Cerebral Cortex, August 2019; 3577–3589

doi: 10.1093/cercor/bhy232
Advance Access Publication Date: 1 October 2018
Original Article

ORIGINAL ARTICLE

Reconfiguration of Dynamic Functional Connectivity in Sensory and Perceptual System in Schizophrenia

Debo Dong [1], Mingjun Duan[1,2], Yulin Wang[3,4], Xingxing Zhang[1], Xiaoyan Jia[1], Yingjia Li[1], Fei Xin[1], Dezhong Yao[1] and Cheng Luo[1]

[1]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, 2006 Xiyuan Avenue, Chengdu 611731, China, [2]Department of Psychiatry, The Fourth People's Hospital of Chengdu, Chengdu 610000, China, [3]Department of Experimental and Applied Psychology, Faculty of Psychological and Educational Sciences, Vrije Universiteit Brussel, Brussels 1040, Belgium and [4]Department of Data Analysis, Faculty of Psychology and Educational Sciences, Ghent University, Henri Dunantlaan 2, Ghent B-9000, Belgium

Address correspondence to Dezhong Yao and Cheng Luo, University of Electronic Science and Technology of China, NO. 2006, Xiyuan Avenue, High-Tech District, Chengdu 611731, China. Email: dyao@uestc.edu.cn (D.Y.), chengluo@uestc.edu.cn (C.L.).

Abstract

Schizophrenia is thought as a self-disorder with dysfunctional brain connectivity. This self-disorder is often attributed to high-order cognitive impairment. Yet due to the frequent report of sensorial and perceptual deficits, it has been hypothesized that self-disorder in schizophrenia is dysfunctional communication between sensory and cognitive processes. To further verify this assumption, the present study comprehensively examined dynamic reconfigurations of resting-state functional connectivity (rsFC) in schizophrenia at voxel level, region level, and network levels (102 patients vs. 124 controls). We found patients who show consistently increased rsFC variability in sensory and perceptual system, including visual network, sensorimotor network, attention network, and thalamus at all the three levels. However, decreased variability in high-order networks, such as default mode network and frontal–parietal network were only consistently observed at region and network levels. Taken together, these findings highlighted the rudimentary role of elevated instability of information communication in sensory and perceptual system and attenuated whole-brain integration of high-order network in schizophrenia, which provided novel neural evidence to support the hypothesis of disrupted perceptual and cognitive function in schizophrenia. The foci of effects also highlighted that targeting perceptual deficits can be regarded as the key to enhance our understanding of pathophysiology in schizophrenia and promote new treatment intervention.

Key words: functional connectivity, schizophrenia, self-disorder, sensory and perceptual system, temporal variability

Introduction

Schizophrenia affects about 1% of the whole adult population and is one of the most mysterious and costliest mental disorders in terms of human suffering and societal expenditure (van Os and Kapur 2009). It has been broadly accepted that schizophrenia can be regarded as a self-disorder (Sass and Parnas 2003; Sass 2014), which can be defined as a difficulty in distinguishing between the self and other individuals and confirming whether their thoughts and actions are independent from external influences (Borda and Sass 2015). Because of consistent observations of cognitive impairments, self -disorder in schizophrenia has always been attributed to deficits in higher

order cognitive functions (Kahn and Keefe 2013) with impaired function of higher order brain regions (Minzenberg et al. 2009). However, the symptomatology in schizophrenia (e.g., auditory hallucinations) was evidenced to be also involved the impaired multisensory and perceptual processing (Javitt 2009). Though deficits of perceptual processing and multisensory integration were increasingly documented in schizophrenia (Javitt and Freedman 2015; Tseng et al. 2015; Hornix et al. 2018), emphasis of the role of impaired function and integration of both the bottom-up and top-down brain systems in self-disorder of schizophrenia was somehow neglected in the research field (Javitt 2009; Javitt and Freedman 2015). Indeed, auditory hallucinations is regarded as a failure of the top-down inhibitory control of bottom-up perceptual processes (Hugdahl 2009). Recent neurobiological model of self-disorder in schizophrenia also started to emphasize the rudimentary role of perceptual incoherence in the deficit of self-integration, in which it was theorized that incoherent self-experiences in schizophrenia is caused by impairment of multisensory integration (Postmes et al. 2014; Borda and Sass 2015; Sass and Borda 2015). Therefore, investigating the functional interaction between and within perceptual and cognitive brain systems is crucial to understanding the pathophysiology mechanisms of schizophrenia.

The abovementioned functional interaction can be explored by characterizing functional connectivity within and between different levels of brain systems (Van Den Heuvel and Pol 2010). Our previous stable resting-state functional connectivity (rsFC) studies have highlighted the crucial role of functional abnormalities within lower order perceptual system in altered self-experience in schizophrenia. This system can be regarded as the target of treatment, such as music intervention (Chen et al. 2015, 2016; He et al. 2018). Also evidenced by our previous meta-analysis of stable FC, as one of the sensory orienting systems the abnormal FC within ventral attention network and its imbalanced communication with other functional networks is the core feature in schizophrenia brain (Dong et al. 2018). However, until recently, most rsFC studies of schizophrenia had implicitly assumed that FC is stationary throughout the entire resting scan period. Time-varying functional interaction enables the brain to dynamically integrate and coordinate different neural systems in response to internal and external stimuli across multiple time scales (Hutchison et al. 2013; Calhoun et al. 2014). Hence, the analysis of time-varying FC has provided insights relating to the dynamic restructuring and temporal evolution of the human connectome and could potentially provide insights related to various neurological and psychiatric conditions (Calhoun et al. 2014; Avena-Koenigsberger et al. 2018). In addition, time-varying FC analysis provides a potential tool to capture sensitive changes that occur in psychiatric or neurologic disorders (Keilholz 2014). For example, Rashid and his colleagues observed some robust time-varying FC features rather than traditional static rsFC to separate schizophrenia and bipolar disorder which share overlapped genetic vulnerability (Rashid et al. 2014, 2016).

In schizophrenia, time-varying properties of brain rsFC in schizophrenia were poorly investigated, thus detailed characterization of the time-varying FC in schizophrenia is warranted. Few previous studies demonstrated that schizophrenia patients showed altered transient states of rsFC within sensory network (Damaraju et al. 2014; Du et al. 2018), reduced dynamic characteristics within default model network (DMN) at rest over time (Du et al. 2016) and aberrant dynamic amplitude of low-frequency fluctuation and its associations with brain connectivity (Fu et al. 2018). Though these earlier studies provided us some insights about the existence of altered temporal variability in long-range cortical FC which reflects the integration of brain information, the variability of local functional connectivity in schizophrenia remained unknown. Additionally, no study has substantially evaluated schizophrenia-related changes in time-varying FC features from integrated multilevel perspectives, that is, voxel level and region level and network level. Given the brain regulates information flow by balancing the segregation and integration of incoming stimuli to facilitate flexible cognition and behavior (Deco et al. 2015), it is necessary to investigate dynamic FC features at these three levels, which would provide us more comprehensive insight into how schizophrenia affects the brain.

This study aims to comprehensively characterize alterations in temporal variability of rsFC in schizophrenia using recent novel methodological approaches. These approaches adopted in the present study allow us to identify voxel-level, region-level, and network-level functional connectivity variability alterations, thus helping to comprehensively map temporal dynamics of rsFC in schizophrenia. Based on previous findings and significant involvement of perceptual incoherence in the symptomatology, we anticipated that altered variability of voxel and region levels in schizophrenia would locate in primary perceptual systems, such as sensorimotor cortex, visual cortex, thalamus, and insula. Furthermore, schizophrenia patients were expected to show altered variability of within-network involved in multisensory and perceptual information processing, such as sensorimotor network (SS), visual network (VN), and ventral attention network (VAN) (also termed as salience network, Uddin (2015)) (Damaraju et al. 2014; Chen et al. 2015; Xu et al. 2015); as well as in self-integration, such as higher order network, that is, DMN (Zhang et al. 2016; Guo et al. 2017; Dong et al. 2018). Last but not least, altered variability of between-networks would occur among these networks. In addition, because altered function of thalamus–cortical circuit has been regarded as a hallmark feature of schizophrenia (Anticevic 2017; Li et al. 2017), we expected to see the alterations of FC variability would appear in this circuit.

Materials and Methods

Participants

One hundred and two patients with schizophrenia were recruited from the Clinical Hospital of Chengdu Brain Science Institute. The diagnosis of schizophrenia was confirmed by the structured clinical interview for DSM-IV axis I disorders-clinical version (SCID-I-CV). Patients with comorbid axis I diagnosis or active substance use disorders were excluded. All patients were treated with antipsychotics. One hundred and twenty-six health controls were recruited from local community through advertisements and word of mouth. Health controls were excluded for current or past axis I disorder, as verified using the Structure Clinical Interview for DSM-IV, history of neurological illness, traumatic brain injury, substance-related disorders or first-degree relatives with history of psychosis. Six patients and two healthy controls with head motion scans exceeding 2.5 mm or 2.5° rotation were excluded. Additionally, two health controls were excluded because of deficiency of data by visual evaluation. Finally, 96 schizophrenia patients and 122 healthy controls were included in the final analysis. Written informed consents were obtained from all healthy participants and his/her guardian of patients, and the experimental procedures were approved by the Ethics Committee of the Clinical Hospital

of Chengdu Brain Science Institute. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The demographic and clinical information of all patients and HC are shown in Table 1.

Some of the patients were part of our previous studies (Chen et al. 2015, 2016, 2017; Duan et al. 2015; He et al. 2018; Jiang, Luo, Li, Li et al. 2018). Twenty-eight of the 96 patients were included in a prior study in which the authors identified abnormal functional integration in the basal ganglia network by using spatial independent component analysis in schizophrenia (Duan et al. 2015). The same 28 patients were also included in a prior article, in which the global functional disconnection was showed by using functional connectivity density analysis in schizophrenia (Chen et al. 2015). Forty-six of the 96 patients were previously included in a prior article in which authors demonstrated dysfunction in the insula with data-driven clustering and functional connectivity analysis in schizophrenia (Chen et al. 2016). Sixty-nine of the 96 patients were included in a prior article in which the authors identified an altered hippocampus–cerebellum cortical circuit with a combination of local consistency analysis and Causal Connectivity analysis in schizophrenia (Chen et al. 2017). Thirty-six (data before the intervention) of the 96 patients were included in a prior study in which the authors found increased insular connectivity after music intervention in schizophrenia (He et al. 2018). Ninety-three of the 96 patients were included in a prior study in which the authors demonstrated abnormalities of white matter networks in schizophrenia (Jiang, Luo, Li, Li et al. 2018). All of these previous studies investigated the dysfunctions of static rsFC, whereas the present study was focused on comprehensive investigation of dynamic functional connectivity in schizophrenia.

Data Acquisition and Image Preprocessing

Resting-state fMRI data were collected on a 3-T GE Discovery MR 750 scanner at the MRI Center of University of Electronic Science and Technology of China. Foam pads were used to reduce head movement and scanner noise. All participants were instructed to keep relax and close their eyes without falling asleep. Scans were performed by a standard echo-planar imaging pulse sequence with the following scan parameters: TR/TE = 2000 ms/30 ms, flip angle (FA) = 90°, matrix size = 64 × 64, field of view (FOV) = 240 × 240 mm^2, 35 interleaved slices and slice thickness = 4 mm (no gap). The scan lasted for 510 s for each subject, and 255 volumes were acquired. T1-weighted anatomical data were acquired using an MPRAGE (MEMPR) sequence (scan parameters: TR/TE = 1900 ms/3.43 ms, FA = 90°, matrix size = 256 × 256, FOV = 240 mm × 240 mm, slice thickness = 1 mm, voxel size = 0.9375 mm × 0.9375 mm × 1 mm, 160 slices). The anatomical data were used to normalize functional data.

All preprocessing steps were carried out using the data processing and analysis for (resting-state) brain imaging (DPABI, http://rfmri.org/dpabi; Yan et al. (2016)) and Matlab home script. Functional images were 1) discarded the first five volumes, 2) slice-time corrected, 3) realigned, 4) coregistered to the high-resolution 3D anatomic volume, 5) warped into Montreal Neurological Institute standard space using the deformations acquired from the realignment of the 3D anatomical data into Montreal Neurological Institute space and resampled the voxel size into 3 × 3 × 3 mm^3, 6) spatially smoothed using a 6-mm full-width half-maximum Gaussian kernel (not smoothed before variability of voxel-level regional homogeneity (ReHo) calculation (Zang et al. 2004)), 7) experienced wavelet despiking head motion artifacts (Patel et al. 2014), 8) regressed out motion and noninteresting signals, including linear trend, Friston 24 head motion parameters (Friston et al. 1996), white matter (CompCor, five principal components) and CSF signal (CompCor, five principal components, Behzadi et al. (2007)), and 9) filtered using a band-pass filter (1/w–0.1 Hz, high pass filtering using 1/w are suggested to remove spurious fluctuations in dynamic FC, when a certain window size w is given (Leonardi et al. 2015)).

There was no significant difference in mean FD between patient and control groups (patient, mean = 0.049, SD = 0.038; control, mean = 0.046, SD = 0.027; T-value = 0.88, P-value = 0.38). To further account for artifact of head motion, we excluded participants with >10% framewise displacements (FD > 0.5 mm, Power et al. (2012)) or rotation > 2.5 or translation > 2.5 mm prior to group comparisons. No participant excessed the 10% FD. We also corrected the head motion in the subsequent statistical comparisons through regarding mean FD as covariate (Yan et al. 2013).

Table 1 Demographic characteristics of the schizophrenia patients and controls

Variables	Patients (N = 96)		Health controls (N = 122)		P-value
	Mean	SD	Mean	SD	
Age (years)	39.78	11.48	37.95	14.74	0.32
Gender (male:female)	66:30		81:41		0.71[a]
Handedness (right:left)	93:3		121:1		0.32[a]
Education (years)[b]	11.64	2.94	11.07	3.22	0.22
Chlorpromazine equivalents (mg/d)[c]	332.95	165.06			
Duration of illness (years)	15.10	10.33	—	—	
PANSS-positive[d]	13.44	5.88	—	—	
PANSS-negative[d]	20.73	6.00	—	—	
PANSS-general[d]	28.22	5.81	—	—	
PANSS-total[d]	62.39	13.11	—	—	

PANSS, positive and negative syndrome scale.
[a]x^2 test.
[b]Data of 76 patients and 111 controls available.
[c]Data of 72 patients available.
[d]Data of 64 patients available

Temporal Variability of Regional Voxel-Level FC Architecture

In the current study, the ReHo Zang et al. (2004) was used to measure the regional voxel-level FC profile considering ReHo can reliably and effectively measure the local voxel-wise FC, which is largely independent from priori parametric setting (Zuo et al. 2013). ReHo is defined as the Kendall's W value between time series of a given voxel with its nearest 26 voxels. As shown in Figure 1*a*, to characterize the temporal variability of the voxel-level functional interactions, all BOLD time series were segmented into nonoverlapping windows with length *l*. In the current study, the nonoverlap windows were adopted. One consideration is that nonoverlap window provides a more accurate measure of the FC variation because of the independence of each window. The other consideration is that enough windows (12–24) can be obtained to evaluate the variation of FC within more than 8-min scanning duration (250 TR). Also, using the nonoverlap window enables the current study to keep consistent with the literature using the similar methods which showed nonoverlap window can effectively reflect brain network variability (Zhang et al. 2016; Sun et al. 2018). The ReHo map was further computed within each window. The mean and standard deviation (SD) maps were calculated across *n* time windows. To characterize the temporal variation of ReHo, the coefficient of variation (CV = SD/mean) map over time window was also calculated. To reduce the individual variations, the individual CV map was normalized by mean value in whole brain. Finally, CV maps were spatially smoothed (6-mm FWHM Gaussian kernel). In order to avoid arbitrary choice of time window length, CV maps were computed at different lengths (*l* = 20, 22, 24,…40 s) and then took the arithmetic average value as the final variability (Zhang et al. 2016). Higher CV of a voxel reflects higher variation of functional community of this voxel with its neighbor voxels across the time. As shown in Supplementary Figure S1, the mean spatial patterns of CV maps are very similar across all the window lengths, which indicated that CV maps are relatively stable. To reduce the potential noise from dynamic fluctuation centering on the low amplitude of feature (the ReHo value does not differ from zeros here), we further limited the variability analysis within areas with relatively high ReHo value. Thus, we computed the stable ReHo, then one-sample *t*-test was used to find the high-activity regions. As shown in Supplementart Figure S2, regions in DMN, FN, SN, and basal ganglia had higher activity (ReHo values) than other brain regions.

Temporal Variability of FC Architecture of Region Brain

In the present study, the Power-264 meta-analytic regions of interest (ROIs, Power et al. (2011)) and Human Brainnetome Atlas (Fan et al. 2016) of 246 ROIs (added the 26 cerebellum regions into the Atlas resulting in 272 ROIs) were adopted to verify the results. These two atlases almost span the whole brain, including the cerebral cortex, subcortical structures, and the cerebellum. We extracted the mean time series for ROIs in each atlas. To characterize the temporal variability of the FC architecture for a brain region (Fig. 1*b*), all BOLD time series were first segmented into *n* nonoverlapping windows with length *l*. Within the *i*th window, a $q \times q$ Pearson correlation matrix (q = the number of nodes) represents the FC of whole brain (Fi). The FC architecture of ROI k at time window i is described by $F(i,k)$ which is an 1D vector (Fig. 1*b*, the shaded column) and characterizes the whole-brain functional architecture of region k. Then, the variability of FC architecture for a brain region k is defined as:

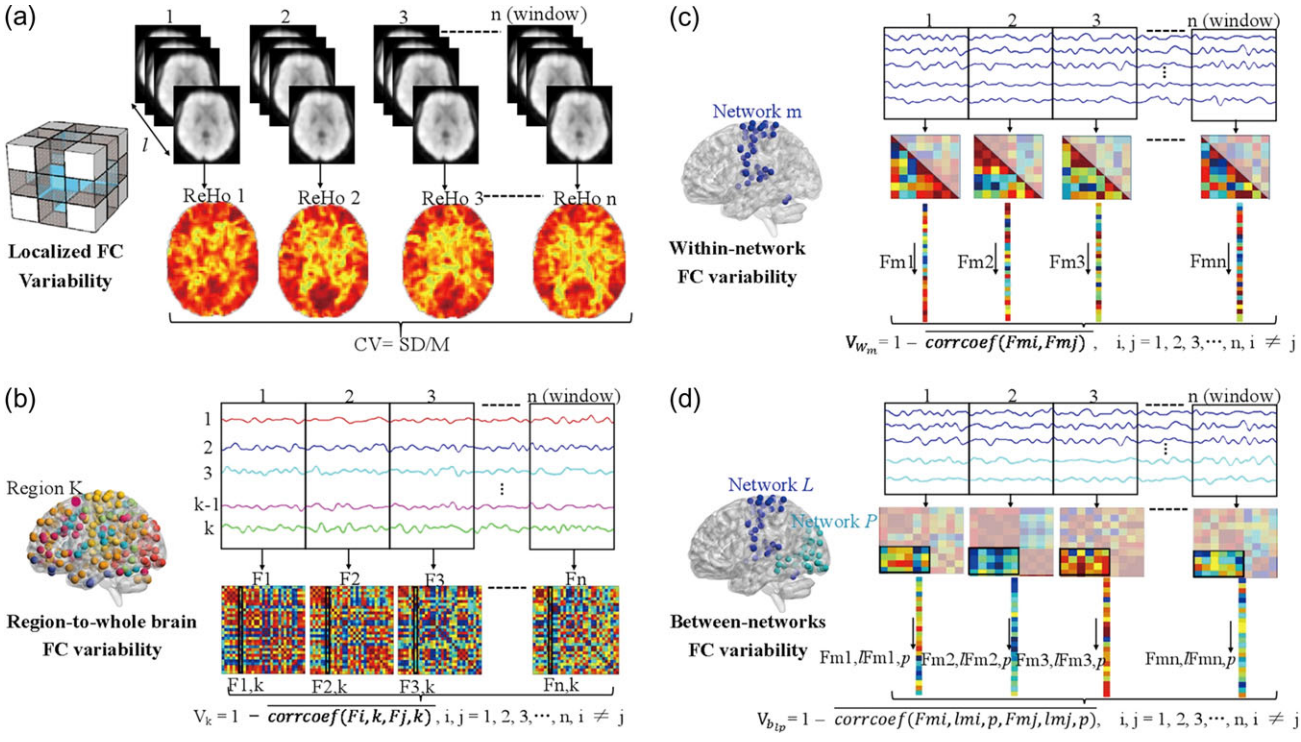

Figure 1. Method overview. (*a*) Temporal variability of local FC architecture. (*b*) Temporal variability of FC architecture of region-to-whole brain. (*c*) Temporal variability of FC architecture within-network. (*d*) Temporal variability of FC architecture between-networks.

$$V_k = 1 - \overline{\text{corrcoef}(F(i,\ k),\ F(j,\ k))}, \quad i, j = 1, 2, 3, \cdots, n;\ i \neq j$$

Likewise, we computed V_k at different window lengths (l = 20, 22, 24, … 40 s) and then took the arithmetic average value as the final variability to avoid arbitrary choice of time window length. Notably, higher V_k of a region indicates more functional communities of this region will be involved across the time (Zhang et al. 2016).

Temporal Variability of FC Architecture Within- or Between-Brain Networks

To characterize the variability of FC architecture within a specific network or between two networks, we first divided the ROIs of each atlas into seven prior brain networks created by a previous whole-brain network segmentation including VN, SS, DAN, VAN, limbic network (LN), FN, and DMN from 1000 health participants (Buckner et al. 2011; Yeo et al. 2011; Choi et al. 2012). The thalamus was treated as a single network, given it was poorly defined into different rsFC networks as well as its special role in understanding pathophysiologic mechanism in schizophrenia (Pergola et al. 2015; Li et al. 2017). Then, similar procedures adopted in regional brain variability above were used to define variability of functional architecture within- or between-brain networks (Sun et al. 2018). For a given brain network m, all FCs within this network in window i were reshaped as 1D vector, F_{mi} (the columns in Fig. 1*c*); similarly, for all FCs' between-network I and p in window i were denoted as 1D vector, $F_{mi,lmi,p}$ (the columns in Fig. 1*d*). Then, the variability of FC architecture within-network m across n windows (which is shortened as within-network variability in the follow-up sections) is defined as:

$$V_{w_m} = 1 - \overline{\text{corrcoef}(F_{mi},\ F_{mj})} \qquad i, j = 1, 2, 3, \cdots, n;\ i \neq j,$$

The variability of FC architecture between-network l and p (which is shortened as between-network variability in the follow-up sections) is defined as:

$$V_{bl_p} = 1 - \overline{\text{corrcoef}(F(mi,\ lmi,\ p),\ F(mj,\ lmj,\ p))} \qquad i, j = 1, 2, 3, \cdots, n;\ i \neq j$$

Variability of within-network describes the extent to which the FC within a specific brain network is changing synchronously across different time windows. Similarly, variability of between-network characterizes the extent to which the FC between two brain networks is changing across different time windows. Higher variability of FC architecture of within or between two brain networks indicates that the network of interest, or the interaction between two networks, demonstrate richer FC patterns possibly underlying frequent information communication (Sun et al. 2018).

Statistical Analysis

Before conducting the test, the distribution of the ReHo CV value was evaluated for each voxel using the Jarque–Bera test (Jarque and Bera 1980). As indicated by Supplementary Figure S3, CV value of ReHo in most regions is normally distributed. To determine variability differences between schizophrenia and HCs, two-sample *t*-test was performed on individual normalized ReHo CV maps, variability of 264 brain regions, within-brain network variability and between-brain networks variability, with age, gender, years of education, and mean displacements of head movement (FD) being regressed out. For the local FC variability, significance was set at $P < 0.05$, which was performed in the DPABI (false discovery rate corrected, FDR). For ROI-based level, network-level FC, and correlation analysis between variability and clinical symptom, results were also corrected using FDR ($P < 0.05$) multiple comparison correction (Benjamini and Hochberg 1995) implemented in Matlab 2013b. For the local FC variability, the correction was conducted within group mask where the voxels are present in at least 90% of participants.

To investigate the correlations between the altered variability of brain's functional connectivity and the clinical features (PANSS-positive, -negative, general psychopathology subscales, and overall scores) in the patient group, we calculated the Pearson correlations between the above four indices of FC variability, which illustrated significant alterations in patients group and the clinical features. Duration of illness was not considered separately because it is highly correlated with age (Moser et al. 2018).

Results

Temporal Variability of Regional Voxel-Level FC

Supplementary Figure S4 shows one-sample *t*-test results for the ReHo CV across all the window lengths of each group, respectively. Visual inspection indicated that the variation of ReHo is high among all the cortices, especially with higher variation in lower level primary sensory and motor areas, as well as subcortical regions but with relatively lower variation in DMN. Given the mean value is important for understanding FC in human brain, we calculated the mean of ReHo across all window lengths for each participant and then performed one-sample *t*-test for each group. As shown in Supplementary Figure S5, the mean value of ReHo is relatively higher in DMN but lower in primary sensory and motor areas. Herein, these within-group maps are merely for visualizing variability and mean of ReHo. Two-sample *t*-test with FDR corrected ($P < 0.05$) demonstrated that patients with schizophrenia relative to HC illustrated significantly increased variability of regional voxel-level FC in regions widely distributed across VN (bilateral lingual gyrus and lateral occipital cortex), SS (bilateral precentral gyrus and postcentral gyrus), VAN (bilateral anterior insular and anterior cingulate gyrus), thalamus, and cerebellum, as shown in Table 2 and Figure 2. We found no decreased variability of regional voxel-level FC in schizophrenia.

Temporal Variability of Brain Region FC

The analysis using two atlases consistently revealed that variability of FC in brain regions from VN, SS, DAN, VAN, and thalamus to whole brain were found to be significantly increased in schizophrenia patients (Supplementary Table S1 and Fig. 3). The variability of FC in brain regions from DMN and FN to whole brain were found to be significantly decreased in schizophrenia patients (Supplementary Table S1 and Fig. 3). Reported results were corrected using FDR ($P < 0.05$).

Temporal Variability of FC Architecture Networks

As shown in Table 3 and Figure 4, schizophrenia patients consistently showed increased within-network variability in VN, SS, and Tha, while decreased within-network variability was found in DMN and FN when using two atlases (FDR corrected, $P < 0.05$). Among all the 28 between-networks temporal

Table 2 Group differences in local voxel-level FC variability

Brain regions	T-value	Voxels(k)	MNI coordinates		
			X	Y	Z
Patients > controls					
L post/precentral Gyrus	8.85	6498	−51	−21	51
R post/precentral Gyrus	8.35		48	−18	54
L postcentral Gyrus	8.04		−39	−36	69
L central opercular cortex	7.52		−48	−14	17
L insular cortex	7.33		−40	12	−9
R central opercular cortex	7.11		46	−16	19
R insular cortex	6.73		44	10	−9
L intracalcarine	8.65	5758	−6	−90	0
R occipital pole	8.61		18	−90	21
R lateral occipital cortex	8.59		51	−72	3
L lateral occipital cortex	7.93		−45	−81	2
Cerebellum vermis_3/4	6.98		1	−46	−21
L thalamus	7.29	376	−9	−21	12
R thalamus	6.64		9	−21	9
R thalamus	6.17		15	−24	0
R pallidum	5.51	29	21	0	0
R frontal pole	5.29	57	30	57	27
R frontal pole	5.21		18	60	30
R supramarginal gyrus	4.66	28	60	−42	48
Patients < controls					
None					

Notes: L, left side of brain; R, right side of brain. This report is based on threshold with $T = 4$ ($k > 10$), which made the clusters separated as sparse as possible.

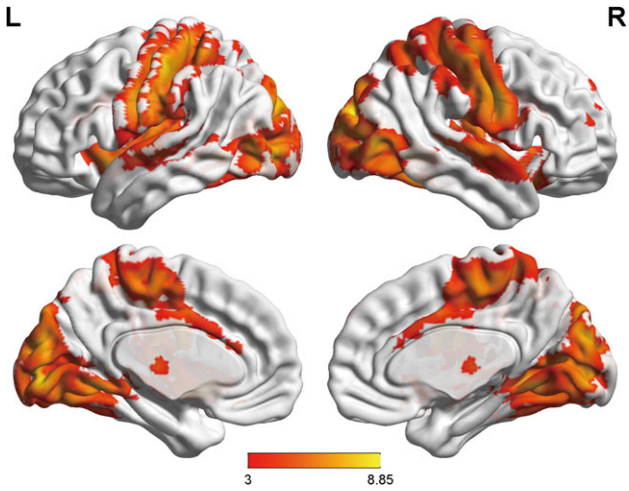

Figure 2. Group differences in temporal variability of local FC. Patients showed only significantly increased value. L refers to left side of brain. R refers to right side of brain. All results are shown after FDR corrected ($P < 0.05$).

variability ($8 \times 7/2$), we found there were three significant increased between-network variability (VN-Tha, SS-VAN, SS-Tha) and one decreased between-network variability (DMN-FN) after FDR correction ($P < 0.05$).

Correlations Between Variability of FC and Clinical Variables

For severity of symptoms, severity of positive symptoms were found to be related to several regions showing group differences in variability of regional voxel-level FC, for example, pre/postcentral gyrus, lateral occipital cortex (Supplementary Table S2 and Fig. 5*a*). The variability of region-to-whole-brain FC in right lingual gyrus showed negative correlation with severity of positive symptoms (Supplementary Table S2 and Fig. 5*b*). There was positive association between scores of negative symptoms subscales and variability of region-to-whole-brain FC in right insula (Supplementary Table S2 and Fig. 5*c*). And, there were negative associations between scores of general psychopathology subscales and variability of region-to-whole-brain FC in the nodes of VN (right lingual gyrus), SS (bilateral precentral gyrus) and thalamus (Supplementary Table S2 and Fig. 5*d*). Likewise, overall symptoms were found to be negatively correlated with variability of FC in nodes of VN, SS and thalamus (Supplementary Table S2 and Fig. 5*e*).

Discussions

Using a time-varying approach, this study presents novel insights into schizophrenia-related alterations of dynamic functional connectivity in a comprehensive set at three different levels. Patients were found to show the consistent increased FC variability in sensory and perceptual system, including VN, SS, VAN, and thalamus at all the three levels. Decreased variability in high-order networks, such as default mode network and frontal–parietal network were also consistently observed at both the region-to-whole brain level and the network level but not at the regional voxel level. Critically, these altered variabilities of FC were associated with the psychotic symptoms. Resonating with recent theory and experiment studies (Postmes et al. 2014; Javitt and Freedman 2015; Kaufmann et al. 2015; Bordier et al. 2018), these novel findings question the mainstream view that schizophrenia is primarily a cognitive illness, highlight the critical role of bottom-up processing in understanding the pathological mechanism in schizophrenia and support that psychiatric symptoms may in fact rather result from cumulative cascade impairments stemming from disrupted dynamic reconfiguration of sensory and perceptual system, in combination with failed dynamic integration in higher order processes.

Previous several studies have investigated the static local FC using ReHo approach in schizophrenia (Liu et al. 2006; Jiang et al. 2010; Chen et al. 2013; Yu et al. 2013). However, no study has explored the temporal variability of local FC. This study is the first one in which schizophrenia patients were observed to show no decreased but increased temporal variability of local FC in low-level primary sensory and perceptual system widely distributed across VN, SS, VAN, and thalamus. Most of these locations were in line with the recent meta-analyses' findings of static ReHo (Xu et al. 2015). Deficits of perceptual processing and multisensory integration were well documented in schizophrenia (Javitt and Freedman 2015; Tseng et al. 2015; Hornix et al. 2018). Heightened instability of local functional synchrony in primary perceptual regions, such as VN regions (bilateral lingual gyrus and lateral occipital cortex), SS regions (bilateral precentral gyrus and postcentral gyrus) in schizophrenia patients might reflect impairments in the integration of various perceptual stimuli (Chen et al. 2015). Interestingly, Kaufmann et al. (2015) also observed altered standard deviation in signal amplitude in a range of visual, sensorimotor areas in schizophrenia. The dACC and insula together constitute the VAN or salience network which plays a cardinal role in psychosis (Palaniyappan and Liddle 2012). Enhanced instability of local functional synchrony in VAN may provide new novel evidence to reflect the inappropriate

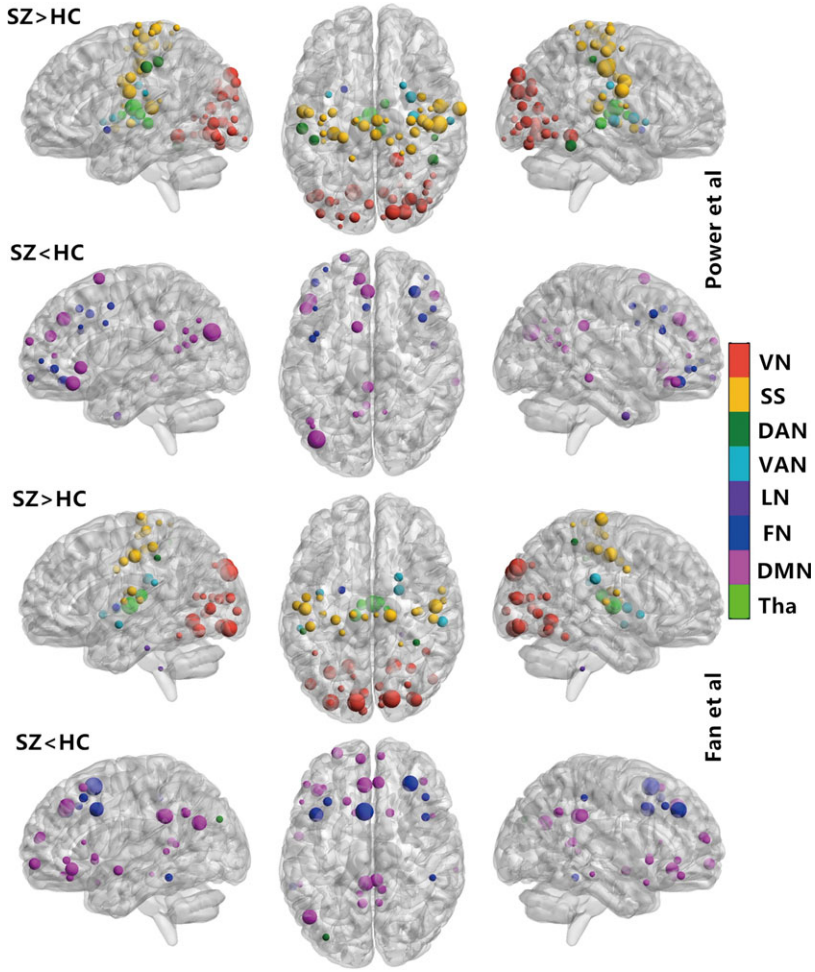

Figure 3. Group differences in temporal variability of FC architecture of region-to-whole brain. VN, visual network; SS, sensorimotor network; DAN, dorsal attention network, VAN, ventral attention network, LN, limbic network LN; FN, frontal–parietal network; DMN, default model network; Tha, thalamus Network; HC, health control; SZ, schizophrenia. Size of plots is weighted by *T*-value. All results were shown after FDR corrected ($P < 0.05$).

Table 3 Group differences in - or between-network(s) FC variability

Network	Atlas			
	Power et al.		Fan et al.	
	T-value	*P*-value	*T*-value	*P*-value
Patients > controls (within-network)				
VN	3.06	2.48×10^{-3}	3.65	3.26×10^{-4}
SS	3.49	5.87×10^{-4}	4.50	1.10×10^{-5}
TN	4.39	1.80×10^{-5}	4.23	3.36×10^{-5}
Patients < controls (within-network)				
FN	−3.24	1.40×10^{-3}	−3.12	2.03×10^{-3}
DMN	−3.37	9.06×10^{-4}	−3.85	1.56×10^{-4}
Patients > controls (between-networks)				
VN-Tha	2.19	2.95×10^{-2}	3.19	1.61×10^{-3}
SS-VAN	3.63	3.58×10^{-4}	3.76	2.21×10^{-4}
SS-Tha	4.09	6.04×10^{-5}	3.50	5.73×10^{-4}
Patients < controls (between-networks)				
DMN-FN	−4.20	3.96×10^{-5}	−4.29	2.72×10^{-5}

Note: FDR corrected ($P < 0.05$).

mapping of saliency that originates from input external or internal perceptual information (Palaniyappan and Liddle 2012; Uddin 2015). Given its topographical connecting to the entire cortex (Behrens et al. 2003) and its critical gating and integration role in both sensory and higher order cognitive functions (Saalmann et al. 2012), altered structure and function of thalamus has been regarded as a hallmark feature of schizophrenia (Anticevic 2017; Li et al. 2017; Jiang, Duan et al. 2018, Jiang, Luo, Li, Duan et al. 2018). The strong sensory and perceptual involvement overlaps with findings from electroencephalogram studies, in which schizophrenia showed a broad range of sensory deficits reflected among various event-related potentials (e.g., reduced prepulse inhibition, mismatch negativity, P1, P3; Javitt and Freedman (2015)). Taken together, these increased local temporal variability in primary function regions provided novel evidence to support heightened instability in processing sensory and perceptual external or internal input in schizophrenia. Critically, these alterations showed close links with severity of positive symptoms, which highlights the importance of distorted perceptual information in understanding the positive symptom in schizophrenia (Borda and Sass 2015; Cassidy et al. 2018).

Interestingly, regions (ROIs) from VN, SS, SN, and thalamus were found to be encountered with increased temporal variability not only in local FC but also in their connectivity with the rest regions of the brain in schizophrenia patients. This supported both focal regions (in sensory and perceptual systems) and its distant FC with other brain regions' alterations in

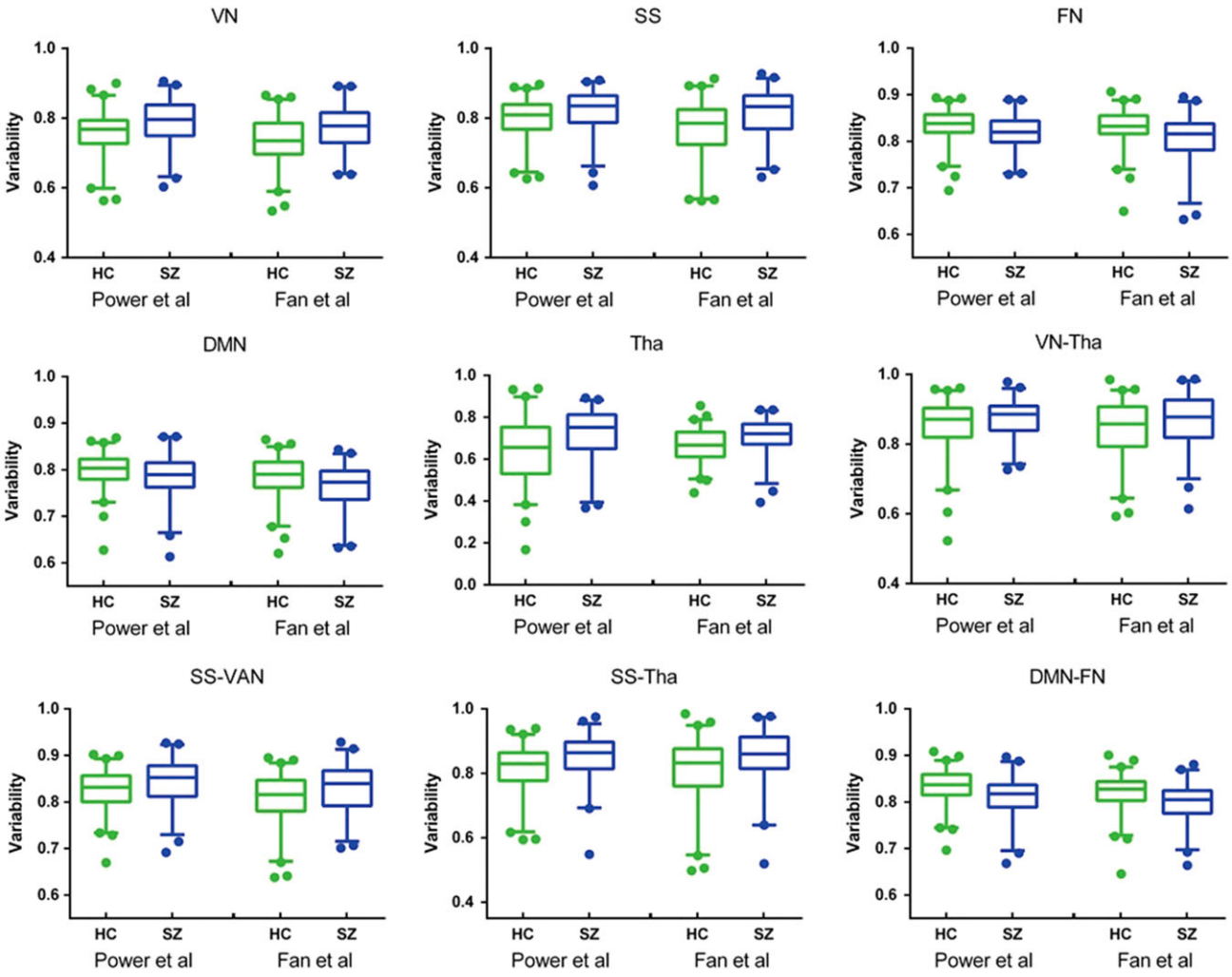

Figure 4. Group differences in temporal variability of FC architecture within- or between-network(s). VN, visual network; SS, sensorimotor network; DAN, dorsal attention network, VAN, ventral attention network, LN, limbic network LN; FN, frontal–parietal network; DMN, default model network; Tha, thalamus Network; HC, health control; SZ, schizophrenia. Plots reflect value below 2.5% or above 97.5%. All results were shown after FDR corrected ($P < 0.05$).

schizophrenia revealed by recent static FC study (Kaufmann et al. 2015; Li et al. 2017). The heightened variability of these regions indicates that these regions are over functionally interacting with other parts of the brain across the time (Zhang et al. 2016). These increased variability of the observed region to whole-brain FC may further result in spreading and amplifying the input incoherent sensory and perceptual information that is not appropriately processed within these local regions to the distant brain regions. This supported significant contributions of early sensory processing dysfunction to higher order cognitive impairments (Adcock et al. 2009; Javitt 2009; Leitman et al. 2010; Bordier et al. 2018). This spreading would be worse when the corresponding networks could not effectively and dynamically integrate the distorted discrete information within-region, as demonstrated by the increased instability of FC within VN, SS, and thalamus and FC between SS and VAN, between thalamus and SS, between thalamus and VN. The increased variability of between thalamus and SS, between thalamus and VN was consistent with previous static FC study (Li et al. 2017), further confirming the special role of thalamocortical circuitry in understanding the pathogenesis of schizophrenia, especially for chronic patients. Similarly, Damaraju et al. (2014) reported that patients showed most pronounced FC abnormalities in connectivity states of increased connectivity among perceptional networks. Through analyzing the modular organization, previous study also observed substantial fragmentation and reorganization involving primary sensory and visual areas in schizophrenia (Bordier et al. 2018). Intriguingly, the increased temporal FC variability in sensory and perceptual system was catering for the previous observation of increased spatial variability of sensory components in schizophrenia (Gopal et al. 2016). Combining previous work and the current novel findings, the various functional properties of sensory and perceptual systems are disrupted and convergent, unfortunately, this disruption is still not regarded as the intervention target.

In addition, decreased temporal variability of FC in vast regions form DMN and FN to distant brain were found in schizophrenia. Meanwhile, the variability of FC within DMN and FN and the variability of FC between DMN and FN were also reduced in schizophrenia. The FN and DMN belong to the high-order networks in the brain, which contribute to coordinating other brain networks to manage the external and internal information and form the integrity of self (Buckner and Carroll 2007; Smallwood et al. 2012). And the abnormal function

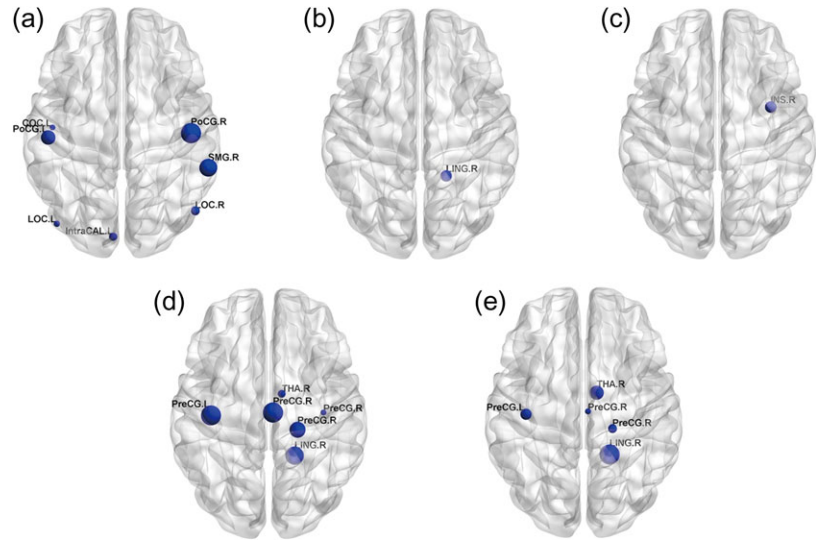

Figure 5. Correlations between variability of FC and clinical variables. (*a*) The negative correlation between altered voxel-level FC variability and positive symptoms. (*b*) The negative correlation between-region whole-brain FC variability and positive symptoms. (*c*) The positive correlation between-region whole-brain FC variability and negative symptoms. (*d*) The negative correlation between-region whole-brain FC variability and general symptoms. (*e*) The negative correlation between-region whole-brain FC variability and overall symptoms. COC.L, L central opercular cortex; INS.R, R insular cortex; IntraCAL.L, L intracalcarine; LING.R, R lingual gyrus; LOC.R, R lateral occipital cortex; LOC.L, L lateral occipital cortex; PoCG.L, L postcentral gyrus; PoCG.R, R postcentral gyrus; PreCG.L, L precentral gyrus; PreCG.R, R precentral gyrus; SMG.R, R supramarginal gyrus. THA.R, R thalamus. Size of plots is weighted by *r* value. All results were shown after FDR corrected ($P < 0.05$).

properties of DMN and FN have well been documented in schizophrenia (Bluhm et al. 2007; Fornito and Bullmore 2015; Dong et al. 2018). Combining with the heightened instability of FC within sensory and perceptual systems, reduced dynamic reconfiguration in higher order network further suggested the weak ability of schizophrenia in coordinating and integrating sensory and perceptual information, which may lead to fragmented self (Postmes et al. 2014; Sass 2014; Borda and Sass 2015; Ebisch and Aleman 2016). We did not find the reduced variability of local FC in DMN and FN, which is consistent with previous static ReHo findings (Xu et al. 2015). Considering consistent alterations of FC variability in high-order networks in both the region-to-whole brain level and the network level but not at the regional voxel level, we speculated that except that the choice of different neuroimaging marker may contribute to this inconsistency, because the sensitivities of each scale may be different to detect the alterations between schizophrenia and patients. Also, we speculated that this observation may further suggest that the altered dynamic reconfiguration of these regions in schizophrenia may be prone to brain network level partially, because these regions belong to hub regions in the brain (Bullmore and Sporns 2009; van den Heuvel and Sporns 2013).

It is recent that neurobiological accounts of schizophrenia have begun to put underline on changes in aberrant sensory (bottom-up) processing, although this deficit has already been suggested earlier. It has been evidenced that the sensory and perceptual deficits can be attributed as the causal role in higher level cognitive processes and clinical symptoms, for example, hallucinations (Stevenson et al. 2017; Cassidy et al. 2018; Hornix et al. 2018). However, the potential neural mechanism of deficits of sensory processing and multisensory integration remained elusive, especially in the field of fMRI. Using recent advanced method of dynamic FC, increased FC variability in primary networks, including VN, SS, and VAN, were consistently found at different scales, which suggest the elevated instability of perceptual processing for intrinsic and outside-world input information in schizophrenia. This could be further regarded as a possible mechanism underlying the distorted perception and cognition in schizophrenia, especially their clinical symptoms such as hallucination, delusion (Jorgensen et al. 2016; Stevenson et al. 2017). Decreased FC variability in high-order networks, such as DMN and FN, were also consistently verified at whole-brain connectome scale, suggesting the attenuated interaction of those so-called hub networks in schizophrenia (less flexible). This could further suggest the vulnerability of external and internal multisensory integration to form self-integrity in schizophrenia. These findings also verified the perceptual incoherence hypothesis of self-disorder in schizophrenia, which emphasizes that the self-disorder in schizophrenia is more due to perceptual incoherence (Sass and Parnas 2003; Postmes et al. 2014; Borda and Sass 2015; Sass and Borda 2015). Present findings provided vivid and strong evidence to build the neural links between perceptual incoherence and self-deficits in schizophrenia. Also, these results encourage future studies to develop the novel intervention strategies, such as complementary sensory-based therapies, which may help to diminish perceptual incoherence and thus improve coherent self-experiences in schizophrenia. This hope is supported by findings of plasticity in temporal precision and notably audiovisual (Powers et al. 2012; Setti et al. 2014) and visual (Stevenson et al. 2013) temporal acuity through perceptual training. Considering the strong associations between audiovisual temporal processing impairments and clinical symptomatology (Stevenson et al. 2017), for example, auditory hallucinations (Hugdahl 2009), training focused on multisensory temporal processing may produce clinical effects through increasing the individual experience level of perceptual coherence in schizophrenia. This hope was also preliminarily bolstered by our recent works (He et al. 2018; Yang et al. 2018), in which the music intervention (listening to Mozart music), as a type of the auditory input, improved the functional integration in VAN and SSs in schizophrenia. In addition, considering numerous studies have shown that noninvasive neuromodulation technique, for example, repetitive transcranial magnetic

stimulation (rTMS) can produce promising clinical effects in patients with schizophrenia, especially for negative symptoms and auditory hallucinations (Lefaucheur et al. 2014; Chen et al. 2018), it is worth for future study to explore whether combing sensory-based and rTMS treatment would produce more significant clinical effects than conducting each modality separately.

Notwithstanding its implications, the main limitations of this study should be acknowledged. The main limitation in the current study, as well as many other studies in the field, is the effect of antipsychotic drug. While we cannot eliminate completely the potential confounding effects of medication, we found that medication was not associated with altered variability of FC after corrected (Supplementary Table S3) except for two weak correlations with *P*-value equaling to about 0.05 (uncorrected), suggesting that these changes are unlikely to be mainly driven by medication. As for any study investigating rsFC, we cannot also fully rule out the effects of head motion. Yet we did our best to address this issue, including wavelet despiking processing, deleting data with high and frequent head motion, regressing out 24 motion parameters and taking relative motion as a covariate in statistical analysis. In addition, we conducted repeated analysis using two groups with well-matched head motion. We did not find evidence for systematic effect of motion on the observed main findings (Supplementary Table S4 and Figs S6–8). Third, although the SZ finding is robust in both atlases, we cannot completely exclude the potential effect of using different scale atlases on our results, especially given it remains unclear choosing how much scale ROIs is optimal to build reliable functional connectivity. Fourth, although the full repertoire of functional networks utilized by the brain is continuously and dynamically "active" even when at "rest" (Smith et al. 2009), it is not clear to what extent schizophrenia-related abnormality in dynamic reconfiguration of sensory and perceptual system would exist during the performance of other tasks, for example, sensory-related task. Fifth, this study cannot allow us to establish the developmental trajectories of altered temporal variability of FC in schizophrenia due to use of a cross-sectional research design. Because the altered stable FC in perceptual system coexisted in childhood-onset and chronic schizophrenia (Chen et al. 2015; Berman et al. 2016), naturally, we inferred that the aberrant dynamic reconfiguration of sensory and perceptual system could be a reliable feature at different state of illness. Once again, the current findings help to justify future research that employs costly longitudinal designs to evaluate the development of FC variability among schizophrenia over repeated assessments. In addition, there are increasing evidences to support that resting-state fMRI can be used to estimate the functional organization of brain white matter (Ji et al. 2017; Ding et al. 2018). Using clustering analysis, we previously found abnormalities of static perception-motor white matter functional networks in schizophrenia (Jiang, Luo, Li, Li et al. 2018). Herein, we focused on our analysis in gray matter ROI. As an important extension, future studies are needed to illustrate the potential impairments of dynamic white matter functional networks and dynamic associations between gray matter and white matter networks in schizophrenia, which may highlight more comprehensive pathological mechanism.

In this study, the global signal of brain was not removed in FC analysis, as altered global signal was the important neuroimaging feature in schizophrenia (Hahamy et al. 2014, Yang et al. 2014) and it has been shown to induce anticorrelations in resting-state data (Murphy et al. 2009). Given the topic of global signal regression (GSR) is still one of the most controversial issues in neuroimaging. To investigate the potential effects of GSR on our findings, we repeated core analyses with GSR, which does not significantly affect trends of overall results. Detained discussion can be found in Supplementary Material (Table S4 and Figs S6–8).

In summary, this study provided novel and strong evidence for functional impairment of sensory and perceptual system in schizophrenia, as demonstrated by consistent increased variability in primary sensory and perceptual system, including VN, SS, VAN across all three different FC levels. In addition, decreased variability in high-order networks, such as DMN and FN, were also consistently verified at whole-brain connectome level but not at the voxel level. These findings highlighted the rudimentary role of heightened dynamic communication of primary network (mainly suggests sensory and perceptual input is unstable in schizophrenia) and attenuated dynamic whole-brain integration of high-order network in schizophrenia. These findings provided novel neural correlates to verify the hypothesis of disintegrated sensory and cognitive processes in schizophrenia, further highlighting the critical role of bottom-up processing in understanding the pathological mechanism in schizophrenia, to some extent, which is overlooked in psychosis. Shifting research focus from the traditional cognitive to the emerging sensory and perceptual domain and investigating their dynamic interactions may be the key to enhance our understanding of pathophysiology in schizophrenia, improve early detection of psychosis, and further extend the range of intervention treatment possibilities.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

Funding

National Nature Science Foundation of China (Nos: 81471638, 81330032, 81861128001, and 81771822), the Chinese Fundamental Research Funding for Central Universities (No. ZYGX2016J124), and the Project of Science and Technology Department of Sichuan Province (Nos. 2017HH0001 and 2017SZ0004).

Notes

Conflict of Interest: None declared.

References

Adcock RA, Dale C, Fisher M, Aldebot S, Genevsky A, Simpson GV, Nagarajan S, Vinogradov S. 2009. When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia. Schizophr Bull. 35(6):1132–1141.

Anticevic A. 2017. Understanding the role of thalamic circuits in schizophrenia neuropathology. Schizophrenia Res. 180: 1–3.

Avena-Koenigsberger A, Misic B, Sporns O. 2018. Communication dynamics in complex brain networks. Nat Rev Neurosci. 19(1): 17–33.

Behrens TEJ, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CAM, Boulby PA, Barker GJ, Sillery EL, Sheehan K, Ciccarelli O, et al. 2003. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci. 6(7):750–757.

Behzadi Y, Restom K, Liau J, Liu TT. 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage. 37(1):90–101.

Benjamini Y, Hochberg Y. 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B-Methodological. 57(1):289–300.

Berman RA, Gotts SJ, McAdams HM, Greenstein D, Lalonde F, Clasen L, Watsky RE, Shora L, Ordonez AE, Raznahan A, et al. 2016. Disrupted sensorimotor and social–cognitive networks underlie symptoms in childhood-onset schizophrenia. Brain. 139(1):276–291.

Bluhm RL, Miller J, Lanius RA, Osuch EA, Boksman K, Neufeld RWJ, Theberge J, Schaefer B, Williamson P. 2007. Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. Schizophr Bull. 33(4):1004–1012.

Borda JP, Sass LA. 2015. Phenomenology and neurobiology of self disorder in schizophrenia: primary factors. Schizophrenia Res. 169(1–3):464–473.

Bordier C, Nicolini C, Forcellini G, Bifone A. 2018. Disrupted modular organization of primary sensory brain areas in schizophrenia. Neuroimage Clin. 18:682–693.

Buckner RL, Carroll DC. 2007. Self-projection and the brain. Trends Cogn Sci. 11(2):49–57.

Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BTT. 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol. 106(5): 2322–2345.

Bullmore ET, Sporns O. 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 10(3):186–198.

Calhoun VD, Miller R, Pearlson G, Adali T. 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron. 84(2):262–274.

Cassidy CM, Balsam PD, Weinstein JJ, Rosengard RJ, Slifstein M, Daw ND, Abi-Dargham A, Horga G. 2018. A Perceptual inference mechanism for hallucinations linked to striatal dopamine. Curr Biol. 28(4):503–514.

Chen X, Duan M, He H, Yang M, Klugah-Brown B, Xu H, Lai Y, Luo C, Yao D. 2016. Functional abnormalities of the right posterior insula are related to the altered self-experience in schizophrenia. Psychiatry Res Neuroimaging. 256:26–32.

Chen X, Duan M, Xie Q, Lai Y, Dong L, Cao W, Yao D, Luo C. 2015. Functional disconnection between the visual cortex and the sensorimotor cortex suggests a potential mechanism for self-disorder in schizophrenia. Schizophrenia Res. 166(1-3):151–157.

Chen X, Ji G-J, Zhu C, Bai X, Wang L, He K, Gao Y, Tao L, Yu F, Tian Y, et al. 2018. Neural correlates of auditory verbal hallucinations in schizophrenia and the therapeutic response to theta-burst transcranial magnetic stimulation. Schizophr Bull. https://doi.org/10.1093/schbul/sby054

Chen X, Jiang Y, Chen L, He H, Dong L, Hou C, Duan M, Yang M, Yao D, Luo C. 2017. Altered hippocampo-cerebello-cortical circuit in schizophrenia by a spatiotemporal consistency and causal connectivity analysis. Front Neurosci. 11:25.

Chen J, Xu Y, Zhang K, Liu Z, Xu C, Shen Y, Xu Q. 2013. Comparative study of regional homogeneity in schizophrenia and major depressive disorder. Am J Med Genet B Neuropsychiatr Genet. 162B(1):36–43.

Choi EY, Yeo BTT, Buckner RL. 2012. The organization of the human striatum estimated by intrinsic functional connectivity. J Neurophysiol. 108(8):2242–2263.

Damaraju E, Allen EA, Belger A, Ford JM, McEwen S, Mathalon DH, Mueller BA, Pearlson GD, Potkin SG, Preda A, et al. 2014. Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. Neuroimage Clin. 5:298–308.

Deco G, Tononi G, Boly M, Kringelbach ML. 2015. Rethinking segregation and integration: contributions of whole-brain modelling. Nat Rev Neurosci. 16(7):430–U81.

Ding Z, Huang Y, Bailey SK, Gao Y, Cutting LE, Rogers BP, Newton AT, Gore JC. 2018. Detection of synchronous brain activity in white matter tracts at rest and under functional loading. Proc Natl Acad Sci U S A. 115(3):595–600.

Dong D, Wang Y, Chang X, Luo C, Yao D. 2018. Dysfunction of large-scale brain networks in schizophrenia: a meta-analysis of resting-state functional connectivity. Schizophr Bull. 44(1):168–181.

Du Y, Fryer SL, Fu Z, Lin D, Sui J, Chen J, Damaraju E, Mennigen E, Stuart B, Loewy RL, et al. 2018. Dynamic functional connectivity impairments in early schizophrenia and clinical high-risk for psychosis. NeuroImage. 180(B):632–645.

Du Y, Pearlson GD, Yu Q, He H, Lin D, Sui J, Wu L, Calhoun VD. 2016. Interaction among subsystems within default mode network diminished in schizophrenia patients: a dynamic connectivity approach. Schizophrenia Res. 170(1):55–65.

Duan M, Chen X, He H, Jiang Y, Jiang S, Xie Q, Lai Y, Luo C, Yao D. 2015. Altered basal ganglia network integration in schizophrenia. Front Hum Neurosci. 9:561.

Ebisch SJH, Aleman A. 2016. The fragmented self: imbalance between intrinsic and extrinsic self-networks in psychotic disorders. Lancet Psychiatry. 3(8):784–790.

Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, Yang Z, Chu C, Xie S, Laird AR, et al. 2016. The human brainnetome atlas: a new brain atlas based on connectional architecture. Cereb Cortex. 26(8):3508–3526.

Fornito A, Bullmore ET. 2015. Reconciling abnormalities of brain network structure and function in schizophrenia. Curr Opin Neurobiol. 30:44–50.

Friston KJ, Williams S, Howard R, Frackowiak RSJ, Turner R. 1996. Movement-related effects in fMRI time-series. Magn Reson Med. 35(3):346–355.

Fu Z, Tu Y, Di X, Du Y, Pearlson GD, Turner JA, Biswal BB, Zhang Z, Calhoun VD. 2018. Characterizing dynamic amplitude of low-frequency fluctuation and its relationship with dynamic functional connectivity: an application to schizophrenia. NeuroImage. 180(B):619–631.

Gopal S, Miller RL, Michael A, Adali T, Cetin M, Rachakonda S, Bustillo JR, Cahill N, Baum SA, Calhoun VD. 2016. Spatial variance in resting fMRI networks of schizophrenia patients: an independent vector analysis. Schizophr Bull. 42(1):152–160.

Guo S, Zhao W, Tao H, Liu Z, Palaniyappan L. 2017. The instability of functional connectivity in patients with schizophrenia and their siblings: a dynamic connectivity study. Schizophrenia Res. 195:183–189.

Hahamy A, Calhoun V, Pearlson G, Harel M, Stern N, Attar F, Malach R, Salomon R. 2014. Save the global: global signal connectivity as a tool for studying clinical populations with functional magnetic resonance imaging. Brain Connect. 4(6): 395–403.

He H, Yang M, Duan M, Chen X, Lai Y, Xia Y, Shao J, Biswal BB, Luo C, Yao D. 2018. Music intervention leads to increased insular connectivity and improved clinical symptoms in schizophrenia. Front Neurosci. 11:744.

Hornix BE, Havekes R, Kas MJH. 2018. Multisensory cortical processing and dysfunction across the neuropsychiatric spectrum. Neurosci Biobehav Rev. https://doi.org/10.1016/j.neubiorev.2018.02.010

Hugdahl K. 2009. "Hearing voices": auditory hallucinations as failure of top-down control of bottom-up perceptual processes. Scand J Psychol. 50(6):553–560.

Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, Della Penna S, Duyn JH, Glover GH, Gonzalez-Castillo J, et al. 2013. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage. 80: 360–378.

Jarque CM, Bera AK. 1980. Efficient tests for normality, homoscedasticity and serial independence of regression residuals. Econ Lett. 6(3):255–259.

Javitt DC. 2009. Sensory processing in schizophrenia: neither simple nor intact. Schizophr Bull. 35(6):1059–1064.

Javitt DC, Freedman R. 2015. Sensory processing dysfunction in the personal experience and neuronal machinery of schizophrenia. Am J Psychiatry. 172(1):17–31.

Ji G-J, Liao W, Chen F-F, Zhang L, Wang K. 2017. Low-frequency blood oxygen level-dependent fluctuations in the brain white matter: more than just noise. Sci. Bull. 62:656–657.

Jiang Y, Duan M, Chen X, Zhang X, Gong J, Dong D, lI H, Yi Q, Wang S, Wang J, et al. 2018. Aberrant prefrontal-thalamic-cerebellar circuit in schizophrenia and depression: evidence from a possible causal connectivity. Int J Neural Syst. https://doi.org/10.1142/S0129065718500326

Jiang Y, Luo C, Li X, Duan M, He H, Chen X, Yang H, Gong J, Chang X, Woelfer M, et al. 2018. Progressive Reduction in gray matter in patients with schizophrenia assessed with MR imaging by using causal network analysis. Radiology. 287(2):633–642.

Jiang Y, Luo C, Li X, Li Y, Yang H, Li J, Chang X, Li H, Yang H, Wang J, et al. 2018. White-matter functional networks changes in patients with schizophrenia. NeuroImage. https://doi.org/10.1016/j.neuroimage.2018.04.018

Jorgensen KN, Nerland S, Norbom LB, Doan NT, Nesvag R, Morch-Johnsen L, Haukvik UK, Melle I, Andreassen OA, Westlye LT, et al. 2016. Increased MRI-based cortical grey/white-matter contrast in sensory and motor regions in schizophrenia and bipolar disorder. Psychol Med. 46(9):1971–1985.

Kahn RS, Keefe RSE. 2013. Schizophrenia is a cognitive illness time for a change in focus. JAMA. Psychiatry. 70(10):1107–1112.

Kaufmann T, Skåtun KC, Alnæs D, Doan NT, Duff EP, Tønnesen S, Roussos E, Ueland T, Aminoff SR, Lagerberg TV, et al. 2015. Disintegration of sensorimotor brain networks in schizophrenia. Schizophr Bull. 41(6):1326–1335.

Keilholz SD. 2014. The neural basis of time-varying resting-state functional connectivity. Brain Connect. 4(10):769–779.

Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, et al. 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 125(11):2150–2206.

Leitman DI, Sehatpour P, Higgins BA, Foxe JJ, Silipo G, Javitt DC. 2010. Sensory deficits and distributed hierarchical dysfunction in schizophrenia. Am J Psychiatry. 167(7):818–827.

Leonardi N, Van De Ville D. 2015. On spurious and real fluctuations of dynamic functional connectivity during rest. Neuroimage. 104:430–436.

Li T, Wang Q, Zhang J, Rolls ET, Yang W, Palaniyappan L, Zhang L, Cheng W, Yao Y, Liu Z, et al. 2017. Brain-wide analysis of functional connectivity in first-episode and chronic stages of schizophrenia. Schizophr Bull. 43(2):436–448.

Liu HH, Liu ZN, Liang M, Hao YH, Tan LH, Kuang F, Yi YH, Xu L, Jiang TZ. 2006. Decreased regional homogeneity in schizophrenia: a resting state functional magnetic resonance imaging study. Neuroreport. 17(1):19–22.

Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry. 66(8):811–822.

Moser DA, Doucet GE, Lee WH, Rasgon A, Krinsky H, Leibu E, Ing A, Schumann G, Rasgon N, Frangou S. 2018. Multivariate associations among behavioral, clinical, and multimodal imaging phenotypes in patients with psychosis. JAMA psychiatry. 75(4):386–395.

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage. 44(3):893–905.

Palaniyappan L, Liddle PF. 2012. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J Psychiatry Neurosci. 37(1):17–27.

Patel AX, Kundu P, Rubinov M, Jones PS, Vertes PE, Ersche KD, Suckling J, Bullmore ET. 2014. A wavelet method for modeling and despiking motion artifacts from resting-state fMRI time series. Neuroimage. 95:287–304.

Pergola G, Selvaggi P, Trizio S, Bertolino A, Blasi G. 2015. The role of the thalamus in schizophrenia from a neuroimaging perspective. Neurosci Biobehav Rev. 54:57–75.

Postmes L, Sno HN, Goedhart S, van der Stel J, Heering HD, de Haand L. 2014. Schizophrenia as a self-disorder due to perceptual incoherence. Schizophrenia Res. 152(1):41–50.

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 59(3):2142–2154.

Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, Vogel AC, Laumann TO, Miezin FM, Schlaggar BL, et al. 2011. Functional network organization of the human brain. Neuron. 72(4):665–678.

Powers AR, Hevey MA, Wallace MT. 2012. Neural correlates of multisensory perceptual learning. J Neurosci. 32(18):6263–6274.

Rashid B, Arbabshirani MR, Damaraju E, Cetin MS, Miller R, Pearlson GD, Calhoun VD. 2016. Classification of schizophrenia and bipolar patients using static and dynamic resting-state fMRI brain connectivity. Neuroimage. 134:645–657.

Rashid B, Damaraju E, Pearlson GD, Calhoun VD. 2014. Dynamic connectivity states estimated from resting fMRI Identify differences among schizophrenia, bipolar disorder, and healthy control subjects. Front Hum Neurosci. 8:897.

Jiang S, Zhou B, Liao Y, Liu W, Tan C, Chen X, Tang J. 2010. Primary study of resting state functional magnetic resonance imaging in early onset schizophrenia using ReHo. J Cent South Univ. 35(9):947–951.

Saalmann YB, Pinsk MA, Wang L, Li X, Kastner S. 2012. The pulvinar regulates information transmission between cortical areas based on attention demands. Science. 337(6095):753–756.

Sass LA. 2014. Self-disturbance and schizophrenia: structure, specificity, pathogenesis (current issues, new directions). Schizophrenia Res. 152(1):5–11.

Sass LA, Borda JP. 2015. Phenomenology and neurobiology of self disorder in schizophrenia: secondary factors. Schizophrenia Res. 169(1–3):474–482.

Sass LA, Parnas J. 2003. Schizophrenia, consciousness, and the self. Schizophr Bull. 29(3):427–444.

Setti A, Stapleton J, Leahy D, Walsh C, Kenny RA, Newell FN. 2014. Improving the efficiency of multisensory integration

in older adults: audio-visual temporal discrimination training reduces susceptibility to the sound-induced flash illusion. Neuropsychologia. 61:259–268.
Smallwood J, Brown K, Baird B, Schooler JW. 2012. Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought. Brain Res. 1428:60–70.
Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, et al. 2009. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A. 106(31):13040–13045.
Stevenson RA, Park S, Cochran C, McIntosh LG, Noel J-P, Barense MD, Ferber S, Wallace MT. 2017. The associations between multisensory temporal processing and symptoms of schizophrenia. Schizophrenia Res. 179:97–103.
Stevenson RA, Wilson MM, Powers AR, Wallace MT. 2013. The effects of visual training on multisensory temporal processing. Exp Brain Res. 225(4):479–489.
Sun J, Liu Z, Rolls ET, Chen Q, Yao Y, Yang W, Wei D, Zhang Q, Zhang J, Feng J, et al. 2018. Verbal creativity correlates with the temporal variability of brain networks during the resting state. Cereb Cortex. https://doi.org/10.1093/cercor/bhy010
Tseng H-H, Bossong MG, Modinos G, Chen K-M, McGuire P, Allen P. 2015. A systematic review of multisensory cognitive-affective integration in schizophrenia. Neurosci Biobehav Rev. 55:444–452.
Uddin LQ. 2015. Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci. 16(1):55–61.
Van Den Heuvel MP, Pol HEH. 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol. 20(8):519–534.
van den Heuvel MP, Sporns O. 2013. Network hubs in the human brain. Trends Cogn Sci. 17(12):683–696.
van Os J, Kapur S. 2009. Schizophrenia. Lancet. 374(9690): 635–645.
Xu Y, Zhuo C, Qin W, Zhu J, Yu C. 2015. Altered spontaneous brain activity in schizophrenia: a meta-analysis and a large-sample study. Biomed Res Int. 2015:204628.
Yan C-G, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, Li Q, Zuo X-N, Castellanos FX, Milham MP. 2013. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage. 76(1):183–201.
Yan C-G, Wang X-D, Zuo X-N, Zang Y-F. 2016. DPABI: data processing & analysis for (resting-state) brain imaging. Neuroinformatics. 14 (3):339–351.
Yang GJ, Murray JD, Repovs G, Cole MW, Savic A, Glasser MF, Pittenger C, Krystal JH, Wang X-J, Pearlson GD, et al. 2014. Altered global brain signal in schizophrenia. Proc Natl Acad Sci U S A. 111(20):7438–7443.
Yang M, He H, Duan M, Chen X, Chang X, Lai Y, Li J, Liu T, Luo C, Yao D. 2018. The effects of music intervention on functional connectivity strength of the brain in schizophrenia. Neural Plast. 2018:2821832.
Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zoeller L, Polimeni JR, et al. 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 106(3): 1125–1165.
Yu R, Hsieh MH, Wang H-LS, Liu C-M, Liu C-C, Hwang T-J, Chien Y-L, Hwu H-G, Tseng W-YI. 2013. Frequency dependent alterations in regional homogeneity of baseline brain activity in schizophrenia. PLoS One. 8(3):e57516.
Zang YF, Jiang TZ, Lu YL, He Y, Tian LX. 2004. Regional homogeneity approach to fMRI data analysis. Neuroimage. 22(1): 394–400.
Zhang J, Cheng W, Liu Z, Zhang K, Lei X, Yao Y, Becker B, Liu Y, Kendrick KM, Lu G, et al. 2016. Neural, electrophysiological and anatomical basis of brain-network variability and its characteristic changes in mental disorders. Brain. 139(Pt 8): 2307–2321.
Zuo X-N, Xu T, Jiang L, Yang Z, Cao X-Y, He Y, Zang Y-F, Castellanos FX, Milham MP. 2013. Toward reliable characterization of functional homogeneity in the human brain: preprocessing, scan duration, imaging resolution and computational space. Neuroimage. 65:374–386.