Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Temporal Dynamics in Degree Centrality of Brain Functional Connectome in First-Episode Schizophrenia with Different Short-Term Treatment Responses: A Longitudinal Study

Yingchan Wang,[1,*] Yuchao Jiang,[2,*] Wenjun Su,[1] Lihua Xu,[1] Yanyan Wei,[1] Yingying Tang,[1] Tianhong Zhang,[1] Xiaochen Tang,[1] Yegang Hu,[1] Huiru Cui,[1] Jinhong Wang,[1] Dezhong Yao,[2] Cheng Luo,[2] Jijun Wang[1,3,4]

[1]Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, 200030, People's Republic of China; [2]The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, Center for Information in Medicine, School of life Science and technology, University of Electronic Science and Technology of China, Chengdu, 610054, People's Republic of China; [3]CAS Center for Excellence in Brain Science and Intelligence Technology (CEBSIT), Chinese Academy of Science, Shanghai, 200031, People's Republic of China; [4]Institute of Psychology and Behavioral Science, Shanghai Jiao Tong University, Shanghai, 200030, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jijun Wang
Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, 200030, People's Republic of China
Tel +86 21 3428 9888
Fax +86 21 6438 7986
Email jjijunwang27@163.com

Purpose: This study investigated temporal dynamics in degree centrality (DC) of the brain functional connectome in first-episode schizophrenia with different short-term treatment responses.

Methods: A total of 127 first-episode patients (FEPs) with schizophrenia and 133 healthy controls (HCs) were recruited in this study. All subjects underwent resting-state functional magnetic resonance imaging. FEPs were scanned at baseline (pretreatment) and at follow-up (posttreatment), while HCs were scanned only at baseline. The patients were exposed to naturalistic antipsychotic treatment for 12 weeks, and classified as schizophrenia responders (SRs) or nonresponders (NRs). Voxel-wise dynamic DC analyses were conducted among the SRs (n=75), NRs (n=52), and HCs (n=133) to assess temporal variability in functional connectivity across the entire neuronal network.

Results: The SRs and NRs showed dissimilar dynamic DC at baseline, with differences mainly involving the temporal lobe. Different DC alteration was observed in the left fusiform gyrus, right fusiform gyrus, left middle cingulate cortex, and left superior parietal gyrus in the SRs and NRs pre- and posttreatment. SRs group and NRs presented opposite changing patterns of dynamic DC in particular regions of the brain.

Conclusion: These findings indicate that dynamic DC abnormalities exist in unmedicated patients with schizophrenia. The NRs differed from the SRs in dynamic DC not only at baseline but in the characteristics of changes before and after treatment as well. Our study may contribute to understanding pathophysiology in schizophrenia with different treatment responses.

Keywords: schizophrenia, degree centrality, dynamics, resting-state functional magnetic resonance imaging, treatment response

Introduction

Schizophrenia refers to a neurodevelopmental psychiatric disorder characterized by psychotic symptoms, cognitive deficits, and behavioral disorders and has a lifetime prevalence of near 1%.[1] The global burden of schizophrenia remains large and continues to increase, and patients suffering from this disease will not be able to achieve their goals in most areas of life.[2,3] Most patients with schizophrenia respond to typical or atypical antipsychotics. However, about 35% have active and persistent psychotic symptoms with lack of response or no response to different

Received: 3 February 2021
Accepted: 14 April 2021
Published: 18 May 2021

medications, even after a sufficient course of treatment. Patients of this type are more likely to experience severe psychotic symptoms with poorer outcomes.[4,5]

Early treatment response is thought to be one of the strongest predictors of subsequent functional outcome in psychosis.[6] Nowadays, functional magnetic resonance imaging (fMRI) has shown promise in helping us understand the neuronal aspects of therapeutic response in psychiatric patients. Researchers have found that higher connectivity between the hippocampus and some brain regions, including the dorsal anterior cingulate, caudate, and auditory cortex, and lower connectivity between the hippocampal region and the lingual gyrus can predict treatment response after 6 weeks of antipsychotic medication.[7] Sarpal et al reported that individual differences in striatal functional connectivity predicted response to antipsychotic treatment in acutely psychotic patients.[8] Another study demonstrated that functional connectivity of the ventral tegmental area/midbrain was correlated with treatment response.[9] Most recently, researchers have turned to exploring the relationship between clinical outcomes and brain function at the network level, and links between clinical response and the functional organization of brain networks have been gradually established.[10–13] Quantifying the relationship between changes in brain function and different treatment responses and understanding whether these changes can be used as predictive biomarkers for therapeutic response could help us understand the mechanisms of schizophrenia and develop therapeutic strategies.

According to the "disconnection hypothesis," the symptoms of schizophrenia are not due to the pathology of a single brain area, but to the abnormal interaction of multiple brain regions.[14,15] In recent years, graph theory has been applied to analyses of neuroimaging data to advance our understanding of the pathogenesis of schizophrenia from brain-organization principles on a global network level.[16] Degree centrality (DC) is a commonly used analytic measurement to reveal the core-hub architecture of brain networks. It is an index of the total weight of connections for a given node, describing the node's role and status in the network.[17] When the brain is regarded as a whole network, each gray-matter voxel is a node of the network. A DC value for each voxel can be calculated, and using these calculations we can form a whole-brain DC map. High voxel-wise DC in a region reflects its role as a central hub in the integration of the global network, while decreased voxel-wise DC might suggest a reduced degree of its global connectivity. Voxel-wise DC has been widely used to investigate alterations of nodal importance in the brain functional connectome in schizophrenia.[18–21] However, there have been few studies to focus on the association of DC abnormalities and antipsychotic-treatment effects among patients with schizophrenia.

We have learned that the brain network is a highly dynamic nervous system with rapidly changing neural activity and always seeking to maintain a dynamic balance.[22–24] Correlations among blood oxygenation level–dependent (BOLD) signals in different regions vary over time, so static metrics may ignore the underlying temporal aspect of brain activity. Studying the dynamic features of intrinsic brain activity in patients with schizophrenia over time may help us discover the basic properties of the brain network, thus revealing the neural mechanisms of the disease more deeply and providing new biomarkers. To capture temporal information, this study used an approach combining the sliding-window technique with voxel-wise DC to measure time-varying features of the DC map.

Methods

Participants

A total of 127 drug-naïve, FEPs with schizophrenia aged 18–40 years were enrolled in this study and underwent resting-state fMRI. All the patients were recruited from the outpatient and inpatient departments of Shanghai Mental Health Center. They were diagnosed with schizophrenia or schizophreniform disorder using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition criteria and met the inclusion criteria of[27] 18–40 years of age, at the first acute episode with duration of illness <3 years, free of antipsychotics, and total score on the Positive and Negative Syndrome Scale (PANSS) ≥60.[28] Patients with schizophreniform disorder at study enrollment were subsequently given a corrected diagnosis of schizophrenia after 6 months of illness duration. Exclusion criteria were history of head trauma or injury, history of substance or alcohol abuse or dependence, pregnant or breastfeeding, in unstable conditions, such as aggressive or stupor, any other psychiatric diagnosis, history of electroconvulsive therapy, and with contraindications to MRI.

In sum, 133 age-, sex-, and ethnicity-matched HCswere recruited from the local community through advertisement. They were administered the Mini

International Neuropsychiatric Interview Plus version 5.0.[29] In addition to the exclusion criteria, participants with any psychiatric or neurological disease or a family history of psychosis were excluded. No gross abnormalities were observed in T_1- orT_2-weighted MRI results in any participants. The study was approved by the Institutional Review Board of Shanghai Mental Health Center and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from each participant.

Clinical Setting

After scanning at the outset, FEPs received various antipsychotic medications in a naturalistic treatment. The type and dose of medication administered was up to their clinicians. Psychotic symptoms were assessed using the PANSS by trained clinical psychiatrists, achieving intraclass correlation coefficients of 0.8. Participants were followed up for 12 weeks (81.29±12.11 days) and subgrouped as schizophrenia responders (SRs) or nonresponders (NRs) based on whether they reached the criteria of a 50% reduction of the baseline score evaluated with the PANSS, ie, SRs consisted of FEPs with PANSS reduction ≥50%, and NRs a reduction <50%.[30,31] Reduction in total PANSS score was calculated:[32,33]

$$\Delta\text{PANSS} = \frac{\text{PANSS}_{t1} - \text{PANSS}_{t2}}{\text{PANSS}_{t1} - 30} \times 100\%$$

All the patients completed the follow-up visit and were scanned both at baseline and after treatment, while HCs were scanned only at baseline.

Imaging-Data Acquisition and Processing

MRI scans were performed as soon as possible after the patient's first visit to the clinic to ensure that they were free of medication at baseline. All MRI data were obtained using a Siemens Verio 3.0 T MRI scanner at Shanghai Mental Health Center. Before scanning, all participants were instructed to keep their eyes closed, stay awake, and let their thoughts come and go.[34] Structure images were acquired with a fast spin echo (SE) sequence with the following parameters: repetition time (TR) =2300 ms, echo time (TE) =2.98 ms, matrix 240×256, flip angle 9°, field of view =256 mm, voxel size =1×1×1 mm^3, slice thickness =1 mm, gap =0 mm, and 196 slices. The BOLD fMRI images were obtained using a gradient-echo echo-planar imaging (EPI) sequence with parameters of TR 2000 ms, TE 35 ms, matrix 64×64, flip angle 90°, field of view 256 mm, voxel size 1×1×1 mm^3, slice thickness 4 mm, gap 0 mm, and 33 slices. Image preprocessing procedures were similar to our previous studies, briefly:[35] removing the first ten volumes, time-slicing and head-motion correction, normalization to the EPI template in Montreal Neurologic Institute space, regressing out 24 head-motion parameters, cerebrospinal fluid, and white-matter signals, as well as the linear trend, and band-pass filtering (0.01–0.10 Hz). Data preprocessing was carried out using SPM12 (www.fil.ion.ucl.ac.uk/spm) and DPABI (http://rfmri.org/dpabi).

Degree Centrality

The calculation of DC was performed using the DPABI.). DC is a robust and widely used data-driven method to characterize intrinsic brain connectivity at a global level. Based on the concept of graphic theory, DC measures global-level functional integration at brain resting–state activity by quantification of functional connectivity strength of any voxel with all other voxels within the whole brain. Therefore, high DC values in a region may reflect increased centrality (hub role) in global information interactions and vice versa. For each subject, an adjacent matrix was generated by computing Pearson correlation coefficients between the time series of each voxel with every other voxel within a gray-matter mask. To eliminate weak correlations possibly introduced by data noise, correlations <0.25 were set to zero.[17,36,37] The DC of each voxel was calculated as the sum of the connections between a given voxel and all other voxels, and thus yielded a voxel-wise DC map. DC was the only graph measure assessed in this study.

Temporal Variability in Dynamic Degree Centrality

To characterize the temporal variability of voxel-wise dynamic DC (dDC) was calculated according to the sliding-window strategy. For each subject, the fMRI time series was segmented into sliding windows with a length of 60 seconds and a sliding step of 30 seconds. The DC map was computed for each window. The standard deviation of DC maps across all sliding windows was calculated to assess dDC variability. To reduce individual variations and improve normality of data distribution, the dDC map was normalized by dividing the mean value across all

voxels. Finally, the dDC maps were spatially smoothed with 6 mm Gaussian kernel.

Statistical Analysis

For comparisons of demographic characteristics between the schizophrenia group and HCs, *t*-tests were used for continuous variables and χ^2 tests for categorical variables. $P<0.05$ was considered statistically significant. To compare changes in dDC, two-sample *t*-tests were performed for comparison of the schizophrenia group (all patients) and HCs. Differences among SRs, NRs, and HCs at baseline were compared using one-way ANOVA and post hoc tests. To compare changes in dDC variability between SRs and NRs, mixed-model repeated-measure ANOVA (RMANOVA) and post hoc paired *t*-tests were performed. RMANOVA was used to investigate the interaction effect between groups (SRs vs NRs) and time (baseline vs follow-up) and post hoc paired *t*-tests to examine longitudinal changes between baseline and follow-up in each patient group. Sex, age, education, scan results, and head motion were used as covariate controls to eliminate interference when conducting the statistical analysis. Multiple-comparison correction for voxel-wise dDC analysis was performed using Gaussian random-field theory (voxel $P<0.005$, cluster-corrected $P<0.05$).

Relationship Between Dynamic DC and Symptom Remission

Changes in dDC variablity were computed as the difference ($\Delta dDC = dDC_{baseline} - dDC_{follow\text{-}up}$) between baseline and follow-up for each subject. Pearson correlation analysis was used to evaluate the relationship between dDC changes and symptom remission (reductive ratios in total PANSS scores) voxel-wise in the combined sample of all schizophrenia patients. In addition, we assessed correlations between baseline dDC variability and baseline symptoms (positive, negative, general and total PANSS scores) voxel-wise. Sex, age, education, scan results, and head motion were used as covariate controls. Multiple-comparison correction was performed based on Gaussian random-field theory (voxel $P<0.005$, cluster-corrected $P<0.05$).

Results

Demographics

Participants' demographic and clinical features are shown in Table 1. Groups were matched for age and sex, but NRs showed less education than SRs. No significant differences were found for age, sex, average antipsychotic dose, duration of untreated psychosis (DUP), or total PANSS scores between the two patient groups, but general PANSS scores were significantly different between SRs and NRs ($P=0.020$, Table 1).

Antipsychotic Treatment

All patients received atypical antipsychotics, with 94 (74%) receiving monotherapy of olanzapine (n=32), risperidone (n=18), aripiprazole (n=17), amisulpride (n=16), paliperidone (n=8), quetiapine (n=2), or ziprasidone (n=1) and 33 (26%) combined medication (antipsychotic combination) aripiprazole and olanzapine (n=9), aripiprazole and risperidone (n=5), amisulpride and olanzapine (n=4), risperidone and olanzapine (n=4), risperidone and quetiapine (n=3), aripiprazole and paliperidone (n=2), quetiapine and paliperidone (n=2), aripiprazole and quetiapine (n=1), ziprasidone and olanzapine (n=1), ziprasidone and aripiprazole (n=1), or amisulpride and paliperidone (n=1). Usually, the dosage increased during the first 2 weeks of treatment and then remained constant until the follow-up scan. When patients had not improved after 4–6 weeks of treatment, combination therapy or changing to another antipsychotic medication would be considered.

Group Differences in Dynamic DC at Baseline

All Patients vs Healthy Controls

When all FEPs were compared with HCs, significant reductions in dDC were observed in the left superior parietal gyrus (SPC.L) and the left calcarine fissure, and increases in dDC were found in the left putamen (Table 2 and Figure 1).

Responders vs Nonresponders vs Controls

One-way ANOVA showed differences among the three groups in brain regions, including the left inferior temporal gyrus (ITG.L) and left middle temporal gyrus (MTG.L) at baseline (Table 3 and Figure 2). Subsequent ROI-wise post hoc comparisons indicated that both NRs and HCs had increased dDC in the ITG.L and MTG.L compared to SRs and that there was no significant difference in dDC values between NRs and HCs in these two regions (Figure 2).

Longitudinal Data Analysis

RMANOVA showed that the interaction of group and time mainly affected the left and right fusiform gyri, left

Table 1 Demographic and clinical data of participants

	Schizophrenia	Healthy controls	*P*
Subjects, n	127	133	
Age (years)	24.61(7.0)	23.7(5.9)	0.254[a]
Sex (male/female)	63/64	66/67	0.998[b]
Education (years)	12.9(2.9)	13.5(2.8)	0.110[a]
Handness (left/right)	0/127	0/133	1[b]
TIV (mm^3)	1,480.5(148.8)	1,476.9(133.0)	0.838[a]
DUP (months)	12.7(14.2)	—	—
Cpz (mg/day)	402.8(188.9)	—	—
Baseline PANSS			
Positive score	24.0(5.1)	—	—
Negative score	19.1(6.7)	–	—
General score	42.4(6.9)	—	—
Total score	85.8(12.9)	—	—
12-week PANSS			
Positive score	12.6(4.1)	—	—
Negative score	14.4(4.8)	—	—
General score	28.8(5.7)	—	—
Total score	55.8(12.5)	—	—
Reduction (%)	53.0(21.1)	—	—
	Responders	**Nonresponders**	*P*
Subjects, n	75	52	
Age (years)	25.3(6.6)	23.6(7.4)	0.176[a]
Sex (male/female)	35/40	28/24	0.426[b]
Education (years)	13.4(2.9)	12.3(2.7)	0.033[a]
Handness (left/right)	0/75	0/52-	1[b]
TIV (mm^3)	1,478.1(147.6)	1,483.9(152.0)	0.832[a]
DUP (months)	12.5(14.2)	14.5(14.0)	0.230[a]
Cpz (mg/day)	406.2(197.9)	397.9(176.9)	0.810[a]
Baseline PANSS			
Positive score	24.6(5.0)	23.2(5.3)	0.125[a]
Negative score	18.4(6.6)	20.2(6.7)	0.146[a]
General score	43.6(7.2)	40.8(6.0)	0.020[a]
Total score	86.9(14.1)	84.1(10.9)	0.221[a]
12-week PANSS			
Positive score	11.0(3.0)	14.9(4.3)	<0.001[a]
Negative score	12.0(3.6)	17.8(4.3)	<0.001[a]
General score	26.0(4.6)	32.8(4.9)	<0.001[a]
Total score	49.0(9.2)	65.7(9.6)	<0.001[a]
Reduction (%)	66.7(12.8)	33.3(13.7)	<0.001[a]

Notes: [a]Two-sample *t*-tests [b]χ^2 tests.
Abbreviations: TIV, total intracranial volume; Cpz, chlorpromazine equivalents; PANSS, Positive and Negative Syndrome Scale.

Table 2 Two-sample *t*-test comparison on whole-brain dynamic DC maps between FEPs and HCs at baseline

Region	x	y	Z	t	Cluster
Left calcarine fissure	–6	–90	6	–3.89	192
Left putamen	–21	3	9	3.11	113
Left superior parietal gyrus	–15	–75	54	–3.69	246

midcingulate cortex, and left superior parietal gyrus (Table 4 and Figure 3). Subsequent post hoc paired *t*-tests were conducted to further show dDC changes in these brain regions between SRs and NRs before and after treatment. Decreased dDC values for the left and right fusiform gyri were found in SRs after antipsychotic treatment, but there was no significant difference in dDC in these two brain regions pre- and post-treatment in NRs. After treatment, the dDC of the left midcingulate cortex and left superior parietal gyrus rose in SRs, while NRs showed decreased dDC in these brain regions compared to pretreatment (Figure 3).

Correlation with Clinical Characteristics at Baseline

Correlation analyses were performed to investigate the relationship of dDC with psychopathology in all FEPs. dDC of the right cerebellum posterior lobe was significantly correlated with total PANSS scores (r=0.38, P<0.0001). dDC of the right medial frontal cortex was negatively correlated with totalPANSS scores (r=–0.34, P<0.001) and general psychopathology (r=–0.35, P<0.0001). dDC of the right postcentral gyrus was negatively correlated with positive symptoms (r=–0.32, P<0.001; Figure 4, Table 5).

Correlation with Treatment Response

Altered dDC of the right middle cingulate cortex (r=0.35, P<0.0001) and left superior parietal cortex (r=0.37, P<0.0001) were significantly correlated with reduction in total PANSS scores (Figure 5, Table 6).

Discussion

This study examined temporal dynamics in DC in a whole-brain functional connectome pattern at voxel level in FEPs classified as SRs and NRs. We found that FEPs with different treatment responses showed dissimilar dDC at baseline. After antipsychotic treatment, different alterations in dDC were observed in the parietal lobe, occipitotemporal gyrus, and cingulate cortex in the SRs and NRs group. The changing pattern of dDC in NRs was quite different from that in SRsp. In fact, SRs and NRs presented opposite changing patterns of dDC in particular regions of the brain.

Previous resting-state fMRI studies have shown that compared with HCs, patients with schizophrenia exhibit significantly increased static DC in the medial prefrontal cortex and significantly decreased DC in the parietal–occipital and temporal–occipital junction.[38,39] Static DC abnormalities within the default-mode network in schizophrenia patients have also have been reported.[21] dDC demonstrates distinct patterns of transient brain activity compared to sustained brain activity with static brain activity. Therefore, the

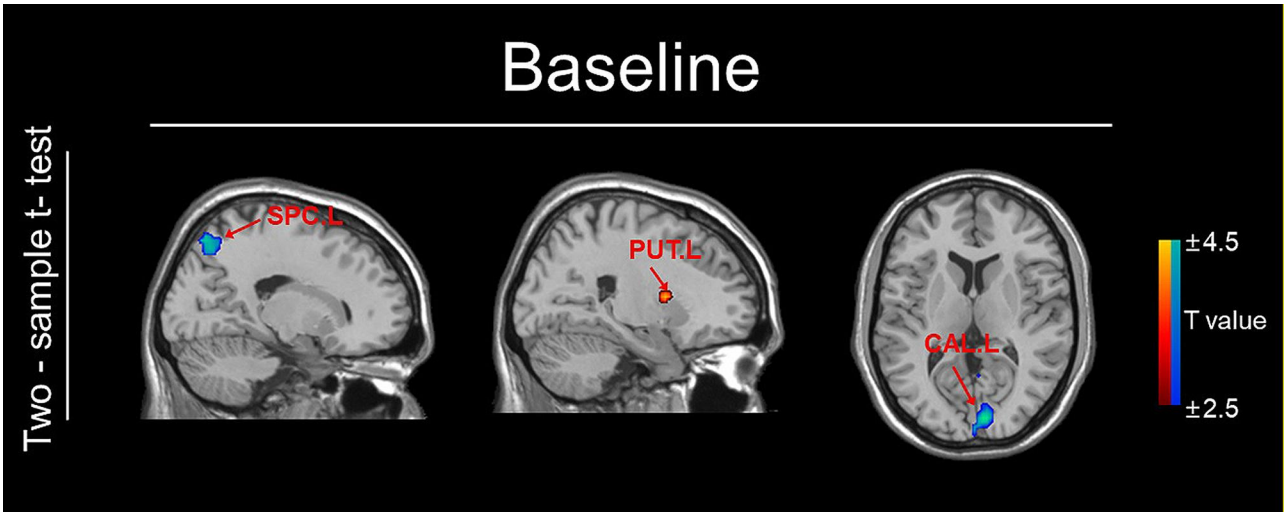

Figure 1 Differences in dynamic DC between FEPs (all patients) and HCs on two-sample *t*-test analysis at baseline.

Table 3 One-way ANOVA comparison on whole-brain dynamic DC maps among SRs, NRs and HCs at baseline

Region	*x*	*y*	*Z*	*F*	Cluster
Left inferior temporal gyrus	–42	0	–42	10.57	109
Left middle temporal gyrus	–57	–42	6	9.62	45

dynamic approach could uncover brain activity or connectivity that differs from the static approach. In the present study, the two-sample *t*-test analysis showed that differences in dDC between FEPs and HCs were in the left superior parietal gyrus, left calcarine fissure, and the left putamen. By far, the dopamine hypothesis of schizophrenia remains the most influential neurobiological theory. In vivo molecular imaging studies have show increased dopamine-release and -synthesis capacity in selected regions (such as the striatum) in schizophrenia patients.[40,41] High DC in the striatum may be associated with hypersensitization and increased stimulus-related activity of dopaminergic receptors. ANOVA in the cross-sectional study revealed differences among the three groups in the temporal lobe (left inferior temporal gyrus and left middle temporal gyrus). Contrary to our initial expectations, we did not find statistical differences between NRs and HCs in these two regions. Using graph analysis, McNabb et al reported no difference in functional network connectivity between TRS-C (treatment-resistant schizophrenia treated with clozapine) SRs and HCs, and TRS-C NRs had weaker functional network connectivity than HCs within the cerebrofrontal, cingulofronttemporal, and fronto-parietal networks.[42] In this study, we observed only initial treatment response, and further follow-up would be needed to see if the patients met the criteria of treatment resistance. The results may be related to sample selection or time of treatment.

On longitudinal analysis, we found decreased dDC of the bilateral fusiform gyrus in SRs, but no significant change in NRs. dDC changes of the left middle cingulate

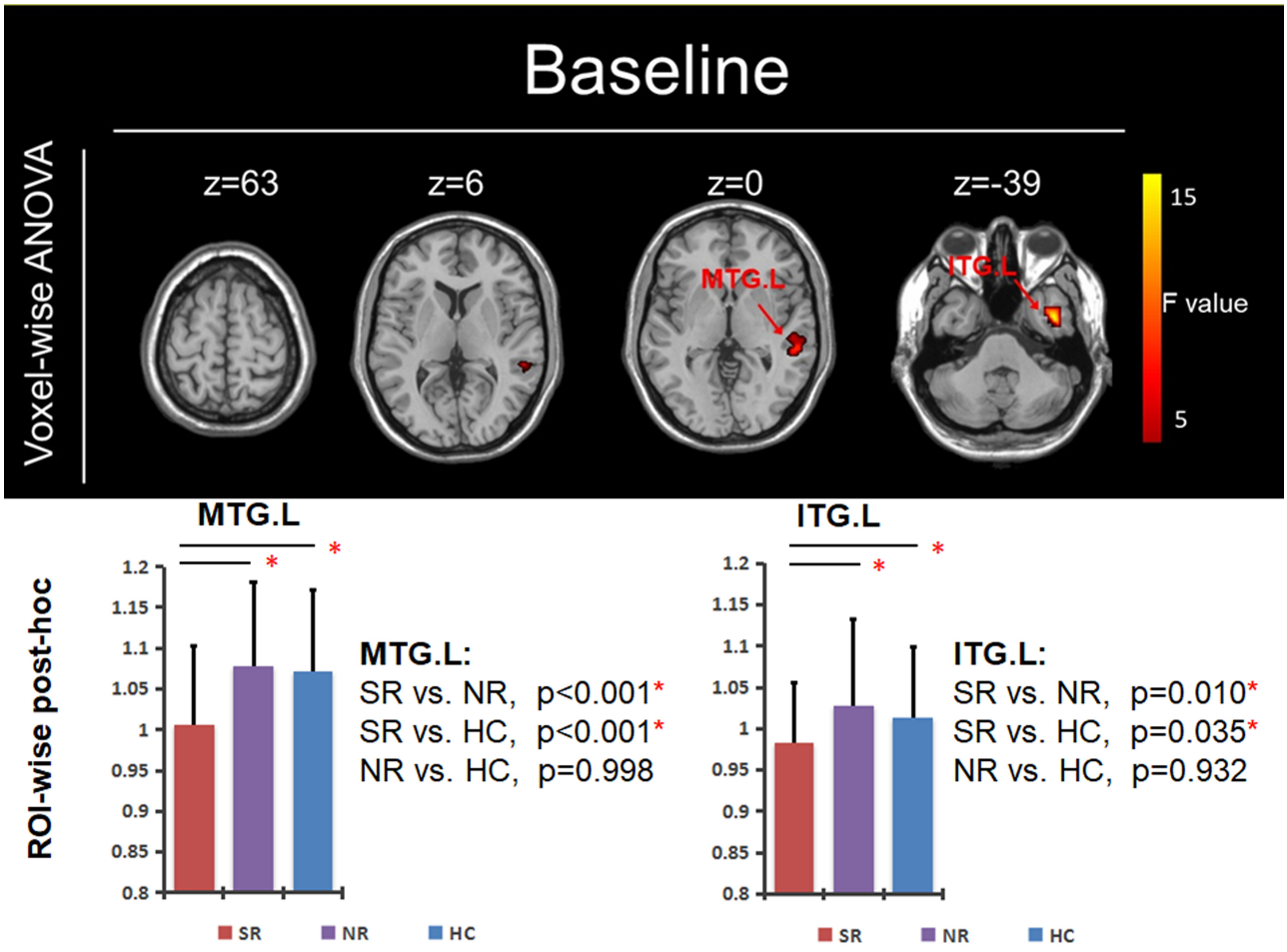

Figure 2 Differences in dynamic DC among the three groups on one-way ANOVA analysis at baseline (upper) and post hoc comparisons of dynamic DC in ITG.L and MTG.L among the three groups (lower). *P<0.05.

Table 4 Interaction effects of repeated-measure ANOVA

Region	x	y	Z	F	Cluster
Left fusiform gyrus	–24	–45	–9	14.07	41
Right fusiform gyrus	27	–48	–9	13.79	48
Left middle cingulate cortex	–2	3	45	23.73	125
Left superior parietal gyrus	–21	–54	72	16.77	39

cortex and left superior parietal gyrus in SRs were opposite to those of NRs. dDC of these two brain regions increased after treatment in SRs and decreased in NRs, showing a different pattern of change in the left middle cingulate cortex and left superior parietal gyrus. Correlation analysis showed that the altered dDC of the right middle cingulate cortex and left superior parietal cortex was significantly related to treatment response.

The fusiform gyrus, part of the temporal and occipital lobes and connecting the striatum to the inferior temporal lobe, plays a key role in visuocognitive functions, such as face perception, object recognition, and reading.[43] Zhang et al found that the fusiform gyrus could be further subdivided into three distinct parts with different functions: the medial portion serves as a transition region that combines multiple stimuli, the lateral portion is responsible for categorical recognition, and the anterior portion is involved in semantic understanding.[44] The midcingulate cortex is hypothesized to be involved in cognitive control and intentional motor control and selection.[45] Larabi et al found that with regard to cognitive insight, patients with poorer self-reflective abilities had lower activation of brain systems managing control and execution of emotion regulation (left middle cingulate gyrus) during

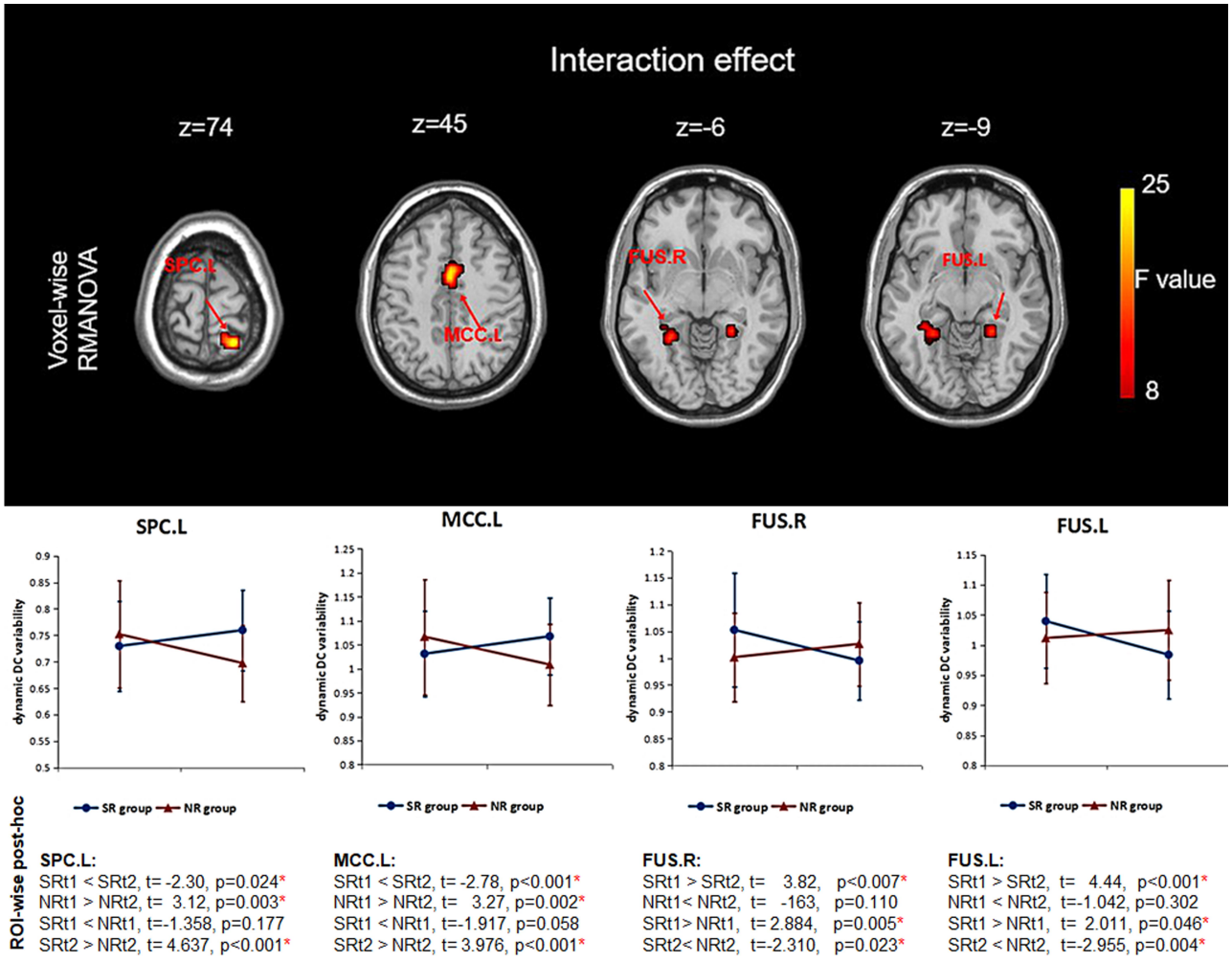

Figure 3 Interaction effects of group and time of dynamic DC in SRs and NRs pre- and posttreatment on RMANOVA analysis (upper) and post hoc comparisons of changes in dynamic DC values before and after treatment in SR and NR (lower). *P<0.05.

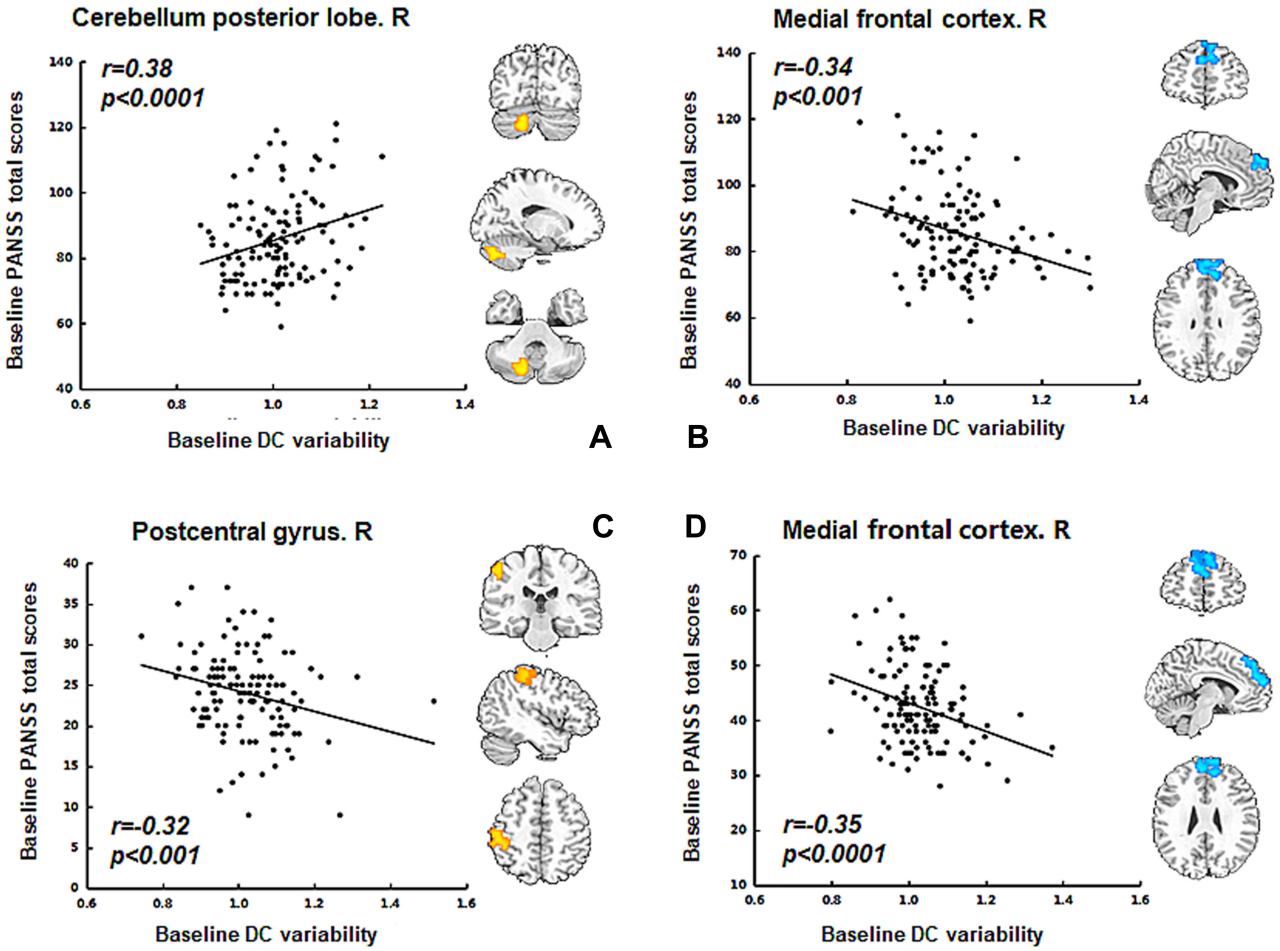

Figure 4 Correlation of dynamic DC variability with clinical characteristics in all FEPs at baseline. (**A**) Dynamic DC of right cerebellum posterior lobe significantly correlated with totalPANSS score (r=0.38, P<0.0001). (**B**) Dynamic DC of right medial frontal cortex negatively correlated with total PANSS score (r=–0.34, P<0.001). (**C**) Dynamic DC of right postcentral gyrus negatively correlated with positive symptoms (r=–0.32, P<0.001) (**D**) Dynamic DC of right medial frontal cortex negatively correlated with PANSS general psychopathology (r=–0.35, P<0.0001).

suppression.[46] The left superior parietal gyrus is part of the frontoparietal control network, providing a causal link between brain and behavior (eg, attention, working memory, and cognitive control). Superior parietal lobule lesions are associated with deficits in the manipulation and rearrangement of information within working memory for both auditory–verbal and visuospatial stimuli.[47] High DC of a region may reflect its role as a central hub of the integration of global resting-state functional connectivity (including local and distant connections): as DC decreases, centrality becomes lower.[48] Therefore, the results of longitudinal comparison suggest that the functional activity of face perception/object recognition–related regions decreases with the relief of such symptoms as hallucinations and delusions while activity of the cognitive control network increases, indicating that although symptoms and insight improved in SRs, more brain-resource allocation needed to be mobilized to make up for their original functions. In contrast, functional activity of visuocognitive-related regions did not change much in NRs posttreatment, while activities of the cognitive control network continued to decline, which may lead to impaired clinical insight and poorer outcomes. These findings suggest that brain function network–activity change varies with different treatment responses.

Several limitations should be considered when discussing the results of this study. First, although we examined the short-term effects of antipsychotics on the brain functional network, our work does not address long-term changes in brain function. Secondly, though changes over time were assumed to be negligible in HCs, some alterations, such as normal neurodevelopment, may have occurred. Future work in this area

Table 5 Correlation of DC variability with clinical characteristics in all patients at baseline

	Region	*x*	*y*	*Z*	*R*	*P*	Cluster
PANSS -base-T	Right cerebellum posterior lobe	18	–75	–39	0.38	<0.0001	123
	Right medial frontal cortex	9	57	18	–0.34	<0.001	223
PANSS-base-P	Right postcentral gyrus	51	–27	51	–0.32	<0.001	190
PANSS-base-G	Right medial frontal cortex	9	60	18	–0.35	<0.0001	338
PANSS-base-N	None						

Table 6 Correlation of changes in DC variability with clinical treatment response in all FEPs

Region	*x*	*y*	*Z*	*r*	*P*	
PANSS-reduction-T	Right middle cingulate cortex	3	0	45	0.35	<0.0001
	Left superior parietal cortex	–33	–51	66	0.37	<0.0001

should keep this in mind. Thirdly, the parameters of dDC, such as window length and step size, are still controversial. To our limited knowledge, window length in previous studies has rangeed 30–100 seconds and step size ranges from 1 TR to 100% (ie, nonoverlapping) of window length.[49–52] In this study, we chose a step size of 50% of the window length, mainly due to the cost of computation of dDC. Therefore, the sliding-window option is still an uncertain factor in the current study. Future work needs to determine the optimal parameters of the sliding window. Finally, this is an observational study in which the type and dose of medication received by patients were determined by clinicians, and whether different drugs have specific effects on brain networks needs to be further clarified in future studies. Overall, this study employed data-driven analysis, and the results here are dependent on the samples that participated. Replication in larger samples and longer-term studies are required.

Conclusion

We used a graph theory–based metric and data-driven method that facilitated the discovery of more objective results than a priori assumptions, which would be limited to specific brain regions or networks. dDC can reflect the importance of nodes or brain regions in complex brain networks. Our work may provide new insight into the benefits of exploring neuroimaging mechanisms as a way to study different treatment responses in schizophrenia.

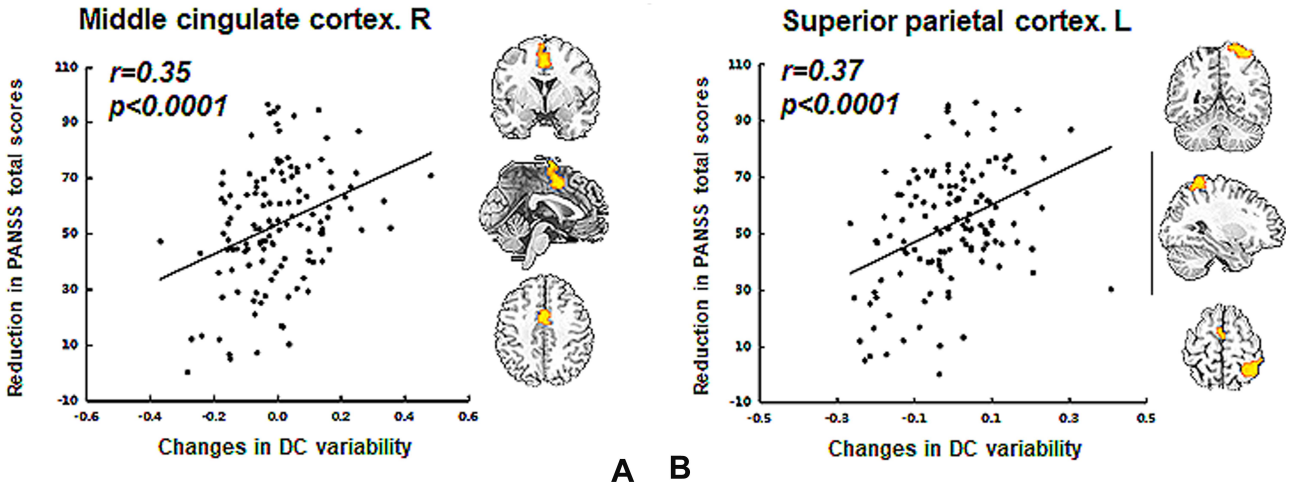

Figure 5 Correlation of changes in dynamic DC variability with clinical treatment response in all FEPs. (**A**) Altered dynamic DC of right middle cingulate cortex (r=0.35, P<0.0001) significantly correlated with reduction in total PANSS scores. (**B**) Altered dynamic DC of left superior parietal cortex (r=0.37, P<0.0001) significantly correlated with reduction in total PANSS scores.

Acknowledgments

This work was supported by the Ministry of Science and Technology of China, National Key R&D Program of China (2016YFC1306800), National Nature Science Foundation of China grants (81671332, 81971251, 81671329, and 81871050), the Shanghai Municipal Science and Technology Major Project (2018SHZDZX01) and ZJLab, Shanghai Science and Technology Committee Foundations (16ZR1430500, 19411969100, 19410710800), Clinical Research Center at Shanghai Mental Health Center grants (CRC2018ZD01, CRC2018ZD04, and CRC2018YB01), and the Clinical Research Center at Shanghai Jiaotong University School of Medicine (DLY201817). These funding agents had no role in study design, collection, analysis, or interpretation of data, writing of the manuscript, or decision to submit the paper for publication.

Disclosure

The authors declare that there are no conflicts of interest in relation to the subject of this study.

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