ORIGINAL ARTICLE

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

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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.[1,2] 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[3] associated with cognitive activation paradigms and is relatively easy to implement in clinical studies.[4] 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-

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

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

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

Characteristic	Mean (SD)			*P* Value
	Baseline (n=34)	After 6 wk (n=34)	Change, %	
Global assessment of function	27.2 (7.4)	54.7 (15.4)	112 (80)↑	<.001
PANSS scores				
Total	104.2 (13.9)	70.0 (16.3)	32 (15)↓	<.001
Positive	26.9 (5.6)	14.3 (4.0)	45 (17)↓	<.001
Negative	19.1 (6.2)	16.2 (6.1)	14 (21)↓	.001
General	49.9 (8.1)	34.9 (8.9)	29 (16)↓	<.001
Thought disturbance	14.5 (3.6)	8.0 (2.9)	42 (22)↓	<.001
Activation	10.4 (2.7)	6.1 (1.6)	37 (26)↓	<.001
Paranoid	11.1 (2.5)	5.9 (2.0)	45 (19)↓	<.001
Depression	9.6 (3.8)	7.6 (3.1)	15 (27)↓	<.001
Anergia	9.4 (4.0)	8.1 (3.4)	9 (29)↓	.01
Impulsive aggression	17.6 (5.1)	9.9 (2.2)	40 (22)↓	<.001

Abbreviations: PANSS, Positive and Negative Syndrome Scale; ↑, increased; ↓, decreased.

tions in neurophysiological, hemodynamic, and metabolic parameters.[5] For example, flow-sensitive imaging in human subjects reveals fluctuations in cerebral blood flow with similar spatial patterns to those seen with rfMRI.[6] Because BOLD signals are thought to reflect primarily dendritic potentials related to synaptic activity,[7] rfMRI measurements are thought to reflect spontaneous neural function. Using rfMRI, 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.[8] This network is hypothesized to be associated with the monitoring of internal thoughts and feelings[9] and has been shown to be affected in a number of neuropsychiatric conditions, including Alzheimer disease[10] and schizophrenia,[11] and after acute psychological trauma.[12]

Resting-state functional magnetic resonance imaging can provide 2 distinct types of information about brain function. Both animal[13] and human[14,15] 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 local activity across brain regions, which can have utility for advancing understanding of dysfunctions in integrated brain networks involved in schizophrenia.[16]

Prior studies have combined rfMRI with measures of functional connectivity to examine chronic[17] and first-episode schizophrenia[4,18,19]; however, only one of them[4] used rfMRI in a large cohort of antipsychotic-naive patients and none of them examined rfMRI 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 rfMRI 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).

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.[20] As expected, significant reductions in psychopathology ratings were observed after treatment (**Table 2**).

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 disorder, 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

fumarate (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 mm^2, resulting in a voxel size of $3.75 \times 3.75 \times 5$ mm^3. 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 Neuroscience, 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 $3 \times 3 \times 3$ mm^3). 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 before 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.[12,23] In brief, after bandpass filtering (0.01-0.08 Hz)[24] 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 to standardize data across subjects analogous to approaches used in positron emission tomography studies,[8] and then a spatial smoothing transformation was conducted with an 8-mm^3 full-width half-maximum gaussian kernel.

FUNCTIONAL CONNECTIVITY ANALYSES

Functional connectivity was first examined using a seed voxel correlation approach.[4,12] As discussed later, significant change in ALFF measurements after treatment was 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 voxelwise 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-induced[25] or respiratory-induced variations.[26] 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-mm^3 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-mm^3 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.[28] 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

P Value Corrected	Talairach Coordinates, mm			No. of Voxels	Brain Region	Side
	x	y	z			
Baseline: Patients < Controls						
<.001	−9	49	−20	151	Ventral medial frontal cortex (BA 11)	R and L
Patients: Week 6 of Treatment > Controls						
<.001	−21	1	15	150	Putamen	L
.03	12	12	9	26	Caudate	R
Patients: Week 6 of Treatment > Baseline						
.006	30	17	49	43	Middle frontal gyrus (BA 8)	R
<.001	53	−50	47	233	Inferior parietal lobule (BA 40)	R
<.001	−30	−70	50	142	Superior parietal lobule (BA 7)	L
<.001	3	47	14	110	Medial frontal cortex (BA 10)	R
<.001	−42	41	−2	149	Medial frontal cortex (BA 10)	L
<.001	50	35	7	117	Inferior frontal gyrus (BA 45)	R
.001	−18	37	48	55	Superior frontal gyrus (BA 8)	L
<.001	−42	5	−13	67	Superior temporal gyrus (BA 38)	L
.02	12	18	5	37	Caudate	R

Abbreviations: ALFF, amplitude of low-frequency fluctuations; BA, Brodmann area; L, left; R, right.

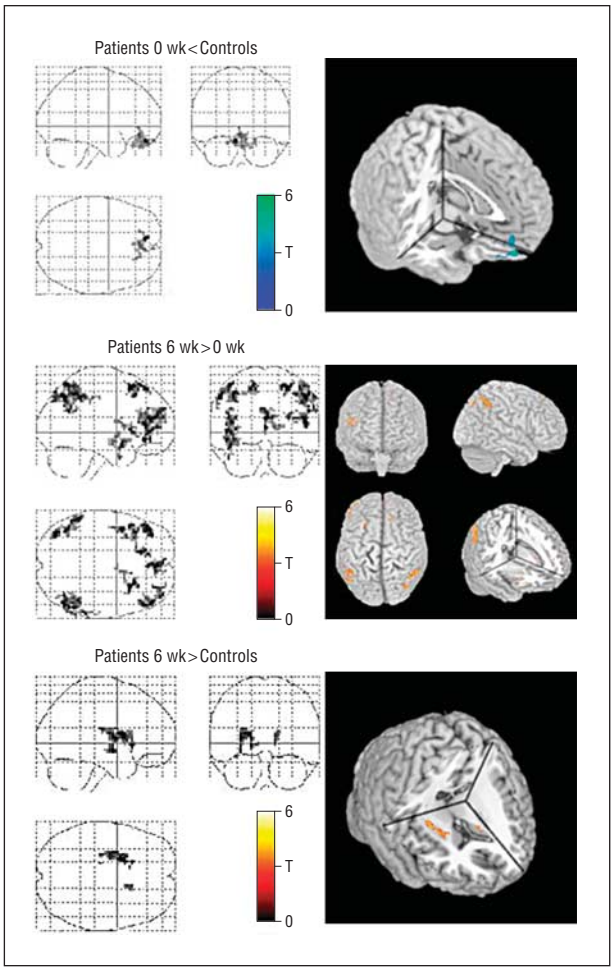

Figure 1. Glass brain images (left panels) and rendered images (right panels) showing results of the amplitude of low-frequency fluctuations (ALFF) analysis. Upper panels: compared with normal controls, patients at baseline showed significantly decreased (blue) ALFF only in the bilateral ventral medial frontal cortex. Middle panels: compared with baseline, patients after 6 weeks of antipsychotic treatment showed significantly increased (red) ALFF in several regions, mainly in the bilateral prefrontal and parietal lobes, left superior temporal gyrus, and right caudate. Lower panels: compared with controls, patients after 6 weeks of treatment showed significantly increased (red) ALFF in the right caudate and left putamen. All analyses were corrected for multiple comparisons. T indicates treatment.

patients, resulting in 23 components. Then, data from all subjects were decomposed into the 23 components using GIFT software (version 1.3e; The MathWorks, Natick, Massachusetts, http://icatb.sourceforge.net/). A systematic process was used to inspect and select components of interest.[29] Components with high correlation to cerebrospinal fluid or white matter, or with low correlation to gray matter, were excluded as reflecting patterns unrelated to neural activity. This left 11 components of interest for further analysis. The ICA algorithm evaluates the degree to which synchronous activity occurs across spatially independent, widely distributed brain regions.[30] This was evaluated by computing a constrained maximal lagged correlation using the FNC toolbox (version 1h; The MathWorks, http://icatb.sourceforge.net/). The time courses from the 11 components were first interpolated to enable detection of sub–repetition time hemodynamic delay differences in patients with schizophrenia.[31] The maximal lagged correlation was then examined between all pairwise combinations from the $11!/(2!(11-2)!)=45$ possible combinations. The 45 pairwise intercorrelations were averaged separately for control and pretreatment and posttreatment patient data. We then compared the correlations in the patient group before and after treatment and subsequently compared the pretreatment and posttreatment patient data with correlations in the control group.

STATISTICAL ANALYSIS

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,[32] we correlated the ALFF in this region with the Positive and Negative Syndrome Scale P3 hallucination scores but found no significant relationship ($r=-0.18$, $P=.15$). No areas with significantly decreased ALFF were found in patients after treatment. Relative to controls, patients showed decreased ALFF in the bilateral ventromedial frontal cortex at baseline and increased ALFF in the right caudate and left putamen after treatment (Table 3 and Figure 1).

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

patients showed increased ALFF relative to controls in the bilateral insula, putamen, caudate, ventromedial prefrontal cortex, and superior temporal gyrus. The findings from this exploratory analysis are available at http://www.hmrrc.org.cn/schizophrenia.pdf.

NEURAL NETWORK FUNCTION

To characterize the impact of regional increases in ALFF on the functional connectivity of regions where significant changes in ALFF values were observed, the 9 areas where ALFF values increased after treatment (Table 3) were used as seeds in a functional connectivity analysis. After 6 weeks of antipsychotic treatment, relative to pretreatment baseline, there was significantly reduced functional connectivity between 7 seeds (right middle frontal gyrus, right inferior parietal lobule, right medial frontal cortex, left medial frontal cortex, right inferior frontal gyrus, left superior temporal gyrus, and right caudate) and a number of cortical and subcortical regions (**Figure 2**). Reductions in functional connectivity after treatment were correlated with the increases in ALFF values in all seed areas ($P<.05$, corrected), but not with changes in psychopathology ratings. In the seed voxel connectivity analyses, there was no significant difference in connectivity between controls and patients at baseline, but after treatment, patients showed decreased connectivity compared with controls in the right middle frontal gyrus to right temporal 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 frontal lobe, left superior temporal gyrus to medial frontal cortex, and right caudate to medial frontal lobe.

Independent component analysis of functional connectivity at pretreatment baseline indicated that patients 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 compared with controls (**Figure 3**). After treatment, patients showed reduced connectivity relative to their pretreatment 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 received risperidone monotherapy also showed significantly decreased functional connectivity after treatment in the ventromedial prefrontal cortex to temporal cortex and parietal lobule, medial frontal cortex to middle frontal gyrus and putamen, superior temporal gyrus to medial frontal cortex, and caudate to medial frontal lobe relative to pretreatment values and controls. Findings from the exploratory analysis of the subsample of patients who received risperidone 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

Areas (Gyrus)	RMF	RIP	LSP	RMeF	LPF	RIF	LSF	LST	RC
GAF		+[a]	+[b]	+[a]	+[a]	+[a]		+[a]	
PANSS scores									
Total		–[a]	–[b]	–[a]	–[a]	–[a]			
Positive	–[a]	–[a]	–[b]	–[b]	–[b]	–[b]	–[a]	–[b]	–[a]
Negative									
General	–[a]	–[a]	–[b]		–[a]	–[b]			
TD			–[b]	–[a]	–[b]	–[a]		–[a]	
Activation	–[a]	–[b]	–[b]	–[a]	–[b]	–[b]	–[a]	–[a]	
Paranoid	–[b]	–[a]	–[b]	–[b]	–[b]	–[b]	–[a]	–[a]	
Depression									
Anergia									
IA	–[a]	–[b]	–[b]	–[b]	–[b]	–[a]		–[b]	

Abbreviations: ALFF, amplitude of frequency fluctuations; GAF, global assessment of function; IA, impulsive aggression; LPF, left prefrontal lobe; LSF, left superior frontal 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; RIP, right inferior parietal lobule; RMeF, right medial frontal lobe; RMF, right middle frontal gyrus; TD, thought disturbance; –, negative correlation; +, positive correlation.

[a] $P<.05$.

[b] $P<.01$.

COMMENT

To our knowledge, this is the first longitudinal study evaluating regional and neural network function by rfMRI in antipsychotic-naive patients with schizophrenia. After 6 weeks of treatment with second-generation antipsychotic drugs, patients showed significantly increased synchronous regional brain function (ALFF values) in the resting state relative to pretreatment in the right middle frontal gyrus (Brodmann area 8), right inferior parietal lobule (Brodmann area 40), left superior parietal lobule (Brodmann area 7), right medial frontal cortex (Brodmann area 10), left medial frontal cortex (Brodmann area 10), right inferior frontal gyrus (Brodmann area 45), left superior frontal gyrus (Brodmann area 8), left superior temporal gyrus (Brodmann area 38), and right caudate. These changes were positively correlated with the degree of improvement in clinical symptoms after treatment (Table 3, Table 4, and Figure 1). In addition, both seed voxel and ICA functional connectivity analyses provided convergent evidence for an attenuating effect of short-term antipsychotic treatment on neural network integration during the resting state. Reductions in functional connectivity were negatively correlated with changes in ALFF values in all regions where ALFF values increased after treatment. These findings indicate that after short-term treatment, changes in cerebral function include increased coherent resting-state activity within several brain regions that is related to clinical recovery and to a reduced coherence of neural activity across widely distributed functional brain systems.

Comparisons with controls revealed several additional findings. First, patients showed decreased ALFF only in the ventromedial prefrontal cortex when antipsychotic naive. Second, ALFF in the right caudate and left putamen after treatment were increased above normal levels (Figure 1). Third, neural network deficits in antipsychotic-naive patients revealed by ICA functional connectivity analysis included both increased (frontoparietal-temporal networks) and decreased (default mode–medial frontal and

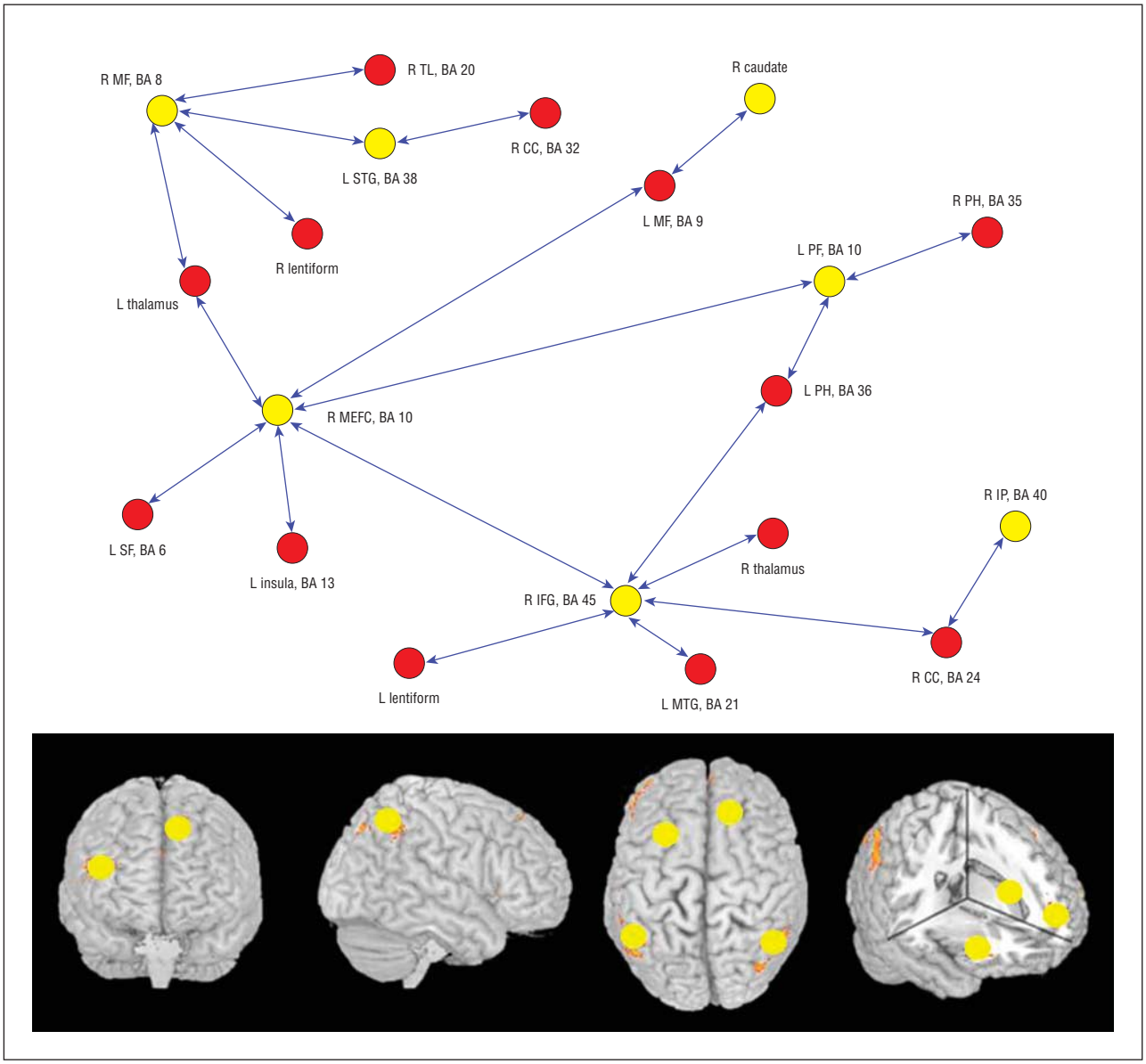

Figure 2. Illustration of widespread decreased functional connectivity (blue arrows) in patients after 6 weeks of treatment compared with baseline involving areas with functional alterations (yellow circles) with other cortical and subcortical areas (red circles) ($P<.05$, corrected for multiple comparisons). 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.

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[33-39] and decreased[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 rfMRI 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[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-

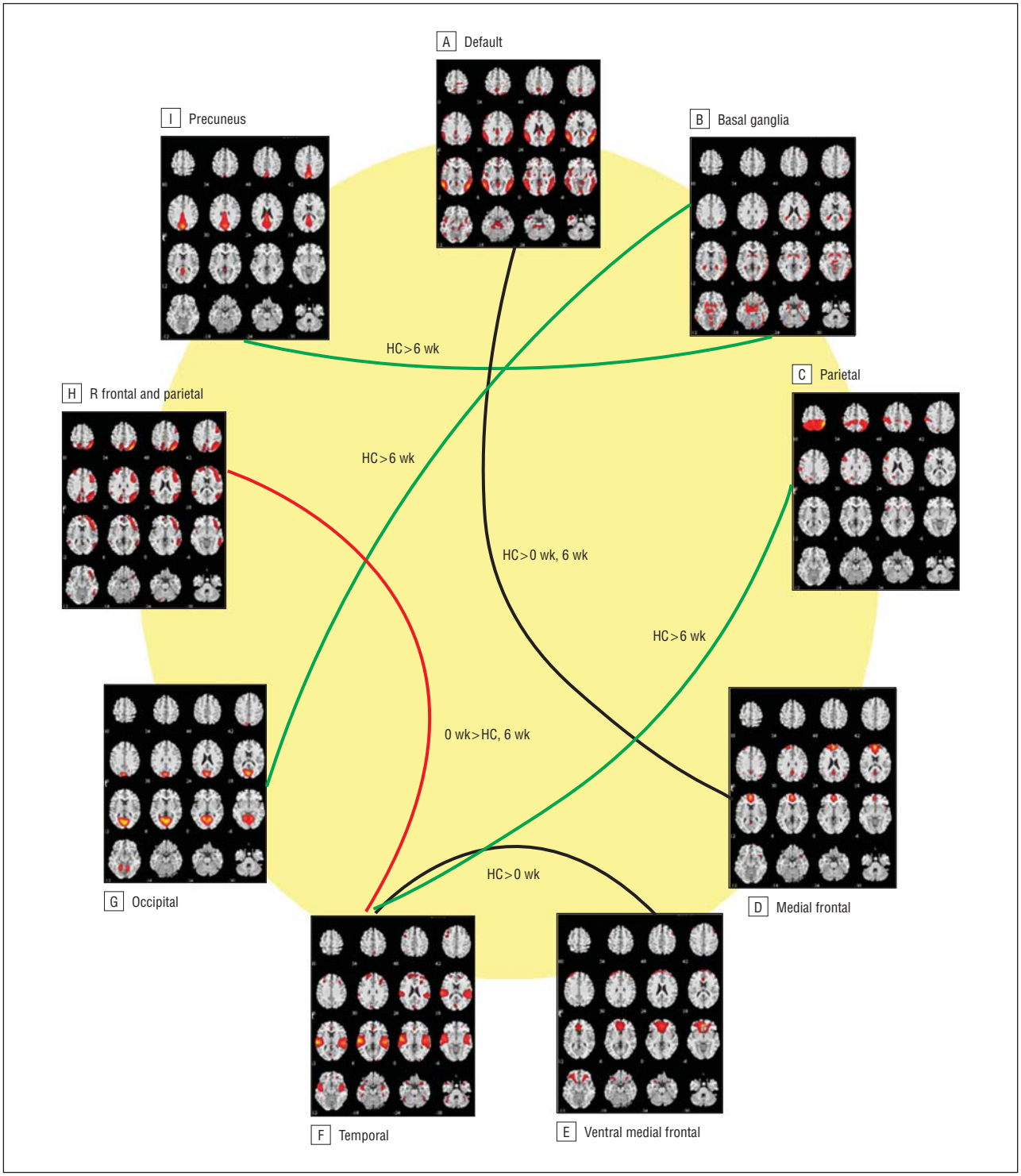

Figure 3. Significant differences of functional network connectivity between groups. The red line identifies connectivity that was abnormal at baseline and normalized after treatment. Green lines indicate connectivity that was normal at baseline and significantly decreased after treatment. Black lines identify connectivity that did not change after treatment. HC indicates healthy controls; 0 wk, patients at antipsychotic-naive state; and 6 wk, patients after 6 weeks of antipsychotic treatment.

sion tomography have revealed strong correlations between the occupancy of dopamine D_2 receptors in the striatum and reductions in positive symptoms.[44] While the neurochemical mechanisms underlying ALFF changes in the present study remain to be established, one possibility is that D_2 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 D_2 receptor antagonists and, as such, tend to increase glutamate levels via corticostriate projection fibers.[45] 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.[46] 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.[47] Enhancing γ-aminobutyric acid tone can increase regionally synchronized neuronal activity,[48] especially gamma band power,[49] which has been found to correlate with ALFF.[13]

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 frontal cortex of patients with untreated schizophrenia has been reported in several[50,51] but not all[52,53] brain imaging studies. Moreover, lower rates of glucose metabolism (especially in prefrontal areas) are generally correlated with negative symptoms[50] and poorer cognitive performance.[54] Potential causes of hypofrontality in schizophrenia include a generalized mitochondrial (energy) dysfunction[55] and deficits in glucose metabolism[56] 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.[57] The role of medication in modulating functional connectivity during the resting state is largely unexplored with the exception of very few studies on antidepressants,[58] cocaine,[59] and methylphenidate.[60] Alteration of functional connectivity in schizophrenia has attracted interest as a potential systems-level substrate of the disorder. Using rfMRI, previous studies[18,19,61] reported alterations of functional connectivity in patients with schizophrenia. Decreased frontoparietal, frontocingulate, and frontothalamic connectivity have been reported[18,19,61]; however, these findings have not been consistent. Furthermore, because regional changes in resting brain physiology are known to occur after antipsychotic treatment,[35,62] findings from previous studies of treated patients with schizophrenia[18,19,61] 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,[13] which reflects increased regionally synchronized neuronal activity and is associated with the capacity of higher cognitive functions.[49] 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,[63] sensorimotor processing,[64] and certain aspects of working memory.[65] 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 ad-

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.[66] Nevertheless, the consistency among the resting-state connectivity patterns evidenced by the present data and other studies[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,[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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