal gyrus; the subcortical network mainly included the amygdala, putamen and pallidum; and the sensorimotor network mainly included the pre-central gyrus and post-central gyrus. Most of the brain regions that reduced betweenness centrality at baseline improved after treatment, and this change was associated with remission of clinical symptoms. Previous studies have also shown the effectiveness of antipsychotics in improving auditory hallucinations ($p$).

Our study showed changes in the structure, function, and network properties in FES after the antipsychotic treatment and their correlation with clinical symptoms. Our study may help to provide a more complete understanding of the pathological changes in patients with schizophrenia following antipsychotic medication.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

**ETHICS STATEMENT**

The study was approved by the Ethics Committee of Peking University People's Hospital. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

**AUTHOR CONTRIBUTIONS**

NH: guarantor of integrity of the entire study and manuscript review. PY and NH: study concepts. PY and CZ: study design, definition of intellectual content, clinical studies, and manuscript editing. PY and YL: literature research and data acquisition. PY and XL: experimental studies and data analysis. PY: statistical analysis. PY, IC, and YL: manuscript preparation. All authors contributed to the article and approved the submitted version.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.735623/full#supplementary-material
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