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Abnormalities of Regional Brain Activity in Patients With Schizophrenia: A Longitudinal Resting-State fMRI Study

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***Background*: Evidence from functional and structural research suggests that abnormal brain activity plays an important role in the pathophysiology of schizophrenia (SZ). However, limited studies have focused on post-treatment changes, and current conclusions are inconsistent. *Study Design*: We recruited 104 SZ patients to have resting-state functional magnetic resonance imaging scans at baseline and 8 weeks of treatment with second-generation antipsychotics, along with baseline scanning of 86 healthy controls (HCs) for comparison purposes. Individual regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), and degree centrality values were calculated to evaluate the functional activity. The Positive and Negative Syndrome Scale (PANSS) and MATRICS Consensus Cognitive Battery were applied to measure psychiatric symptoms and cognitive impairment in SZ patients. *Results*: Compared with HCs at baseline, SZ patients had higher ALFF and ReHo values in the bilateral inferior temporal gyrus, inferior frontal gyrus, and lower ALFF and ReHo values in fusiform gyrus and precuneus. Following 8 weeks of treatment, ReHo was increased in right medial region of the superior frontal gyrus (SFGmed) and decreased in the left middle occipital gyrus and the left postcentral gyrus. Meanwhile, ReHo of the right SFGmed was increased after treatment in the response group (the reduction rate of PANSS ≥50%). Enhanced ALFF in the dorsolateral of SFG correlated with improvement in depressive factor score. *Conclusions*: These findings provide novel evidence for the abnormal functional activity hypothesis of SZ, suggesting that abnormality of right SFGmed can be used as a biomarker of treatment response in SZ.**

Key words: schizophrenia/regional homogeneity/resting-state functional magnetic resonance imaging/prediction/treatment response

Introduction

Schizophrenia (SZ) is a serious psychiatric disorder that affects 1% of the world's population and the main symptoms can be classified as positive, negative, and general psychopathology symptoms.[1,2] Several hypotheses have been proposed to explain the etiology of SZ, the most widely accepted being neurodevelopmental abnormalities.[3] Evaluation of brain activity may therefore aid in clarifying the pathophysiological mechanisms underlying SZ.[4]

Resting-state functional magnetic resonance imaging (rs-fMRI) can be effectively used to assess regional brain function and functional connectivity (FC) and is readily accepted by patients with neuropsychiatric disorders since a complex experimental design is not required.[5] Regional brain function is measured by assessing the amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), and degree centrality (DC).[6–8] ALFF measures spontaneous low-frequency neural activity fluctuations in a voxel. ReHo reflects the regional homogeneity of neural activity between adjacent voxels, and DC is the most direct measure of node centrality in network analysis to portray a stable property of cortical network architecture at the voxel level. These 3 voxel-based metrics define brain functional characteristics from

different perspectives and show a progressive relationship that allows for more sensitive identification of regional abnormalities.

Many studies have reported functional changes in multiple brain regions of patients with SZ.[9,10] An earlier meta-analysis showed that in SZ, foci with decreased ALFF and ReHo in SZ were mainly located in the somatosensory, posterior parietal, and occipital cortexes. In contrast, foci with increased ALFF and ReHo were predominant in the bilateral striatum, medial temporal cortex, and medial prefrontal cortex.[11] Patients with SZ exhibit extensive emotional and cognitive dysfunction, which may be attributable to changes in brain activity. A significant correlation between abnormal local activity with the neuropathological mechanism of auditory verbal hallucination has been demonstrated.[12] The ReHo values in the right inferior frontal gyrus/insula are reported to be positively correlated with negative symptom scores and negatively correlated with Hopkins verbal learning test-revised/verbal learning.[13] However, no consensus has been reached on alterations of these indexes and their relationship with symptom changes in the disorder.[11] More importantly, the researchers also found that the specific changes in ReHo, ALFF, and DC before and after treatment may provide markers for differentiating SZ from healthy controls (HCs),[13,14] and the prediction of treatment effects.[15–17]

To date, few relevant studies have focused on the changes in local brain activities in patients with SZ after short-term treatment. Moreover, evaluation of limited sample sizes has led to inconsistent conclusions. Therefore, we propose the hypothesis that patients with SZ have abnormal local activity in multiple brain regions and exhibit corresponding clinical symptoms according to the function of this brain region. And after treatment, there may be a relationship between the improvement of brain activity and the relief of clinical symptoms.

Materials and Methods

Participants

We recruited patients with SZ between March 2021 and February 2022 from the Second Affiliated Hospital of Xinxiang Medical University, China. All HCs were enlisted from the surrounding community. The inclusion criteria were as follows: (1) age range of 18–55 years, (2) Han Chinese origin, (3) right-handed, (4) normal intelligence, and (5) diagnostic criteria were met according to structured clinical interviews for DSM-IV-TR disorders (SCID), (6) HCs and their paternal or maternal relatives within 3 generations did not meet the diagnostic criteria for Axis I disorders in DSM-IV based on SCID. The exclusion criteria were as follows: (1) severe and unstable physical symptoms and/or diabetes, thyroid disease, hypertension, and heart disease, (2) history of head injury, (3) history of epileptic seizures, (4) meeting the DSM-IV-TR diagnostic criteria for alcohol and drug dependence (methamphetamine, ketamine, and cocaine), (5) having been treated using modified electroconvulsive therapy for 1 month prior to selection, (6) having suffered or currently suffering from the neuroleptic malignant syndrome or severe tardive dyskinesia, (7) state of pregnancy or lactation, and (8) presence of implanted metal frames or electronic devices that could prevent MRI scanning. Positive and Negative Syndrome Scale (PANSS) and MATRICS Consensus Cognitive Battery (MCCB)[18] were applied to assess the symptoms and neurocognitive functioning of SZ. Five factors were derived from PANSS, specifically, positive symptoms, negative symptoms, cognition, depression, and excitement.[2] Patients were treated with second-generation antipsychotic drugs for 8 weeks before magnetic resonance reexamination, with dose and drug selection conducted by the psychiatrist. The Ethics Committee approved this study at the Second Affiliated Hospital of Xinxiang Medical University, and all patients and control subjects provided written informed consent.

Data Acquisition and Preprocessing

MRI data were acquired using a 3.0-T MR scanner (Siemens, Verio). rs-fMRI data were obtained using an echo planar imaging sequence sensitive to BOLD contrast (repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, matrix size = 64 × 64, resolution of axial slice 3.4 × 3.4 mm^2, slice thickness = 4 mm, gap between slices = 0.6 mm). Resting-state data were acquired for 8 min (240 time points).

rs-fMRI data were processed using Resting-State fMRI Data Analysis Toolkit plusv1.24 (RESTplus v1.24, http://restfmri.net/forum/restplus) using the following steps: (1) removing the first 10 time points, (2) slice-timing, (3) head motion correction, (4) spatial normalization to the Montreal Neurological Institute (MNI) space, (5) spatial smoothing with an isotropic Gaussian kernel with full width at half-maximum (FWHM) of 6 mm, (6) eliminating the linear trend of the time course, (7) regression of head motion effect, gray matter, white matter, and cerebrospinal fluid signals from the fMRI data, and (8) bandpass filtering (0.01–0.08 Hz). Participants with head motion exceeding 3 mm or rotation exceeding 3°C during scanning were excluded.

ALFF Calculation

After data preprocessing, the time course of each voxel was transformed into the frequency domain using a fast Fourier transform, and the power spectrum was subsequently obtained. The square root was calculated at each frequency of the power spectrum, and the average square root was obtained as the ALFF value in the range of 0.01–0.08 Hz for each voxel, which was further divided by the global mean ALFF of each individual for group comparison.[6]

ReHo Calculation

A single ReHo map was generated by calculating the Kendall's coefficient of concordance (KCC) of the time series of a given voxel and its nearest neighbor (26 voxels) in a voxel-wise way.[7] The formula for calculating the KCC value has been clarified in previous studies. For standardization, the ReHo value of every voxel was divided by the global mean ReHo of each individual. The spatial smoothing (FWHM = 6 mm) was performed after ReHo calculation.

DC Calculation

Pearson's correlation of time series was performed between each voxel and every other voxel in the entire brain to calculate a correlation matrix $R = (r_{ij})$, $j = 1 \ldots N$ (N is the number of voxels), $i \neq 1$. The correlation coefficients with $r_{ij} \geq 0.32$ ($P < .05$, Bonferroni-corrected over whole-brain voxels) were summed up for each voxel and then a weighted DC was obtained for each voxel. The weighted DC of each voxel was further divided by the global mean weighted DC of each individual for group comparison.[8,19]

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Science version 26.0 (SPSS 26.0). Age and years of education for the 2 groups were compared using 2-sample *t*-tests. The sex composition ratio was compared using the Pearson Chi-square test. PANSS and MCCB scores before and after treatment in the patient group were compared with paired *t*-tests. RESTplus software was employed to analyze fMRI data. ALFF, ReHo, and DC maps were compared at baseline and after treatment, respectively. Individual age, sex, and years of education were treated as covariates in the group comparison. The false discovery rate (FDR) theory was applied to correct for multiple comparisons. Significance was set at $P < .05$ (FDR corrected and cluster size >10). Partial correlation analyses with age, sex, illness duration, and years of education as covariates were conducted between change values and the change of PANSS/MCCB scores. In addition, in order to further evaluate whether the changes in brain function activity before and after treatment were related to the efficacy, SZ patients were divided into the response and nonresponse group based on the reduction rate (RR) of PANSS. Improvement in clinical symptoms was calculated by the RR of the PANSS total scores. RR ≥50% represent responders, and RR <50% represent nonresponders.[20] The clinical information of the 2 subgroups and the changes of ALFF, ReHo, and DC before and after treatment were compared.

Results

Analysis of Demographics and Clinical Characteristics

The flowchart of the study subjects is shown in figure 1. 104 SZ patients and 86 HCs were recruited for the study. Finally, 88 SZ patients and 81 HCs were included for statistical analyses. Sociodemographic and clinical data of

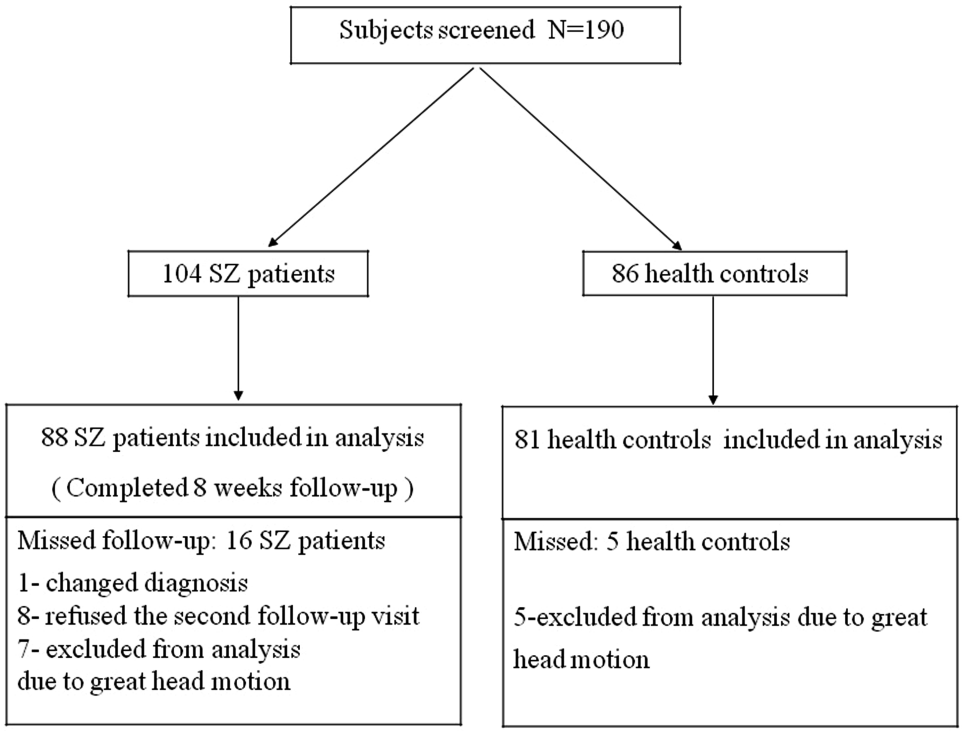

Fig. 1. Chart flow for the study subjects.

Table 1. Demographic Data and Clinical Characteristics of All Subjects

Variables	SZ (n = 88)	HC (n = 81)	$t/Z/\chi^2$	P
Age (y)	28.76 ± 8.29	30.93 ± 10.75	−0.735	.462
Sex (M/F)	38/43	47/41	0.712	.399
Education (y)	10.93 ± 3.15	13.52 ± 4.12	−4.156	.000
Disease duration (mo)	74.84 ± 65.80	N/A	N/A	N/A
Response/nonresponse	47/41	N/A	N/A	N/A
	Baseline	8 wk		
PANSS total	93.16 ± 14.99	59.83 ± 14.18	N/A	21.290	.000
PANSS positive	13.22 ± 3.97	7.20 ± 3.12	N/A	15.558	.000
PANSS negative	25.75 ± 6.25	18.35 ± 6.36	N/A	11.473	.000
PANSS cognitive	20.52 ± 4.73	14.22 ± 3.65	N/A	11.616	.000
PANSS depressive	8.35 ± 3.33	5.59 ± 2.22	N/A	9.783	.000
PANSS excitement	19.83 ± 5.59	10.39 ± 3.53	N/A	17.097	.000
TMT	72.07 ± 38.00	52.77 ± 24.03	N/A	6.500	.000
Symbol coding	37.71 ± 12.07	38.73 ± 12.60	N/A	−1.174	.243
HVLT-R	16.16 ± 6.06	20.51 ± 6.11	N/A	−8.051	.000
Spatial span	11.60 ± 3.15	12.34 ± 3.26	N/A	−2.345	.021
Mazes	7.84 ± 4.75	10.00 ± 6.12	N/A	−4.640	.000
BVMT-R	17.10 ± 8.73	21.75 ± 10.15	N/A	−4.982	.000
Category fluency	14.99 ± 5.50	17.35 ± 6.06	N/A	−3.953	.000
CPT-IP	1.28 ± 0.66	1.28 ± 0.72	N/A	−0.051	.959
Cpz (mg/d)	345.73 ± 235.49	622.64 ± 275.43	N/A	−9.026	.000

Note: Unless otherwise indicated, data are means ± SD; BVMT-R, The revised Brief Visuospatial Memory Test; CPT-IP, The Continuous Performance Test Identical Pairs; Cpz, chlorpromazine equivalents; HC, healthy control; HVLT-R, The revised Hopkins Verbal Learning Test; N/A, not applicable; PANSS, Positive and Negative Syndrome Scale; SZ, schizophrenia; TMT, trail making test.

study groups are presented in table 1. The demographic data and clinical characteristics separately for response and nonresponse group of SZ in supplementary table 1. Of the 88 patients with SZ enrolled in this study, 7 of them had not taken medication in baseline, 81 of them were adherent to second-generation antipsychotics prior to enrollment. Specific antipsychotic and comorbid medication use are shown in supplementary table 2. Antipsychotic drug doses were converted to the chlorpromazine equivalent.[21]

Abnormalities in Brain ALFF, ReHo, and DC at Baseline

Compared with HCs at baseline, SZ patients had higher ALFF values in the bilateral inferior temporal gyrus (ITG) (t = 5.570/5.274, P < .05), right orbital part of inferior frontal gyrus (ORBinf) (t = 3.803, P < .05), right amygdala (t = 4.384, P < .05), bilateral caudate (t = 5.288/7.093, P < .05), right triangular part of inferior frontal gyrus (IFGtriang) (t = 4.383, P < .05), right cerebellar hemisphere, lobule 8 (t = 4.094, P < .05), and lower ALFF values in left precentral gyrus (PreCG) (t = −3.751, P < .05), left supramarginal gyrus (t = −4.978, P < .05), right fusiform gyrus (FFG) (t = −3.581, P < .05), left precuneus (PCUN) (t = −5.747, P < .05), left superior parietal gyrus (t = −4.451, P < .05) (supplementary table 3 and supplementary figure 1).

SZ patients exhibited higher ReHo in the bilateral ORBinf (t = 5.363/3.852, P < .05), bilateral ITG (t = 5.725/4.973, P < .05), left cerebellar hemisphere, lobule 9 (t = 4.809, P < .05), right thalamus (t = 4.519, P < .05), left IFGtriang (t = 4.612, P < .05), vermis (t = 4.946, P < .05), left hippocampus (t = 4.251, P < .05), left putamen (t = 4.729, P < .05), and lower ReHo in the left ventromedial prefrontal cortex (t = −3.830, P < .05), right middle temporal gyrus (t = −4.358, P < .05), left PCUN (t = −5.570, P < .05), right inferior parietal gyrus (t = −4.557, P < .05), left supplementary motor area (t = −4.157, P < .05), left median cingulate and paracingulate gyri (t = −4.032, P < .05), and right FFG (t = −3.861, P < .05) compared with HCs (supplementary table 4 and supplementary figure 2). No regions showed significant differences between SZ and HCs in terms of DC.

Changes in Brain ALFF, ReHo, and DC After Treatment of SZ

After treatment, SZ patients showed increased ALFF in the right dorsolateral region of superior frontal gyrus (SFGdor) (t = 5.622, P < .05). Conversely, ALFF was decreased in the bilateral middle occipital gyrus (MOG) (t = −4.898/−4.745, P < .05), left paracentral lobule (t = −5.354, P < .05), light lingual (t = −4.727, P < .05), and right PreCG (t = −5.058, P < .05) (figure 2A; supplementary table 3).

Following 8 weeks of treatment, ReHo was increased in the right medial region of superior frontal gyrus (SFGmed) (t = 4.721, P < .05) and decreased in the left MOG (t = −4.922, P < .05) and the left postcentral gyrus (PoCG) (t = −5.213, P < .05) (figure 3A; supplementary table 4). In contrast, no differences in DC were observed.

Correlation Analysis Between PANSS and ALFF or ReHo

The degree of ALFF increase in SFGdor after treatment was significantly and positively related to the magnitude of decrease in depression score (r = .347, P = .001, $P_{\text{FDR-corrected}}$ = .014) (figure 2B, supplementary tables 5). Longitudinal increases of ReHo in SFGmed were negatively correlated with the change in negative scores (r = −.255, P = .019) (figure 3B), this correlation was not found when corrected by FDR (P = .266, supplementary tables 6). The remaining brain regions showing significant differences in regional activity were not correlated with changes in other subscores of PANSS (supplementary tables 5 and 6). We further performed correlation analysis between CPZ and PANSS RR, ALFF, and ReHo. There was significant negatively correlation only between CPZ and PANSS RR (r = −.355, P = .001) (supplementary table 7).

Analysis of Correlations Among MCCB, ALFF, and ReHo

The increase in ALFF in SFGdor after treatment was positively correlated with a decrease in the trail making test score to a significant extent (r = .272, P = .012) (figure 2C). A longitudinal decrease in ReHo in the left

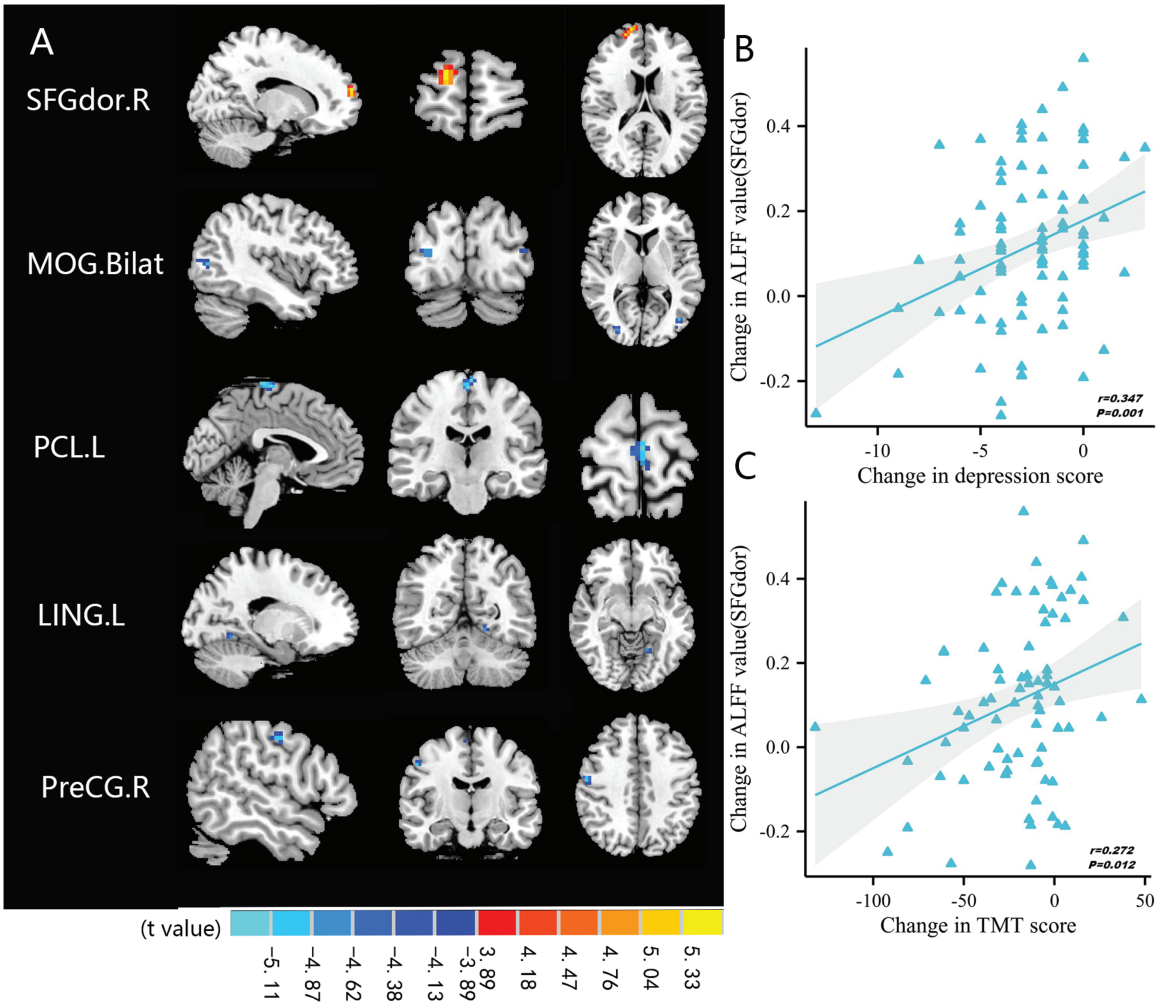

Fig. 2. Comparison and correlation results of ALFF. (A) Differences in ALFF before and after treatment (FDR-corrected P < .05). (B) After 8 weeks of treatment, altered ALFF of SFGdor.R significantly correlated with reduction in depression score. (C) After treatment, altered ALFF of SFGdor.R significantly correlated with reduction in TMT score. *Note*: ALFF, amplitude of low-frequency fluctuations; Bilat, bilateral; FDR, false discovery rate; L, left; LING, lingual; MOG, middle occipital gyrus; PCL, paracentral lobule; PreCG, precentral gyrus; R, right; SFGdor, superior frontal gyrus, dorsolateral; TMT, trail making test; Post->pretreatment in SFGdor.R; Post-<pretreatment in MOG.Bilat, PCL.L, LING.L, and PreCG.R.

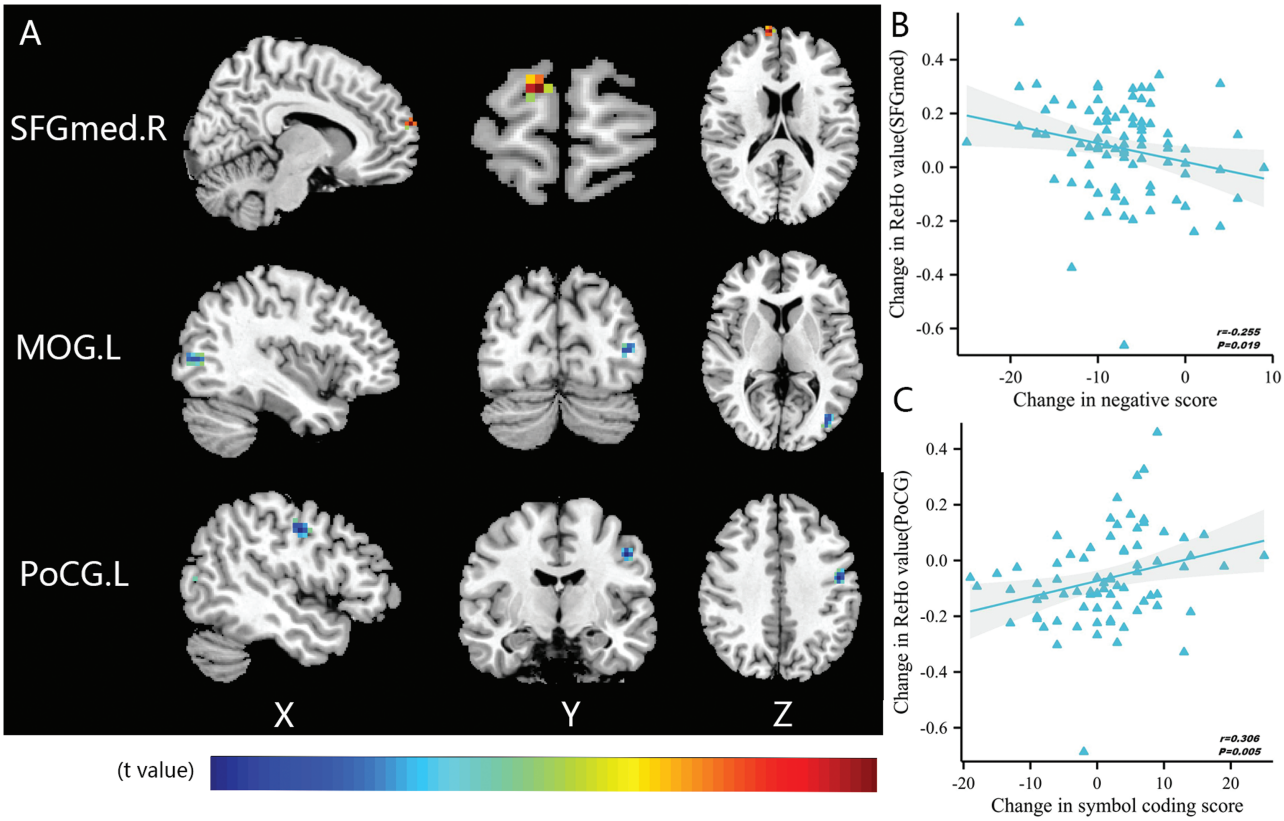

Fig. 3. Comparison and correlation results of ReHo. (A) Differences in ReHo before and after treatment (FDR-corrected $P < .05$). (B) After 8 weeks of treatment, altered ReHo of SFGmed.R significantly correlated with reduction in negative score. (C) After treatment, altered ReHo of PoCG.L significantly correlated with increase in symbol-coding score. *Note*: FDR, false discovery rate; L, left; MOG, middle occipital gyrus; PoCG, postcentral gyrus; R, right; ReHo, regional homogeneity; SFGmed, superior frontal gyrus, medial; Post->pretreatment in SFGmed.R; Post-<pretreatment in MOG.L and PoCG.L.

PoCG was positively correlated with changes in symbol-coding scores ($r = .306$, $P = .005$) (figure 3C). Those correlations were not found when corrected by FDR. No associations were observed between the remaining brain regions showing significant changes before and after treatment and changes in MCCB (supplementary tables 5 and 6).

Specific ReHo Differences Between the Response and Nonresponse Group

Eighty-eight patients with SZ were divided into the response (53.41%) and nonresponse (46.59%) group (table 1). There were significant differences in PANSS symptoms between the 2 groups after treatment ($P < .05$), but no differences in MCCB cognitive function ($P > .05$) (supplementary table 1). No significant changes were found in ALFF and DC in both groups before and after treatment ($P > .05$). We only found that the ReHo in the right SFGmed increased after treatment in the response group (cluster size = 53, $t = 5.741$, $P_{\text{un-corrected}} = .000$, $P_{\text{FDR-corrected}} = .004$, figure 4). At the same time, no such change was observed in the nonresponse group.

Discussion

In this study, we analyzed the differences in ALFF, ReHo, and DC between SZ patients and HCs at baseline and changes in SZ after treatment. Compared with ALLF and DC, the change of ReHo is closely related to antipsychotic drug treatment, and serves as a sensitive indicator of drug efficacy. We observed a marked decrease or increase in local activity of multiple brain regions at baseline and after treatment, indicating extensive alterations in SZ brain. Moreover, the present study provides novel evidence that the increased ReHo in the right SFGmed may serve as a predictor for treatment response in SZ.

We observed overlaps between brain regions with ALFF and ReHo abnormalities at baseline, including ITG, ORBinf, IFGtriang, FFG, PCUN, and cerebellar hemisphere. Those findings provided complementary information on regional spontaneous brain activity, further validating the results.[22,23] Brain activity changes in the frontal and temporal lobe regions are common in patients with SZ.[24] Altered temporal lobe function is associated with hallucinations and delusional symptoms in SZ.[25] ITG and FFG have long been associated with object and face/body recognition,[26,27] and changes in these

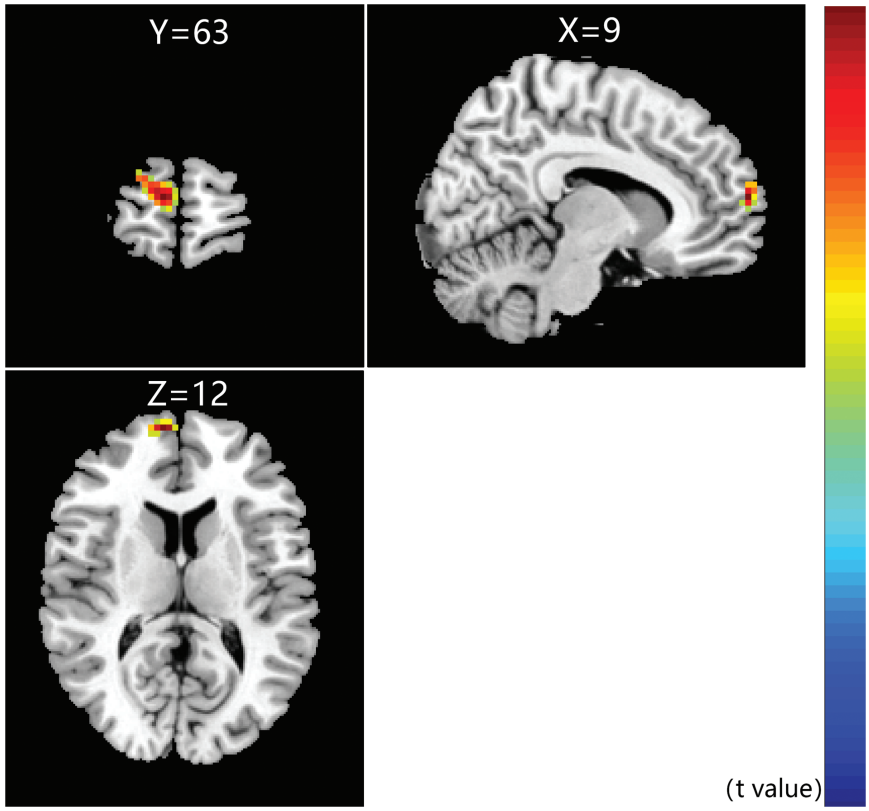

Fig. 4. Specific ReHo differences in the response group (FDR-corrected $P < .05$). ReHo increased in the right medial of superior frontal gyrus in response group after treatment. *Note*: FDR, false discovery rate; ReHo, regional homogeneity.

parameters may contribute to the development of hallucination symptoms in SZ. Damage to the orbitofrontal gyrus cortex is closely associated with apathy symptoms[28] and may play an important role in the development of negative symptoms in patients with SZ. IFGtriang is an important part of the prefrontal lobe. The prefrontal lobe is associated with sensory information processing, memory, thinking, emotional function and is an important brain area for processing emotions.[29] The PCUN is one of the core areas of the default network and is involved in contextual memory and emotional processing.[30] During negative emotional stress, increased activity in the precuneus can facilitate distraction and thus alleviate negative emotions.[31] This study found reduced spontaneous brain activity in the PCUN of SZ patients, which may lead to reduced modulation of negative emotions.

MOG is an important part of the occipital lobe, and its functional changes are closely related to cognitive impairment and visual hallucinations.[32] However, the results of previous studies are inconsistent.[23,33,34] No changes in the MOG were observed at baseline in our study, which may be attributable to population heterogeneity and different experimental parameters. However, local brain activity in the MOG decreased after treatment, consistent with data from a previous 1-year follow-up functional MRI study on SZ.[14] Higher ALFF values in the MOG at baseline were recovered toward normal levels at 1 year of follow-up.[35] Our results suggest that brain activity in the MOG is altered from the beginning of the treatment period, indicating that potential pathological changes are triggered in SZ during treatment.

PoCG is the central node of the somatosensory network showing a high degree of integration.[36] In the present study, decreased ReHo in PoCG after treatment was positively correlated with an increase in the symbol-coding score. Symbol-coding test in the MCCB reflects the information processing speed of subjects. Our findings are consistent with previous results showing that the activity of PoCG is negatively correlated with processing speed in SZ.[37,38] Abnormalities in PoCG affect the speed of information processing through effects on the reaction time,[39] suggesting that PoCG could serve as a critical target of antipsychotic drugs to improve cognitive impairment.

The prefrontal lobe has been identified as one of the critical regions affecting affective and cognitive disorders in SZ.[40,41] Spontaneous neuronal activity changes in the frontal cortex are evident in the early stages of SZ.[42,43] Moreover, the FC also exhibits abnormalities. One study found that decreased FC between left SFG and bilateral PCUN, right hippocampus, right parahippocampal gyrus, left thalamus, left caudate, insula, and right superior

parietal lobule, whereas increased FC was seen between the left SFG and right middle frontal gyrus in the youth-onset drug-naive SZ. The dysfunctional connectivity of the left SFG may be a potential pathophysiological mechanism in youth-onset drug-naive SZ.[44] At present, rs-fMRI longitudinal studies of SZ are still lacking, including antipsychotic treatment for 1-week,[17] 12-week,[16] and 1-year follow-up.[14] We observed enhanced regional brain activity in SFG after 8 weeks of treatment, which was correlated with improvement in symptoms. Moreover, the changes of SFGmed were only observed in the response group after treatment. Previous study found that early reduction of functional activity in the right putamen[17] and interhemispheric connectivity[15] may be the predictor for treatment response in SZ. Our results suggest that different brain regions of the prefrontal lobe contribute differentially to SZ, validating an essential role of the prefrontal lobe in the pathophysiological mechanism of the disease, and the changes of SFGmed may be related to the prediction of efficacy, which needs further study.

Previous study has demonstrated that DC is sensitive to the functional disconnectivity of SZ.[45] The nonresponders differed from the responders in dynamic DC not only at baseline but in the characteristics of changes before and after treatment.[16] However, the majority of subjects in our study were patients with chronic SZ, which may be the underlying reason for inconsistency with previous results.

The current study has several potential limitations. Firstly, we did not strictly limit the drugs used by the subjects to exclude potential confounding effects caused by variable mechanisms of action of the different drugs. Secondly, brain function data of HCs were not collected after treatment for multivariate ANOVA analysis. Thirdly, the possible problem is that the partial volume effects are particularly salient for voxels close to the boundaries between different tissues in the ReHo calculation, which may have some impact.

Conclusion

In conclusion, SZ patients exhibit abnormal functional activities in a wide range of brain regions, further supporting the pathological features identified with neuroimaging. Increased regional brain activity in right SFGmed may predict efficacy in SZ. Increased functional activity of SFG brain regions could be effectively used as an indicator to assess the improvement of symptoms. Our collective findings provide further insights into the regional changes in brain functional activities before and after SZ treatment. Further studies are warranted to identify biomarkers that serve as reliable predictors of efficacy.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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