Short-term Effects of Antipsychotic Treatment on Cerebral Function in Drug-Naive First-Episode Schizophrenia Revealed by “Resting State” Functional Magnetic Resonance Imaging

Su Lui, MD, PhD; Tao Li, MD, PhD; Wei Deng, MD, PhD; Lijun Jiang, MM; Qizhu Wu, PhD; Hehan Tang, MM; Quang Yue, MD; Xiaoqi Huang, MD, PhD; Raymond C. Chan, PhD; David A. Collier, PhD; Shashwath A. Meda, MS; Godfrey Pearlson, MD; Andrea Mechelli, PhD; John A. Sweeney, PhD; Qiyong Gong, MD, PhD

Context: Most of what we know about antipsychotic drug effects is at the receptor level, distal from the neural system effects that mediate their clinical efficacy. Studying cerebral function in antipsychotic-naive patients with schizophrenia before and after pharmacotherapy can enhance understanding of the therapeutic mechanisms of these clinically effective treatments.

Objective: To examine alterations of regional and neural network function in antipsychotic-naive patients with first-episode schizophrenia before and after treatment with second-generation antipsychotic medication.

Design: Case-control study.

Setting: Huaxi MR Research Center and Mental Health Centre of the West China Hospital.

Participants: Thirty-four antipsychotic-naive patients with first-episode schizophrenia were scanned using gradient-echo echo-planar imaging while in a resting state. After 6 weeks of antipsychotic treatment, patients were rescanned. Thirty-four matched healthy control subjects were studied at baseline for comparison purposes.

Main Outcome Measures: The amplitude of low-frequency fluctuations (ALFF) of blood oxygen level-dependent signals, believed to reflect spontaneous neural activity, was used to characterize regional cerebral function. Functional connectivity across brain regions was evaluated using a seed voxel correlation approach and an independent component analysis. Changes in these measures after treatment were examined to characterize effects of antipsychotic drugs on regional function and functional integration.

Results: After short-term treatment with second-generation antipsychotic medications, patients showed increased ALFF, particularly in the bilateral prefrontal and parietal cortex, left superior temporal cortex, and right caudate nucleus. Increased regional ALFF was associated with a reduction of clinical symptoms, and a widespread attenuation in functional connectivity was observed that was correlated with increased regional ALFF.

Conclusions: We demonstrate for the first time, to our knowledge, that widespread increased regional synchronous neural activity occurs after antipsychotic therapy, accompanied by decreased integration of function across widely distributed neural networks. These findings contribute to the understanding of the complex systems-level effects of antipsychotic drugs.

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SCHIZOPHRENIA IS A COMMON psychiatric disorder typically associated with significant functional disability. It is believed to have a complex etiopathogenesis and to affect widely distributed neural circuitry. Antipsychotic drugs are standard therapy, but the systems-level mechanisms by which they exert therapeutic effects are not well understood. Thus, studying cerebral function in the antipsychotic-naive state and again after pharmacotherapy may lead to better understanding of medication effects, with the longer-term potential for developing clinical biomarkers of drug effect and more effective, individualized therapies for patients with schizophrenia.

In recent years, a new noninvasive method for assessing regional and neural circuitry function at rest has been developed. This method, known as “resting-state” functional magnetic resonance imaging (rfMRI), avoids potential performance confounds associated with cognitive activation paradigms and is relatively easy to implement in clinical studies. Spontaneous low-frequency blood oxygen level–dependent (BOLD) fluctuations have been observed by rfMRI during the resting state in both human beings and in animal models. These signals bear numerous similarities to fluctua-
tion in neurophysiological, hemodynamic, and metabolic parameters. For example, flow-sensitive imaging in human subjects reveals fluctuations in cerebral blood flow with similar spatial patterns to those seen with fMRI. Because BOLD signals are thought to reflect primarily dendritic potentials related to synaptic activity, rfMRI measurements are thought to reflect spontaneous neural function. Using fMRI, the so-called default mode network has been identified, which includes the ventromedial prefrontal cortex, posterior cingulate/precuneus, and lateral parietal cortex. It is typically more active at rest than during task performance. This network is hypothesized to be associated with the monitoring of internal thoughts and feelings and has been shown to be affected in a number of neuropsychiatric conditions, including Alzheimer disease and schizophrenia, and after acute psychological trauma.

Resting-state functional magnetic resonance imaging can provide 2 distinct types of information about brain function. Both animal and human studies indicate that the regional amplitude of low-frequency fluctuations (ALFF) (0.01-0.08 Hz) reflects spontaneous synchronous neural activity during resting-state studies. Second, measures of functional connectivity reflect the level of integration of that activity during resting-state fMRI. The so-called default mode network has been identified, which includes the ventromedial prefrontal cortex, posterior cingulate/precuneus, and lateral parietal cortex. It is typically more active at rest than during task performance. This network is hypothesized to be associated with the monitoring of internal thoughts and feelings and has been shown to be affected in a number of neuropsychiatric conditions, including Alzheimer disease and schizophrenia, and after acute psychological trauma.

Prior studies have combined fMRI with measures of functional connectivity to examine chronic and first-episode schizophrenia. However, only one of them used fMRI in a large cohort of antipsychotic-naive patients and none of them examined fMRI in schizophrenia before and after treatment. Thus, the effects of antipsychotic medication on these measures are not yet well understood. Investigating changes after the initiation of antipsychotic therapy can therefore not only provide new insights into the systems-level effects of antipsychotic drugs, but also clarify the extent to which previously reported effects in patients with chronic disease might be treatment rather than illness related.

The aim of the present study was to use fMRI to characterize changes in regional and neural network function in drug-naive patients with schizophrenia after second-generation antipsychotic treatment. The relationship between changes in ALFF indices and reductions in symptom severity after treatment was also examined. Functional connectivity was evaluated with both a seed voxel correlation approach, using the regions with significant change in ALFF values after treatment as seeds, and a more exploratory independent component analysis (ICA).

**RESULTS**

Thirty-four antipsychotic-naive patients with first-episode schizophrenia and 34 healthy controls were recruited at the Mental Health Centre of the West China Hospital (Table 1). The study was approved by the local research ethics committee and all subjects gave written informed consent to their participation. Diagnoses were determined using the Structured Clinical Interview for DSM-IV Patient Edition and confirmed after at least 1-year follow-up. All patients were evaluated at baseline and 6 weeks after treatment, using the Positive and Negative Syndrome Scale. As expected, significant reductions in psychopathology ratings were observed after treatment (Table 2).

**DISCUSSION**

Healthy controls were recruited from the local area by poster advertisement and screened using the Structured Clinical Interview for DSM-IV Non-Patient Edition to confirm the lifetime absence of Axis I illness. Selected control subjects had no known history of psychiatric illness in first-degree relatives. Patients with schizophrenia and control subjects were matched in age, sex, height, weight, and years of education (Table 1). The following exclusion criteria applied to all subjects: history of neurological illness, alcohol or drug abuse, pregnancy, or any major medical illness. T1- and T2-weighted magnetic resonance images were inspected by an experienced neuroradiologist, and no gross abnormalities were observed for any subject.

All patients were treated with second-generation antipsychotic drugs for 6 weeks before magnetic resonance reexamination, with drug choice and dose based on the treating psychiatrist’s clinical judgment. Among them, 13 were prescribed more than 1 such medication and 12 received risperidone monotherapy. Treatment during the 6 weeks consisted of risperidone (24 cases) at a mean (SD) dose of 4.2 (1.3) mg/d, olanzapine (7 cases) at a mean (SD) dose of 16.9 (6.9) mg/d, clozapine (7 cases) at a mean (SD) dose of 52.5 (44.5) mg/d, quetiapine

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**METHODS**

**PARTICIPANTS**

Thirty-four antipsychotic-naive patients with first-episode schizophrenia and 34 healthy controls were recruited at the Mental Health Centre of the West China Hospital (Table 1). The study was approved by the local research ethics committee and all subjects gave written informed consent to their participation. Diagnoses were determined using the Structured Clinical Interview for DSM-IV Patient Edition and confirmed after at least 1-year follow-up. All patients were evaluated at baseline and 6 weeks after treatment, using the Positive and Negative Syndrome Scale. As expected, significant reductions in psychopathology ratings were observed after treatment (Table 2).

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**Table 1. Demographic Information for Antipsychotic-Naive Patients With First-Episode Schizophrenia and Healthy Controls**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=34)</th>
<th>Controls (n=34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, No.</td>
<td>13/21</td>
<td>13/21</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Age, y</td>
<td>24.6 (8.5)</td>
<td>25.0 (8.0)</td>
<td>.87</td>
</tr>
<tr>
<td>Education, y</td>
<td>12.1 (3.0)</td>
<td>13.4 (2.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166.4 (4.5)</td>
<td>167.8 (5.8)</td>
<td>.73</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.2 (13.1)</td>
<td>59.5 (11.2)</td>
<td>.77</td>
</tr>
<tr>
<td>Illness duration, mo</td>
<td>7.8 (12.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Clinical Symptoms in Antipsychotic-Naive Patients With First-Episode Schizophrenia Before and After 6 Weeks of Short-term Treatment With Antipsychotic Medication**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline (n=34)</th>
<th>After 6 wk (n=34)</th>
<th>Change, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global assessment of function</td>
<td>27.2 (7.4)</td>
<td>54.7 (15.4)</td>
<td>112 (80)↑</td>
<td>.001</td>
</tr>
<tr>
<td>PANSS scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>104.2 (13.9)</td>
<td>70.0 (16.3)</td>
<td>32 (15)↓</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive</td>
<td>26.9 (5.6)</td>
<td>14.3 (4.0)</td>
<td>45 (17)↓</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Negative</td>
<td>19.1 (6.2)</td>
<td>16.2 (6.1)</td>
<td>14 (21)↓</td>
<td>.001</td>
</tr>
<tr>
<td>General</td>
<td>49.9 (8.1)</td>
<td>34.9 (8.9)</td>
<td>29 (16)↓</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thought disturbance</td>
<td>14.5 (3.6)</td>
<td>8.9 (2.9)</td>
<td>42 (22)↓</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Activation</td>
<td>10.4 (2.7)</td>
<td>6.1 (1.6)</td>
<td>37 (26)↓</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paranoid</td>
<td>11.1 (2.5)</td>
<td>5.9 (2.0)</td>
<td>45 (19)↓</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression</td>
<td>9.6 (3.8)</td>
<td>7.6 (3.1)</td>
<td>15 (27)↓</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anergia</td>
<td>9.4 (4.0)</td>
<td>8.1 (3.4)</td>
<td>9 (29)↓</td>
<td>.01</td>
</tr>
<tr>
<td>Impulsive aggression</td>
<td>17.8 (5.1)</td>
<td>9.9 (2.2)</td>
<td>40 (22)↓</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: PANSS, Positive and Negative Syndrome Scale; ↑, increased; ↓, decreased.
fumurate (6 cases) at a mean (SD) dose of 495 (336.7) mg/d, sulpiride (2 cases) at 800 mg/d and 200 mg/d for each, and aripiprazole (2 cases) at 20 mg/d. Drug dosage was increased during the first 2 weeks of treatment and then held constant for 4 weeks until the follow-up scan.

Controls were scanned only once to define the range of normal function; thus, it was not possible to test for schizophrenia-specific changes between the first and second scan. However, in an independent pilot study of 18 healthy subjects scanned twice using the resting-state paradigm with a 6-week interval, we found no significant changes in ALFF or functional connectivity ("P > .05, uncorrected"). This observation is consistent with previous studies indicating a high level of consistency over time in resting-state ALFF measurements in healthy individuals.21,22

DATA ACQUISITION AND PREPROCESSING

Subjects were scanned using a 3-T magnetic resonance imaging system (EXCITE; General Electric, Milwaukee, Wisconsin). Magnetic resonance images sensitized to changes in BOLD signal levels (repetition time = 2000 milliseconds; echo time = 30 milliseconds; flip angle = 90°) were obtained with a gradient-echo echo-planar imaging sequence with a slice thickness of 5 mm (no slice gap), 64 × 64 matrix size, and a field of view of 240 × 240 mm², resulting in a voxel size of 3.75 × 3.75 × 5 mm³. Each brain volume comprised 30 axial slices and each functional run contained 200 image volumes.

Functional image preprocessing was carried out using Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neurosciences, London, England; http://www.fil.ion.ucl.ac.uk) including slice timing, realignment, and normalization to the Montreal Neurological Institute echo-planar imaging template (each voxel was resampled to 3 × 3 × 3 mm³). For the patients' follow-up scans, functional images were coregistered to baseline images before being normalized. Analysis of head motion parameters in SPM2 did not reveal differences in motion correction parameters between the control group (mean [SD], 0.32 [0.15] mm for translation, 0.35° [0.16°] for rotation) and the patient group (mean [SD], before treatment: 0.39 [0.13] mm for translation, 0.41° [0.12°] for rotation; after treatment: 0.36 [0.17] mm for translation, 0.4° [0.16°] for rotation) or between baseline and after treatment scans in the patient group ("P > .05").

ALFF CALCULATION

The amplitude of low-frequency fluctuations was calculated using REST software (http://www.restfmri.net/forum/rest_v11) with an approach similar to that used in an earlier study.21,22 In brief, after bandpass filtering (0.01-0.08 Hz)23 and linear-trend removal, the time series were transformed to the frequency domain using fast Fourier transform (parameters: taper percentage = 0, fast Fourier transform length = shortest) and the power spectrum was obtained. Since the power of a given frequency is proportional to the square of its amplitude in the original time series, the power spectrum obtained by fast Fourier transform was square root transformed and then averaged across 0.01 to 0.08 Hz to yield a measure of ALFF from each voxel. For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF value for the entire brain. Then, for each seed, we obtained an R value map, ie, a functional connectivity map between the seed to all other brain voxels. The resultant R value maps were transformed to z values using the Fisher R to z transformation to improve normality, and then spatial smoothing was applied with an 8-mm³ full-width half-maximum gaussian kernel.

FUNCTIONAL CONNECTIVITY ANALYSES

Functional connectivity was first examined using a seed voxel correlation analysis.5,11 As discussed later, significant changes in ALFF measurements after treatment were demonstrated in 9 brain regions (Table 3). These 9 regions were used as seeds for functional connectivity analysis. For these analyses, the time series of raw functional magnetic resonance imaging (fMRI) data for each voxel was temporally bandpass filtered (0.01-0.08 Hz). Then, for each seed, a reference time series was extracted by averaging the filtered fMRI time series of all voxels in each of the 9 regions showing significant change in ALFF values from pretreatment to posttreatment. Correlation analysis was carried out between each of these 9 time series and the filtered time series in the rest of the brain in a voxel-wise manner. We removed components with high correlation to cerebrospinal fluid or white matter or with low correlation to gray matter, which are thought to be associated with artifacts such as cardiac-induced24 or respiratory-induced variations.25 For each seed, we obtained an R value map, ie, a functional connectivity map of the seed to all other brain voxels. The resultant R value maps were transformed to z values using the Fisher R to z transformation to improve normality, and then spatial smoothing was applied with an 8-mm³ full-width half-maximum gaussian kernel.

In addition to the seed voxel correlation approach, functional connectivity was also characterized using an ICA of spatially independent resting-state components.27 After routine image normalization to Montreal Neurological Institute space and spatial smoothing with an 8-mm³ full-width half-maximum gaussian kernel, the same data used for the seed voxel analyses were analyzed separately for the patients at pretreatment and posttreatment and for the healthy controls using the infomax algorithm.26 First, principal component analysis was used to estimate the number of components in the combined data sets of controls and pretreatment

Table 3. Regions That Showed Significant Changes in ALFF Values Between Patients and Controls and Between Baseline and Posttreatment Measurements in Patients With Schizophrenia

<table>
<thead>
<tr>
<th>P Value Corrected</th>
<th>Talairach Coordinates, mm</th>
<th>No. of Voxels</th>
<th>Brain Region</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>.05</td>
<td>-9 49 -20</td>
<td>151</td>
<td>Ventral medial front cortex (BA 11)</td>
<td>R and L</td>
</tr>
<tr>
<td>.03</td>
<td>-21 1 15</td>
<td>150</td>
<td>Putamen</td>
<td>L</td>
</tr>
<tr>
<td>.02</td>
<td>12 18 5</td>
<td>37</td>
<td>Caudate</td>
<td>R</td>
</tr>
<tr>
<td>&lt;.001</td>
<td>30 17 49</td>
<td>Middle frontal gyrus (BA 8)</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>&lt;.001</td>
<td>53 -50 47</td>
<td>233</td>
<td>Inferior parietal gyrus (BA 40)</td>
<td>R</td>
</tr>
<tr>
<td>&lt;.001</td>
<td>-30 -70 50</td>
<td>142</td>
<td>Superior parietal lobe (BA 7)</td>
<td>L</td>
</tr>
<tr>
<td>&lt;.001</td>
<td>3 47 14</td>
<td>110</td>
<td>Medial frontal cortex (BA 10)</td>
<td>R</td>
</tr>
<tr>
<td>&lt;.001</td>
<td>-42 41 -2</td>
<td>149</td>
<td>Medial frontal cortex (BA 10)</td>
<td>L</td>
</tr>
<tr>
<td>&lt;.001</td>
<td>50 35 7</td>
<td>117</td>
<td>Inferior frontal gyrus (BA 45)</td>
<td>L</td>
</tr>
<tr>
<td>&lt;.001</td>
<td>-18 37 48</td>
<td>55</td>
<td>Superior frontal gyrus (BA 8)</td>
<td>L</td>
</tr>
<tr>
<td>&lt;.001</td>
<td>-42 5 -13</td>
<td>67</td>
<td>Superior temporal gyrus (BA 38)</td>
<td>R</td>
</tr>
</tbody>
</table>

Abbreviations: ALFF, amplitude of low-frequency fluctuations; BA, Brodmann area; L, left; R, right.
The primary analyses involved a comparison of patients before and after treatment in terms of (1) regional cerebral ALFF values, (2) functional connectivity between different regions by the seed voxel method, and (3) functional connectivity within neural networks evaluated by ICA. Secondary analyses compared pretreatment and posttreatment patient data separately with data from healthy subjects tested at 1 point on each of the earlier-mentioned indices. These analyses were performed across the whole brain using 2-sample t tests as implemented in SPM2 software. Inferences were made with a statistical threshold of $P < .05$ (corrected with familywise error). Two correlation analyses were performed: (1) ALFF values in regions where changes were observed after treatment were correlated with psychopathology ratings before and after treatment and (2) ALFF values in these regions were also correlated with connectivity z scores in areas with significant connectivity alterations. The statistical threshold for these exploratory analyses was set at $P < .05$ (2-tailed), with Bonferroni correction. Coordinates are reported in Talairach space after conversion from Montreal Neurological Institute space using mni2tal (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

**RESULTS**

**REGIONAL CEREBRAL FUNCTION**

After treatment, ALFF in patients increased significantly relative to pretreatment in the right middle frontal gyrus, right inferior parietal lobule, left superior parietal lobule, right medial frontal cortex, left medial frontal cortex, right inferior frontal gyrus, left superior frontal gyrus, left superior temporal gyrus, and right caudate (Table 3 and Figure 1). These increases in ALFF were significantly intercorrelated across regions and significantly correlated with clinical improvement in positive but not negative symptoms (Table 4). Because auditory hallucinations have been associated with neuronal abnormalities in the left superior temporal gyrus, we correlated the ALFF in this region with the Positive and Negative Syndrome Scale P3 hallucination scores before and after treatment and (2) ALFF values in these regions were also correlated with connectivity z scores in areas with significant connectivity alterations. The statistical threshold for these exploratory analyses was set at $P < .05$ (2-tailed), with Bonferroni correction. Coordinates are reported in Talairach space after conversion from Montreal Neurological Institute space using mni2tal (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

To explore the effect of risperidone monotherapy, we repeated these analyses comparing patients ($n = 12$) who received risperidone monotherapy against 12 controls matched for age, sex, height, weight, and years of education. Patients who received risperidone monotherapy showed increased ALFF after treatment, relative to pretreatment measurements, in the bilateral insula, putamen, ventromedial prefrontal cortex, and superior temporal gyrus. There was no difference between this subgroup of patients at baseline and controls in ALFF measurements; however, after 6 weeks of treatment, these
network, and medial frontal areas) connectivity com-
ventromedial frontal network, the so-called default mode
temporal network) and decreased (within the temporal-
tal cortex, and right caudate to medial frontal lobe. 

patients showed decreased connectivity compared with 
controls in the right middle frontal gyrus, right inferior 
parietal lobule, right medial frontal cortex, left medial 
cortex, right inferior frontal gyrus, left superior temporal 
gyrus, and right caudate) and a number of cortical and subcor-
tical regions (Figure 2). Reductions in functional con-
nectivity after treatment were correlated with the 
increases in ALFF values in all seed areas (P < .05, cor-
corrected), but not with changes in psychopathology rat-
ings. In the seed voxel connectivity analyses, there was 
no significant difference in connectivity between con-
trols and patients at baseline, but after treatment, 
patients showed decreased connectivity compared with 
controls in the right middle frontal gyrus to right tem-
poral cortex, right inferior parietal lobule to cingulate 
cortex, right medial frontal cortex to left frontal lobe 
and right caudate, left medial frontal cortex to left fron-
tal lobe, left superior temporal gyrus to medial frontal 
cortex, and right caudate to medial frontal lobe. 

Independent component analysis of functional con-
nectivity at pretreatment baseline indicated that pa-
tients showed both increased (within the frontoparietal-
temporal network) and decreased (within the temporal-
ventromedial frontal network, the so-called default mode 
network, and medial frontal areas) connectivity com-
pared with controls (Figure 3). After treatment, patients 
showed reduced connectivity relative to their pretreat-
ment baseline in 4 networks including the temporal-
parietal, the occipital-basal ganglia, the precuneus-basal 
ganglia, and the network between the regions of the default 
mode and medial frontal areas (Figure 3). Patients who re-
cieved risperidone monotherapy also showed signifi-
cantly decreased functional connectivity after treatment 
in the ventromedial prefrontal cortex to temporal cortex and 
parietal lobule, medial frontal cortex to middle frontal gy-
rus and putamen, superior temporal gyrus to medial fron-
tal cortex, and caudate to medial frontal lobe relative to pre-
treatment values and controls. Findings from the exploratory 
analysis of the subsample of patients who received risperi-
done monotherapy are available at http://www.hmrrc.org .cn/schizophrenia.pdf.

Table 4. Association of Changes in Regional ALFF With 
Change in Clinical Symptoms in First-Episode Schizophrenia 
Patients After Treatment

<table>
<thead>
<tr>
<th>Areas (Gyrus)</th>
<th>RMF</th>
<th>RIF</th>
<th>LSP</th>
<th>RMeF</th>
<th>LPF</th>
<th>RIF</th>
<th>LSF</th>
<th>LST</th>
<th>RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAF PANSS scores</td>
<td>+a</td>
<td>+a</td>
<td>+b</td>
<td>+a</td>
<td>+a</td>
<td>+a</td>
<td>+a</td>
<td>+a</td>
<td>+a</td>
</tr>
<tr>
<td>Total Positive</td>
<td>_a</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
</tr>
<tr>
<td>Negative General</td>
<td>_a</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
</tr>
<tr>
<td>TD</td>
<td>_b</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
</tr>
<tr>
<td>Activation</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
</tr>
<tr>
<td>Paranoid</td>
<td>_b</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
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<tr>
<td>Depression Anergia</td>
<td>_a</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_b</td>
<td>_a</td>
<td>_a</td>
<td>_a</td>
</tr>
</tbody>
</table>

Abbreviations: ALFF, amplitude of frequency fluctuations; GAF, global assessment of function; IA, impulsive aggression; LPF, left prefrontal lobe; LSF, left superior temporal gyrus; LSP, left superior parietal lobule; LST, left superior temporal gyrus; PANSS, Positive and Negative Syndrome Scale; RC, right caudate; RIF, right inferior frontal gyrus; RIF, right inferior parietal lobule; RMeF, right medial frontal lobe; RMF, right middle frontal gyrus; TD, thought disturbance; −, negative correlation; +, positive correlation. 

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temporal–ventromedial frontal networks) connectivity compared with controls (Figure 3). After treatment, frontoparietal-temporal and temporal–ventromedial frontal network connectivity was no longer significantly different from controls, while the default mode–medial frontal network abnormality remained unchanged (Figure 3).

CHANGES IN REGIONAL CEREBRAL FUNCTION

Prior resting-state studies of cerebral blood flow and metabolism have reported inconsistent effects of antipsychotic treatment including increased\textsuperscript{33-39} and decreased\textsuperscript{35,36,39,40} metabolism or blood flow in the basal ganglia and frontal and temporal cortex. The inconsistency of these results may be due to the small sample size in many prior studies. Using rsfMRI in a relatively large cohort of antipsychotic-naive patients with schizophrenia, our study demonstrated increased coherent neural activity within neocortical and striatal areas after short-term medication treatment. One neocortical area where we observed significantly increased regional synchronous activity after treatment was in the bilateral parietal lobe. Previous morphometry and functional studies\textsuperscript{41-43} have reported parietal lobe deficits in schizophrenia, which are believed to have implications for deficits in visual attention and working memory. Thus, enhanced function in this brain area may be associated with treatment-related improvements in these functions.

Regional changes in resting coherent activity were associated with reduction of psychotic symptoms, and the striatum was the only area after treatment with increased ALFF levels relative to controls. Studies with positron emis-

Figure 2. Illustration of widespread decreased functional connectivity (blue arrows) in patients after 6 weeks of treatment compared with baseline involving areas with functional alterations (yellow circles) with other cortical and subcortical areas (red circles) ($P<.05$, corrected for multiple comparisons). BA indicates Brodmann area; CC, anterior cingulate cortex; IFG, inferior frontal gyrus; IP, inferior parietal lobule; L, left; MEFC, medial frontal cortex; MF, middle frontal gyrus; MTG, middle temporal gyrus; PF, prefrontal cortex; PH, parahippocampus; R, right; SF, superior frontal gyrus; STG, superior temporal gyrus; and TL, temporal lobe.
sion tomography have revealed strong correlations between the occupancy of dopamine D₂ receptors in the striatum and reductions in positive symptoms. While the neurochemical mechanisms underlying ALFF changes in the present study remain to be established, one possibility is that D₂ receptor effects of antipsychotic drugs on the striatum may serve to organize and modulate thalamocortical drive to alter neocortical function and reduce psychotic symptoms. Both typical and atypical antipsychotics act as dopamine D₂ receptor antagonists and, as such, tend to increase glutamate levels via corticostriate projection fibers. Though the exact mechanism of how antipsychotic drugs elevate glutamate levels is not known, several studies in schizophrenia indicate such increases are...
associated with antipsychotic drug efficacy. Because glutamatergic synapses are the key excitatory synapses within the brain, increased glutamatergic function would be expected to lead to increased local neural activity, as is indicated by the ALFF increases observed in the present study after treatment. Antipsychotic drugs also modulate cortical γ-aminobutyric acid neurons, an effect that is believed to be an indirect effect secondary to their effects on dopamine and serotonin receptors. Enhancing γ-aminobutyric acid tone can increase regionally synchronized neuronal activity, especially gamma band power, which has been found to correlate with ALFF.

Decreased regional ALFF in antipsychotic-naive patients with schizophrenia was only observed prior to treatment in the ventromedial prefrontal cortex, and the functional integration of this region was also found to be abnormal. Hypofrontality in terms of decreased cerebral blood flow or glucose metabolic rate in the frontoal cortex of patients with untreated schizophrenia has been reported in several studies but not all brain imaging studies. Moreover, lower rates of glucose metabolism (especially in prefrontal areas) are generally correlated with negative symptoms and poorer cognitive performance. Potential causes of hypofrontality in schizophrenia include a generalized mitochondrial (energy) dysfunction and deficits in glucose metabolism that may interact with neurodevelopmental alterations in prefrontal systems. More work is needed to identify the biochemical mechanisms that contribute to systems-level alterations and to treatment effects as observed in the present study.

ALTERATIONS IN NETWORK-LEVEL BRAIN FUNCTION

Patterns of resting-state connectivity are a direct result of the anatomical and functional architecture of the brain. The role of medication in modulating functional connectivity during the resting state is largely unexplored with the exception of very few studies on antidepressants, cocaine, and methylphenidate. Alteration of functional connectivity in schizophrenia has attracted interest as a potential systems-level substrate of the disorder. Using rsfMRI, previous studies reported alterations of functional connectivity in patients with schizophrenia. Decreased frontotemporal, frontocingulate, and frontothalamic connectivity have been reported; however, these findings have not been consistent. Furthermore, because regional changes in resting brain physiology are known to occur after antipsychotic treatment, findings from previous studies of treated patients with schizophrenia may have been affected by antipsychotic medication as well as direct illness effects on brain function. To our knowledge, the present study provides the first examination of alterations in resting-state functional connectivity after short-term treatment of antipsychotic-naive patients with second-generation antipsychotic medication. Both the seed voxel method and ICA functional connectivity analysis provided convergent results indicating attenuation of functional connectivity in widely distributed neural networks after second-generation antipsychotic treatment. The subgroup of patients who received risperidone monotherapy also showed widespread decreased functional connectivity. Among regions with decreased functional connectivity after treatment, some showed abnormally increased connectivity before treatment vs controls, while others did not. Thus, some of these changes normalized function, while others shifted brain network function away from normal patterns of functional connectivity.

The pattern of increased ALFF together with reduced network-level connectivity provides important new insights into the effects of second-generation antipsychotic medications on functional brain systems. Importantly, decreased connectivity was correlated with increased regional function (ALFF values) after treatment. This inverse relationship indicates that increased coherent resting-state activity within several brain regions after treatment was associated with a parallel reduction rather than enhancement in the coherence of activity across these brain regions. The enhancement of ALFF seems likely to be a beneficial effect of treatment in reflecting the ability of neurons in a region to function in a synchronous state, as reflected in the significant positive correlation of ALFF and clinical change after treatment. In previous studies, ALFF has been correlated with activity in gamma band power, which reflects increased regionally synchronized neuronal activity and is associated with the capacity of higher cognitive functions. The increases in ALFF after treatment could reflect an enhanced ability of regional neuron populations to synchronously function, or potentially a reduced randomness of regional neuronal activity that could interfere with psychological processes.

From a network perspective, treatment resulted in a reduction of the integration of synchronous activity across brain networks, reflected in the attenuation of functional connectivity. It is less clear and more complex to determine whether this reduced connectivity is beneficial. Antipsychotic treatment shifted activity in some neuronal circuits showing abnormal function before treatment toward more normal function, ie, between the right frontoparietal and temporal cortex. By ICA, this connectivity was higher in antipsychotic-naive patients with schizophrenia before treatment than in controls. After treatment, this connectivity decreased significantly relative to pretreatment levels and was no longer abnormal compared with controls. However, the impact of medication in reducing neural network integration appeared rather nonspecific, also affecting networks where abnormal function was not observed before treatment, particularly in the frontostriatal and thalamocortical networks. While reducing abnormal connectivity in some circuits may be important therapeutically, such as in reducing or modulating thalamocortical drive, reducing functional connectivity in other circuits may contribute to some adverse effects of second-generation antipsychotics, including secondary negative symptoms and adverse changes in some complex cognitive functions including planned volitional behavior, sensorimotor processing, and certain aspects of working memory. The posttreatment alterations of ALFF and regional connectivity may be associated with a temporal reorganization of local circuit neural activity and an alteration in the temporal integration of activity across regions. Further research is needed to clarify the beneficial and adverse effects of antipsychotic medications on functional brain systems.
verse consequences of reduced functional connectivity after treatment and to determine whether the increased ALFF or decreased connectivity are sustained effects after longer-term antipsychotic treatment.

Two additional issues should be considered when interpreting the present results. First, though we temporally bandpass filtered all fMRI data (0.01-0.08 Hz), and removed components with high correlation to cerebrospinal fluid or white matter or with low correlation to gray matter, we cannot completely rule out the influence of physiological noise on our findings due to its variation over time and across subjects. Simultaneous recording of heart rate and respiratory rate and depth during fMRI scanning might help further reduce physiological noise artifacts. Nevertheless, the consistency among the resting-state connectivity patterns evidenced by the present data and other studies\textsuperscript{21,22} does reduce the concern about the magnitude of such potential artifacts. Second, there is a lack of consensus about the exact physiological nature of ALFF. Though ALFF is thought to reflect spontaneous neural activity,\textsuperscript{5} its exact basis remains to be fully characterized.

Overall, the current study revealed that short-term antipsychotic treatment in schizophrenia leads to increased regional synchronous neural activity while at the same time causing attenuated functional integration across widely distributed neural networks. These findings provide new insight into neural system effects of antipsychotic medication. Longer-term follow-up of patients with first-episode schizophrenia may help clarify how alterations in brain function evolve over time in schizophrenia and how these relate to the emergence of treatment resistance, persistent functional disability, and recovery of function in some individuals. Lastly, findings from the present study offer promise that novel neuroimaging approaches have the longer-term potential to provide useful biomarkers for both investigating mechanistic aspects of drug therapy and for tracking drug effects clinically to optimize and individualize patient care.

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Author Affiliations: Huaxi MR Research Center, Department of Radiology (Drs Lui, Wu, Tang, Yue, Huang, and Gong), and Department of Psychiatry and Psychiatric Laboratory (Drs Li, Deng, and Jiang), State Key Lab of Biotherapy, West China Hospital of Sichuan University, Chengdu, and Neuropsychology and Applied Cognitive Neuroscience Laboratory, Institute of Psychology, Chinese Academy of Sciences, Beijing (Prof Chan); Center for Cognitive Medicine, University of Illinois at Chicago, Chicago (Prof Sweeney); Olin Neuropsychiatry Research Center, Institute of Living, Hartford (Mr Meda and Prof Pearlson), and Department of Psychiatry, Yale University School of Medicine, New Haven (Prof Pearlson), Connecticut; and Section of Neuroimaging, Division of Psychological Medicine, Institute of Psychiatry King’s College London, London, England (Drs Li and Mechelli and Prof Collier).

Correspondence: Qiyong Gong, MD, PhD, Department of Radiology, West China Hospital, Chengdu 610041, China (qiyonggong@hwrcc.org.cn) or Tao Li, MD, PhD, Department of Psychiatry, West China Hospital, Chengdu 610041, China (xuntao26@hotmail.com).

Author Contributions: Drs Lui and Deng contributed to this work equally. Drs Lui, Gong, Li, and Deng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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