OXFORD

Cerebral Cortex, 2023, 1–10
https://doi.org/10.1093/cercor/bhad185
Original Article

Spatiotemporal dynamics of functional connectivity and association with molecular architecture in schizophrenia

Changyue Hou[1,2], Sisi Jiang[1,2], Mei Liu[1,2], Hechun Li[1,2], Lang Zhang[3], Mingjun Duan[1,3], Gang Yao[1,3], Hui He[1,2,3], Dezhong Yao[1,2,4], Cheng Luo[1,2,4,*]

[1]The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, 611731, P. R. China,
[2]Research Unit of NeuroInformation, Chinese Academy of Medical Sciences, 2019RU035, Chengdu, 611731, P. R. China,
[3]Department of Psychiatry, The Clinical Hospital of Chengdu Brain Science Institute, University of Electronic Science and Technology of China, Chengdu, 611731, People's Republic of China,
[4]High-Field Magnetic Resonance Brain Imaging Key Laboratory of Sichuan Province, Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu, 611731, P. R. China

*Corresponding author: No.2006, Xiyuan Ave, West HiTech Zone, 611731, Chengdu, Sichuan. Email: chengluo@uestc.edu.cn

Schizophrenia is a self-disorder characterized by disrupted brain dynamics and architectures of multiple molecules. This study aims to explore spatiotemporal dynamics and its association with psychiatric symptoms. Resting-state functional magnetic resonance imaging data were collected from 98 patients with schizophrenia. Brain dynamics included the temporal and spatial variations in functional connectivity density and association with symptom scores were evaluated. Moreover, the spatial association between dynamics and receptors/transporters according to prior molecular imaging in healthy subjects was examined. Patients demonstrated decreased temporal variation and increased spatial variation in perceptual and attentional systems. However, increased temporal variation and decreased spatial variation were revealed in higher order networks and subcortical networks in patients. Specifically, spatial variation in perceptual and attentional systems was associated with symptom severity. Moreover, case–control differences were associated with dopamine, serotonin and mu-opioid receptor densities, serotonin reuptake transporter density, dopamine transporter density, and dopamine synthesis capacity. Therefore, this study implicates the abnormal dynamic interactions between the perceptual system and cortical core networks; in addition, the subcortical regions play a role in the dynamic interaction among the cortical regions in schizophrenia. These convergent findings support the importance of brain dynamics and emphasize the contribution of primary information processing to the pathological mechanism underlying schizophrenia.

Key words: Dynamics; Functional connectivity; Molecular architecture; Schizophrenia; Spatiotemporal variability.

Introduction

Schizophrenia, a chronic and severe mental illness, affects 1% of the population (Marder and Cannon 2019). Its positive symptoms, negative symptoms, and cognitive deficits, which seriously affect patients' learning and daily life, impose a large burden on their families and society (Mueser and McGurk 2004; Kahn et al. 2015). Self-disorder is thought to be a typical feature of schizophrenia that leaves patients unable to distinguish between themselves and others (Chen et al. 2015). Previous studies have suggested that self-disorder is associated with higher order brain dysfunction (Kahn and Keefe 2013). However, according to the clear clinical symptoms of schizophrenia, some researchers have further proposed that self-disorder in schizophrenia involves dysfunction of bottom-up and top-down processing (Allen et al. 2012; Javitt and Freedman 2015).

Schizophrenia is often considered to be a disease of widespread "dysconnection" characterized by the inability to coordinate multiple brain regions (Dong et al. 2018a). For example, our previous study on schizophrenia reported altered functional connectivity density (FCD) in the frontal areas, primary sensorimotor area, and occipital lobe, as well as abnormal functional connectivity (FC) in the primary sensorimotor area and visual cortex. These findings may indicate abnormal integration of low-level perceptual processing (Chen et al. 2015). Previous studies have mostly focused on static FC, but it is believed that the brain shows an extensive variety of connectivity patterns and dynamics, which are involved in information integration and processing during cognitive and behavioral processes (Avena-Koenigsberger et al. 2017). Dynamic FC (dFC) better represents the interaction and integration of brain information over time and may shed light on the underlying pathophysiological mechanisms of various neurological and psychiatric disorders (Liu et al. 2017; Jiang et al. 2020a; Xue et al. 2022). For instance, Jiang et al. (2021) found different connectivity features in different epileptic networks and altered antagonism between dynamic and static FC in patients with generalized epilepsy. Additionally, some studies have shown that dFC is associated with demographic characteristics, clinical symptoms, cognition, and consciousness (Preti et al. 2017). In conclusion, static and dFC can provide complementary information to improve our understanding of the neural network mechanisms of the brain.

Received: January 25, 2023. **Revised:** May 1, 2023. **Accepted:** May 2, 2023

Several studies have investigated the temporal features of brain dynamics in schizophrenia. In our prior study, patients with schizophrenia showed altered dFC in the sensory and perceptual systems and higher order networks at different levels (Dong et al. 2019). Luo et al. (2019) found decreased dFC strength in salience, visual, auditory, and sensorimotor networks (SMNs) and increased dFC strength in the cerebellum, prefrontal, and basal ganglia networks in different frequency bands in patients with schizophrenia. These studies mainly paid attention to temporal variation in schizophrenia, providing some preliminary analyses of dFC that revealed the dynamic neuropathological mechanisms related to self-disorder in schizophrenia. However, few studies have focused on spatial variation, which is equally important for revealing the brain function of healthy people or patients (Iraji et al. 2019). Moreover, few studies have combined temporal, spatial, and spatiotemporal variability to assess the characteristics of FC in schizophrenia. In addition, the calculation of temporal, spatial, and spatiotemporal variation in FCD is a novel method of capturing spatiotemporal variation within and between functional organizations that was used in our previous study of epilepsy (Jiang et al. 2020a).

Previous studies have shown that the functional brain network in schizophrenia is associated with molecular architecture (Limongi et al. 2020). Furthermore, dopaminergic and serotonergic systems were found to be involved in the functional mapping of brain networks related to cognitive symptoms in schizophrenia (Chen et al. 2021). Therefore, we further explored whether the spatiotemporal dynamics of FC could reflect the spatial topography of potential molecular characteristics.

In this work, we used a method that combined temporal, spatial, and spatiotemporal variability in FCD to investigate the dynamic characteristics of schizophrenia. We hypothesized that schizophrenia patients would show widespread abnormal dynamics in brain regions ranging from primary perceptual networks to higher order networks, and these dynamic abnormalities would be associated with molecular characteristics and clinical symptoms. This method could shed further light on the pathophysiological mechanisms of schizophrenia.

Materials and methods

Participants

A total of 98 patients with schizophrenia (SZ) were recruited from the Clinical Hospital of Chengdu Brain Science Institute in this study. All patients were diagnosed by the structured clinical interview for DSM-V axis I disorders-clinical version (SCID-I-CV). We excluded patients with comorbid axis I diagnosis or active drug use disorders. All patients were taking antipsychotics. A total of 124 sex- and age-matched healthy controls (HC) without neurological and psychiatric disorders were also recruited. This study was approved by the Ethics Committee of the Clinical Hospital of Chengdu Brain Science Institute. Written informed consent was obtained from the guardians of patients and all healthy controls. Detailed demographic and clinical characteristics for patients with schizophrenia and healthy controls are shown in Table 1.

Data acquisition

Magnetic resonance imaging (MRI) images were collected on a 3 T MRI scanner (GE Discovery MR 750, USA) equipped with an 8-channel-phased array head coil at the MRI Center of the University of Electronic Science and Technology of China. All subjects were asked to remain relaxed, close their eyes, and stay awake. A standard echo-planar imaging pulse sequence was performed to collect resting-state functional images in this study using the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, matrix size = 64 × 64, field of view (FOV) = 24 × 24 cm^2, 35 interleaved slices, and slice thickness = 4 mm (no gap). Each subject was scanned for 510 s, and 255 volumes were obtained. T1-weighted anatomical data were obtained with an MPRAGE (MEMPR) sequence. The parameters were as follows: TR/TE = 1900 ms/3.43 ms, FOV = 24 × 24 cm^2, matrix size = 256 × 256, slice thickness = 1 mm, FA = 9°, voxel size = 0.9375 mm × 0.9375 mm × 1 mm, and 160 volumes.

Preprocessing

Preprocessing was performed by an independently developed software package NIT (Dong et al. 2018b). The steps of preprocessing included (1) removing the first 10 volumes, (2) slice-timing correction, (3) realignment, (4) spatial normalization to Montreal Neurological Institute (MNI) space, (5) resampling the voxel size into 3 mm × 3 mm × 3 mm, (6) removing the participants with head motion greater than 2 mm or/and 2°, (7) regressing out the 24 head motion parameters, white matter, linear trend, and cerebrospinal fluid signal, and (8) filtering with a bandpass filter (0.01–0.08 Hz).

Variability of FCD

We used global FCD to measure the number of direct connections between one voxel and other voxels in the whole brain (Tomasi and Volkow 2010). The definitions and the detailed calculations of FCD and the temporal variability can be found in our previous study (Jiang et al. 2020a). In short, we used a sliding-window method with a window width of 50 TR and a step of 1 TR. For every window, according to the atlas proposed by Fan et al. (2016), the computed voxel-wise FCD map was converted into the values in 246 regions in the whole brain, and then we computed the mean FCD value of all voxels in each region. Finally, the standard deviation of the average FCD values between different windows was used to characterize the temporal variability of FCD (tvFCD) in a given region.

The calculation principle of the spatial variability of FCD (svFCD) was performed using an analysis method similar to that in our prior study (Jiang et al. 2020a). For a given time window m, the FCD spatial distribution of region i was described as $F_{i,m}$, where $F_{i,m}$ was a column vector arranged by the FCD of all the voxels in this region. For region i, the mean of the correlation coefficients between different time windows was used to represent the stability of the spatial distribution of FCD, and then 1 minus the stability coefficient was used to represent the variability of the spatial distribution as follows:

$$SV_i = 1 - \overline{corr\left(F_{i,m}, F_{i,n}\right)};$$

$$i = [1, 246]\,;\ m, n = [1, k.]$$

The product of tvFCD and svFCD was proposed as an index that characterizes the spatiotemporal variability of FCD (stvFCD). For 3 features within a region, the Student t test was utilized to investigate the within- and between-group differences with age, sex, and mFD as nuisance covariates. In addition, canonical correlation analysis (CCA) was used to investigate the relationships of the changed tvFCD, svFCD, or stvFCD in schizophrenia with clinical variables (PANSS scores).

Table 1. Demographic characteristics and clinical features of schizophrenia patients and controls(mean ± SD).

	Patients ($N = 98$)	Healthy controls($N = 124$)	P value
Age (year)	41.66 ± 11.89	38.78 ± 14.35	0.111[a]
Gender (male/female)	69:29	77:47	0.195[b]
Education (years)[c]	11.51 ± 2.97	11.54 ± 3.61	0.063[a]
Duration (years)	15.89 ± 10.28		
Chlorpromazine equivalents (mg/d)[d]	338.05 ± 160.89		
PANSS-positive[e]	12.81 ± 5.84		
PANSS-negative[e]	20.60 ± 6.04		
PANSS-general[e]	27.88 ± 5.78		
PANSS-total[e]	61.29 ± 12.92		

PANSS, positive and negative syndrome scale. [a]Two-sample t-test. [b]χ^2 test. [c]Data of 76 patients and 112 controls available. [d]Data of 73 patients available. [e]Data of 73 patients available.

Variability at the brain network level

To further investigate the distribution of FCD variability, the variability ratio of regions was analyzed in different functional networks. The nodes (246) were labeled by membership in 8 brain networks, including the visual network (VN), SMN, dorsal attention network (DAN), ventral attention network (VAN), limbic network (Limbic), frontoparietal network (FPN), default mode network (DMN), and subcortical network (SCN), according to the network division used in a previous study (Yeo et al. 2011). At the individual level, the tvFCD, svFCD, and stvFCD values were first normalized in the whole brain to eliminate individual differences. Nodes with high or low variability were determined by being above or below the whole-brain average, respectively. Then, high or low variability ratios were defined for each network. The high variability ratio was calculated by the number of nodes with high variability divided by the total number of nodes, and the low variability ratio was calculated by the number of nodes with low variability divided by the total number of nodes. Finally, the difference between the high and low ratios was calculated for 3 features (tvFCD, svFCD, and stvFCD), which were standardized using the z-score method. We used Student t test to evaluate intragroup and intergroup differences of 3 high and low variability ratios. In addition, we summed the absolute values of nodes with high or low tvFCD, svFCD, or stvFCD in each network to determine the overall high or low variability in each network.

Altered subnetworks in schizophrenia

To investigate the features of regions with abnormal FCD variability, we defined a deficit FC subnetwork in schizophrenia patients. The network properties were performed by a software package GRETNA (http://www.nitrc.org/projects/gretna/) using graph theory. First, regions with abnormal tvFCD, svFCD, or stvFCD were selected as nodes of the subnetwork, and Pearson's correlation coefficient between each pair of nodes was calculated to define the edge strength. We used the graph theory method to determine the node characteristics of a series of binary networks with a sparsity of 0.15–0.5 and a step size of 0.05, including node local efficiency, clustering coefficient, node efficiency, betweenness centrality, and degree centrality. Finally, the area under the curve (AUC) for each node characteristic was calculated and tested using Student t test.

Spatial association of FCD variability with molecular architecture

Finally, we assessed the spatial associations between regions with abnormal tvFCD, svFCD, or stvFCD and several receptor/transporter densities. According to the receptor/transporter system linked to schizophrenia, dopamine, and serotonin receptors (dopaminergic: D_1 and D_2 receptors; serotonergic: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_4 receptors), mu-opioid receptor [MOR], metabotropic glutamate receptor 5 [mGluR5], and several transporters (serotonin reuptake transporter [5-HTT], norepinephrine transporter [NET] and dopamine transporter [DAT]), together with the GABAergic $GABA_a$ receptor and F-DOPA (a reflection of presynaptic dopamine synthesis capacity), were chosen for analysis.

We obtained receptor/transporter densities from average group maps of healthy populations scanned in previous multitracer molecular imaging studies (Dukart et al. 2021). The spatial relationship was used to assess the association between increased or decreased FCD variability in patients and receptor/transporter densities. Then, the significance of a spatial correlation compared with chance levels was evaluated using a permutation test. The 5,000 spin test permutations were used to control the spatial autocorrelation.

Results

Disrupted tvFCD, svFCD, and stvFCD patterns in schizophrenia

Disrupted tvFCD, svFCD, or stvFCD patterns were observed in all 8 brain networks. In the VN, decreased tvFCD and stvFCD were observed in patients with schizophrenia. In addition, increased svFCD was found in patients. In schizophrenia patients, decreases in tvFCD and stvFCD and an increase in stvFCD were found in the SMN. In the DAN, decreased tvFCD and increased svFCD were observed in schizophrenia patients. In the VAN, decreased tvFCD and increased svFCD were observed in patients. The Limbic showed increased tvFCD and stvFCD in schizophrenia patients. In the FPN, schizophrenia patients showed decreased svFCD. The DMN showed increased tvFCD and stvFCD and decreased svFCD. In the SCN, increased tvFCD, decreased svFCD and stvFCD were found in patients with schizophrenia. Three-dimensional brain maps of nodes with significant group differences and violin plots of a representative node in each network are shown in Fig. 1.

Figure 2 and Supplementary Fig. S1–S3 show different ratios of high and low tvFCD, svFCD, or stvFCD in patients with schizophrenia and HC. Regarding tvFCD, the schizophrenia patients demonstrated a decreased ratio of high tvFCD in the VN and SMN. An increased ratio of high tvFCD was found in Limbic of patients. Regarding svFCD, an increased ratio of high svFCD was observed in the SMN of patients with schizophrenia. Schizophrenia patients exhibited a decreased ratio of high svFCD in the FPN and DMN.

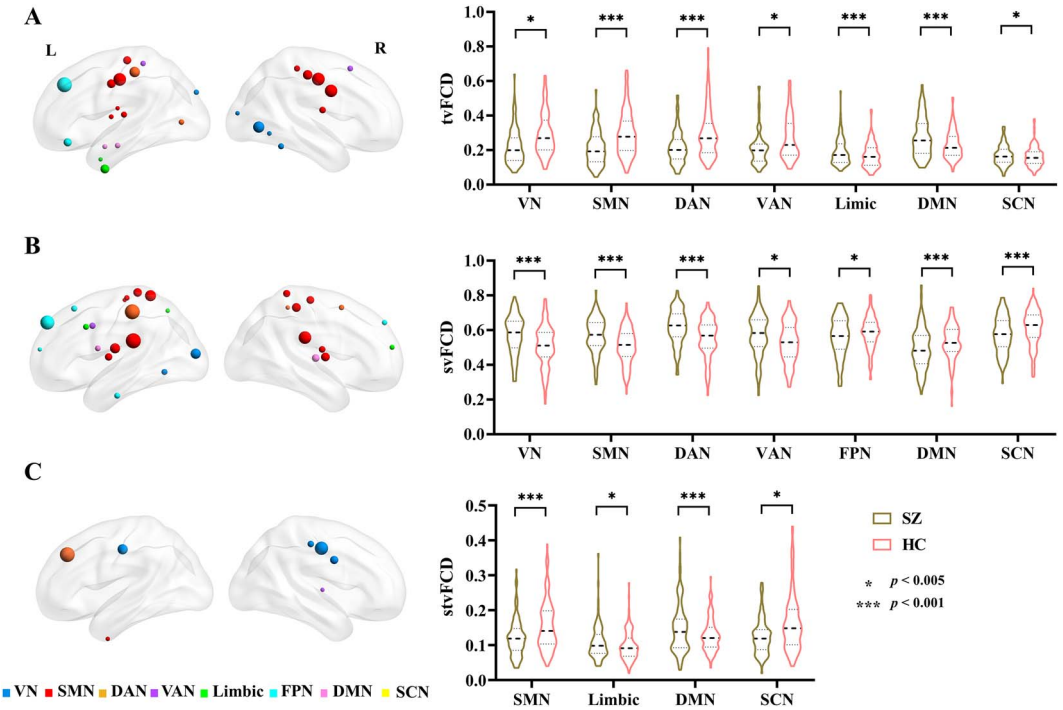

Fig. 1. Significant alterations in tvFCD, svFCD, and stvFCD in patients with schizophrenia. Brain panels show nodal changes, and violin plots demonstrate the value of a representative node in each network.

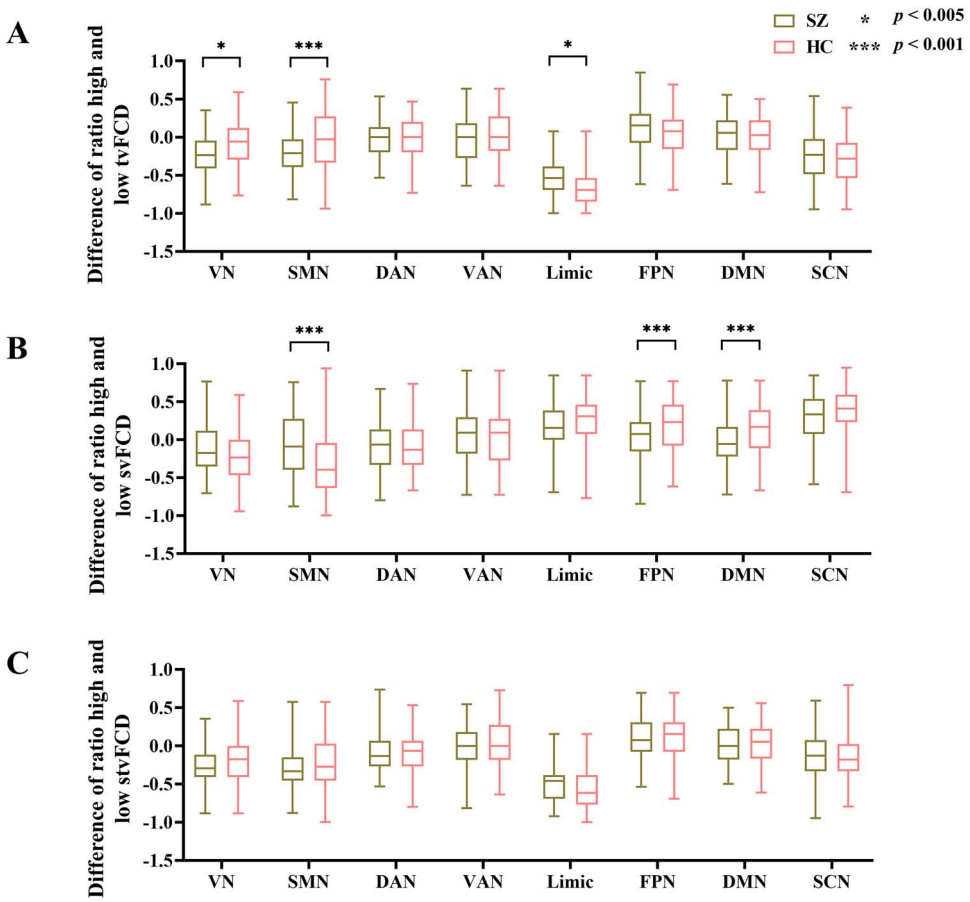

Fig. 2. The significantly altered ratios of high and low tvFCD, svFCD, and stvFCD in patients with schizophrenia.

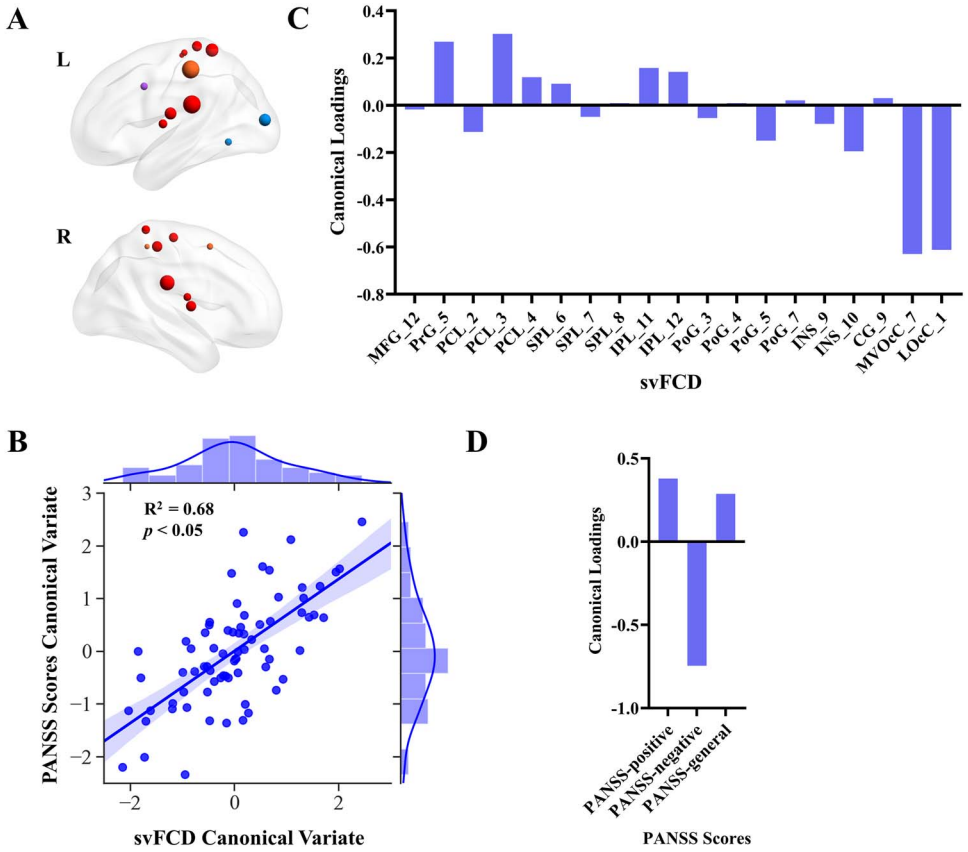

Fig. 3. Associations between svFCD and clinical variables. (A) Brain panels show 19 nodes with abnormal svFCD in perceptual and attentional systems. (B) The canonical correlation between svFCD and clinical features. (C) Canonical loadings of the svFCD. (D) Canonical loadings of the PANSS scores.

Associations with clinical outcomes

The CCA indicated a significant association of the svFCD of 19 nodes within perceptual and attentional systems with clinical characteristics ($R^2 = 0.68$, $P < 0.05$) in schizophrenia patients (Fig. 3). The canonical loadings demonstrated that the global svFCD canonical variate was associated with svFCD in the precentral gyrus ($r = 0.269$), paracentral lobule ($r = 0.302$), medioventral occipital cortex ($r = -0.630$), and lateral occipital cortex ($r = -0.612$). The canonical loading showed that PANSS scores canonical variate was associated with positive symptom scores ($r = 0.379$), negative symptom scores ($r = -0.746$), and general scores ($r = 0.288$).

Abnormal functional architecture in the relevant subnetwork

In this study, 50 nodes showing altered FCD variations were found in patients with schizophrenia. For every subject, a 50×50 FC matrix was constructed and analyzed according to the graph theoretic approach.

Compared with HC, the nodes with increased betweenness centrality in schizophrenia patients were mainly in the VN, SMN, and DAN. The nodes with decreased betweenness centrality were mainly in the DMN and SCN. Compared with HC, schizophrenia patients showed decreased degree centrality, nodal cluster coefficient, nodal efficiency, and nodal local efficiency in almost all identified nodes in the VN, SMN, DAN, and VAN. Schizophrenia patients exhibited increased degree centrality, nodal cluster coefficient, nodal efficiency, and nodal local efficiency in nearly all of the identified nodes in Limbic, FPN, DMN, and SCN (Fig. 4).

Relationship to molecular architecture

Notably, we found that the positive SZ-HC t value of tvFCD was negatively correlated with the densities of D1 ($r = -0.246$, $P = 0.007$) and D2 ($r = -0.218$, $P = 0.023$). The negative SZ-HC t value of nodes with distinct tvFCD was positively associated with the densities of 5-HT_4 ($r = 0.309$, $P < 0.001$) and MOR ($r = 0.336$, $P = 0.020$). The positive svFCD difference showed negative correlations with the densities of 5-HTT ($r = -0.211$, $P = 0.037$), D1 ($r = -0.250$, $P = 0.012$), D2 ($r = -0.240$, $P = 0.024$), DAT ($r = -0.248$, $P = 0.017$), F-DOPA ($r = -0.226$, $P = 0.029$), and MOR ($r = -0.290$, $P = 0.005$). The negative t value of stvFCD was positively related to the densities of 5-HT_4 ($r = 0.371$, $P < 0.001$) and F-DOPA ($r = 0.207$, $P = 0.017$) (Fig. 5).

Discussion

Using a dynamic spatiotemporal FCD approach, this study explored the brain function of patients with schizophrenia to reveal specific profiles of brain dynamics and their associations with clinical variables and the architecture of multiple molecules. Decreased temporal variation and increased spatial variation were found in the perceptual and frontoparietal attentional networks of schizophrenia patients relative to those of healthy controls. However, SCN and DMN showed an increase in temporal variation and a decrease in spatial variation. Interestingly, SCN showed decreased spatiotemporal variation. Network architectures in the relevant subnetwork further highlighted the involvement of visual and SMNs in patients. The spatial variation in perceptual and attentional networks was significantly associated with psychiatric symptom scores. Moreover, spatiotemporal features were also correlated with multiple neurotransmissions.

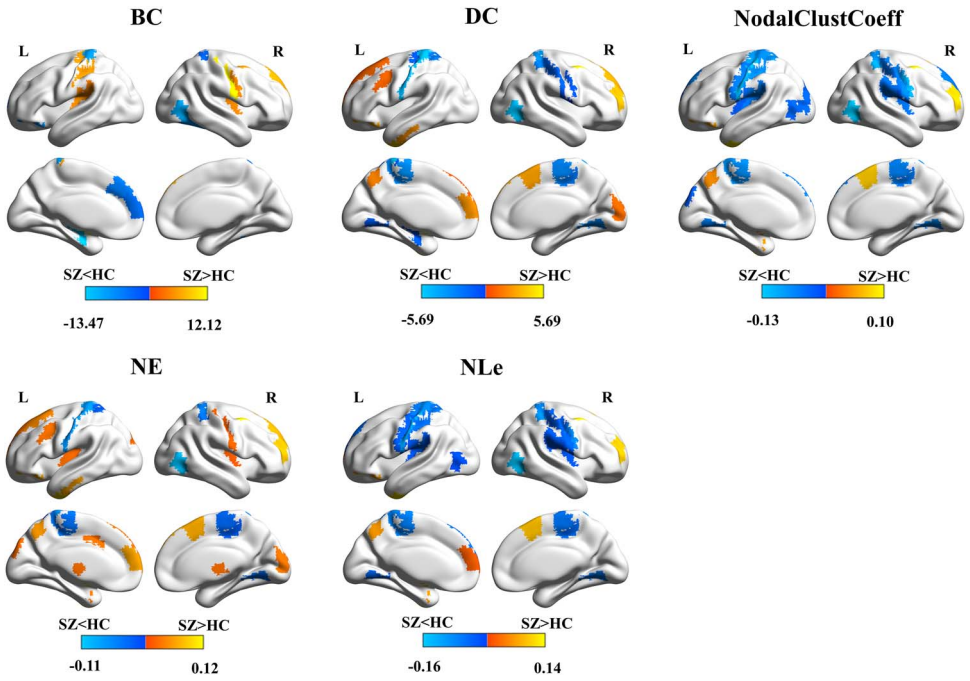

Fig. 4. Subregions in schizophrenia patients that exhibited abnormal regional topology in relevant subnetworks ($P < 0.05$, FDR-corrected). The color bars represent the intergroup difference values. Abbreviation: BC, betweenness centrality; DC, degree centrality; NodalClustCoeff, nodal cluster coefficient; NE, nodal efficiency; and NLE, nodal local efficiency.

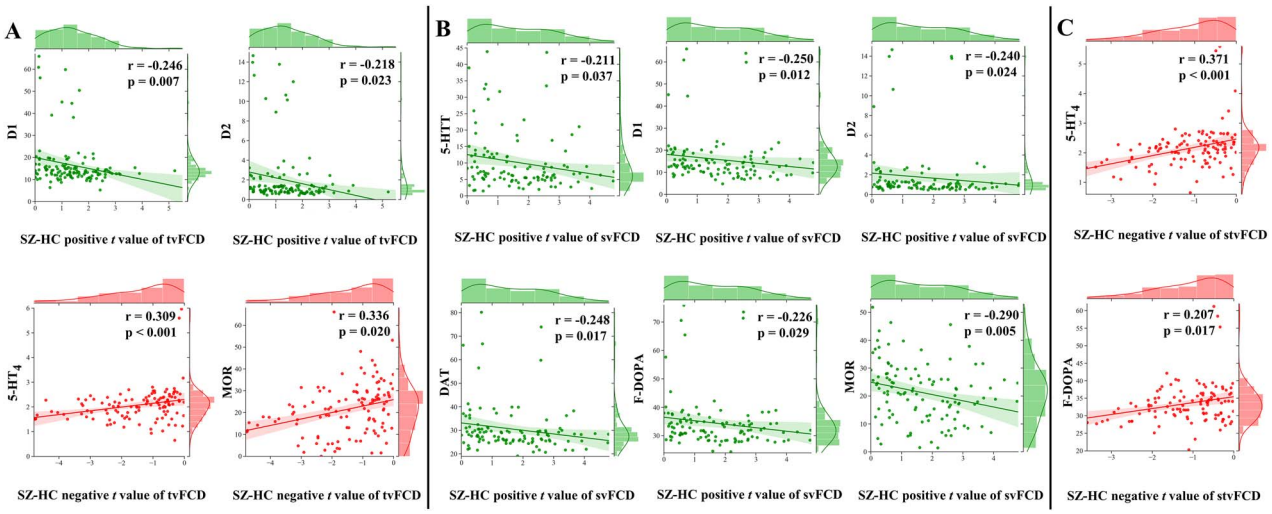

Fig. 5. Spearman correlations of the temporal, spatial, and spatiotemporal variation differences with the nodal receptor/transporter density estimates (spin test permutations, repeated 5,000 times). (A) Association of receptor/transporter density with tvFCD differences. (B) Association of receptor/transporter density with svFCD differences. (C) Association of receptor/transporter density with stvFCD differences. Abbreviation: 5-HT, serotonin; D, dopamine; DAT, dopamine transporter; MOR, mu-opioid receptor.

The present findings revealed aberrant spatiotemporal dynamics across networks and their relationship to clinical symptoms and neurotransmitters, suggesting abnormal dynamic interactions between primary functional network and cortical core networks with higher order function; in addition, the subcortical regions played an important role in the dynamic interaction among the cortical regions. Therefore, this study might provide insight into the pathological mechanism underlying schizophrenia.

Abnormal dynamics of FCD in cortical core networks

Several previous researches have used the FCD to investigate FC changes in the whole brain of patients with schizophrenia (Chen et al. 2015). This study investigated both temporal and spatial variations in FCD and found decreased temporal variation and increased spatial variation in the VN, SMN, VAN, and DAN in patients with schizophrenia. Perceptual processing dysfunction in schizophrenia has been comprehensively investigated by neurophysiological methods (Javitt 2009; Javitt and Freedman 2015; Bordier et al. 2018). We found decreased temporal variation in the perceptual system, including the VN and SMN, in schizophrenia patients. These variations suggested reduced flexibility of response to external demands in the lower order functional system, which might affect its interactions with other networks. Additionally, increased spatial variation was also found in patients with schizophrenia, which might indicate

unstable structures of connectivity with other brain regions. These results supported the view of impairments in multisensory integration in schizophrenia (Tseng et al. 2015). A previous study also revealed decreased dFC strength of sensorimotor and VNs in schizophrenia (Luo et al. 2019). Moreover, independent vector analysis also revealed increased spatial variance in the perceptual and integrative networks of schizophrenia patients (Gopal et al. 2016). Attentional control deficits are thought as a central clinical feature and a key factor in cognitive dysfunction in schizophrenia. Previous studies have found perceptual disorders related to the VAN in schizophrenia, including the processing of both visual and auditory emotional information and the neuronal representations of the self that may contribute to hallucinations and delusion (Wylie and Tregellas 2010; Fan et al. 2022). VAN includes bilateral anterior insula and dorsal anterior cingulate cortex, which was also named salience network (SN)(Menon and Uddin 2010; Uddin 2015). Abnormal FC in the SN could explain the multiple negative symptoms of patients with schizophrenia (Fan et al. 2022). The decreased temporal variation and increased spatial variation in the SN found here may indicate decreased interactions with other lower and higher order networks and a reduced ability to integrate internal and external information. Changes in the activation, FC, or interaction of the DAN have also been found when schizophrenia patients perform tasks associated with cognitive demands (Li et al. 2019). Moreover, analysis of relevant subnetworks showed reduced nodal features in many regions of the VN, SMN, DAN, and SN, which was consistent with previous studies reporting lower local information transfer in schizophrenia (Jiang et al. 2020b). Notably, these spatial variations in perceptual and attentional systems were closely related to clinical outcomes. These findings further highlighted the disruption of multisensory integration and indicated that disordered information in perceptual and attentional systems was associated with symptoms in schizophrenia. In summary, the altered temporal and spatial variation in primary perceptual and attentional systems provides the network evidence supporting the pathological mechanism of abnormal internal and external information processing in patients with schizophrenia.

Furthermore, we identified abnormal variations in the DMN and FPN in patients with schizophrenia. Previous studies have shown that DMN is related to unconstrained thought and introspection. Higher inhibition in the DMN led to better performance on tasks requiring more attention (Mason et al. 2007). In schizophrenia, the DMN is hyperactivated and hyperconnected, which may be associated with self-disorder and some cognitive dysfunction (Whitfield-Gabrieli and Ford 2012; Zhou et al. 2016). Moreover, a prior study revealed that the spatial variance in the DMN was decreased in schizophrenia and suggested that this decrease was related to self-reflection (Gopal et al. 2016). In this study, temporal variation was increased in the DMN, demonstrating a hypervariability state of this network when interacting with other regions. Spatial variation was decreased, indicating increased rigidity of spatial organization. The high spatiotemporal variation also showed complementary effects between temporal and spatial variability in schizophrenia. Our results may suggest abnormal internal and external information regulation in the DMN of schizophrenia patients. Indeed, cognitive deficits in patients with schizophrenia are not a rare phenomenon and are thought to be related to FPN dysfunction (Ray et al. 2017). The FPN, which is associated with cognitive function, including attention and central executive, may be uniquely positioned to adjudicate the competition of internal and external orientation processes (Smallwood et al. 2012). The decrease in the spatial variation of the FPN may indicate that its internal structure cannot undergo flexible spatial reorganization when communicating with other regions. Altered nodal properties of DMN and FPN may further reveal abnormalities in the ability to regulate internal and external information in higher order networks in schizophrenia (Jiang et al. 2020b). Combined with reduced temporal variation and increased spatial variation in lower order functional systems, these variations in higher order networks reveal a weaker ability to regulate internal and external information in schizophrenia patients. These findings provided the temporal and spatial dynamics in cortical core networks including DMN, SN, FPN, and primary networks to understand the relationship between cortical triple networks, perceptual system, and the symptom of schizophrenia.

Abnormal dynamics of FCD in subcortical and limbic systems

The SCN is considered to be a collection of highly interconnected network hubs, including core areas such as the thalamus and basal ganglia (Bell and Shine 2016). The thalamus plays an important role in the interaction of information between cortical and subcortical regions and between different cortical regions. It also serves a gating function in multiple brain pathways involved in the processing of sensory input (Pergola et al. 2015). In addition, many studies have shown that specific thalamocortical network disorders are characteristic of schizophrenia (Anticevic 2017; Gong et al. 2019). The basal ganglia, a group of subcortical nuclei, receives information from the cerebral cortex and jointly participates in several efferent circuits involved in motor, cognition, and emotion with the cerebral cortex through the thalamus (Duan et al. 2015; Hirjak et al. 2015; Cobia et al. 2021). Previous studies have revealed that the structure and function of the basal ganglia in schizophrenia are abnormal (He et al. 2021). In this study, the SCN exhibited high temporal variation and low spatial and spatiotemporal variation in schizophrenia, which may be related to dysfunction of the subcortical dopamine system as well as multiple other neurobiological systems, including the serotonin and glutamate systems (Conio et al. 2020). Combined with the contrasting variation between lower order systems and higher order networks in the cortex, this variation in the SCN may further indicate an imbalance within and between primary and higher level networks, and suggest that the subcortical regions play an important role in the dynamic interaction among the cortical regions.

The limbic network is a set of interconnected cortical and subcortical regions that links visceral states and emotions to cognition and behavior (Catani et al. 2013). The limbic network has long been thought to be involved in the pathogenesis of schizophrenia (White et al. 2008). For example, some of the positive symptoms of schizophrenia, such as hallucinations, have been attributed to hyperactivity in regions of the limbic network (e.g. medial temporal lobe) (Allen et al. 2008). Some studies have found abnormal pathways from limbic areas to subcortical and cortical areas in schizophrenia (Hua et al. 2020). Patients with schizophrenia showed increased temporal and spatiotemporal variation in the limbic network in this study. This variation indicates hyperflexibility of the limbic network in functional interactions with other regions, which may be associated with the positive symptoms of schizophrenia.

Variation changes related to molecular architecture

In this study, we found that abnormal variations in FCD were related to the dopamine system, serotonin system, and mu-opioid receptors. Our findings are consistent with the current hypothesis that schizophrenia widely affects neural networks other than the classic mesolimbic dopaminergic pathway (Stahl 2018). In fact, in addition to the classic dopamine theory, other theories including the serotonin hypothesis and endogenous opioid theory, which involve functional interactions, are also thought to be involved in the pathophysiological mechanisms of schizophrenia (de Bartolomeis et al. 2013; Ashok et al. 2019; Blokhin et al. 2020). Therefore, we speculated that the abnormal variability may be related to multiple systems and their interconnected pathways. Combined with the association of svFCD with clinical features, this further suggested that abnormal variability may be associated with the positive symptoms (hallucinations and delusions) and negative symptoms of schizophrenia.

Limitations

This study has several limitations. First, all patients with schizophrenia in this study were taking antipsychotics; thus, patients were in stable condition, which may have impacted the dynamics of networks. Second, the receptor/transporter maps did not belong to the subjects in this study; additionally, the sample sizes of some of the receptor/transporter maps that we obtained from previous molecular imaging researches were small. Third, the results of this study need to be replicated in studies with a larger sample size.

Conclusion

Using resting-state functional MRI data, we investigated the temporal and spatial dynamics of FC in patients with schizophrenia and explored the associations of these dynamics with clinical symptoms and receptor/transporter densities. Schizophrenia patients showed abnormal variation in cortical core networks; this abnormal variation was also significantly correlated with receptor/transporter densities. These findings support the importance of dynamic neural characteristics in schizophrenia. Moreover, subnetwork attribute analysis indicated that abnormalities were predominantly in the perceptual and attentional systems, in which spatial variation was associated with clinical symptoms, similarly emphasizing the potential involvement of primary information processing in patients. Taken together, the present findings provide considerable evidence from a dynamic perspective that enhances understanding of the pathological mechanism of schizophrenia.

Acknowledgments

The authors thank all participants in this study.

CRediT author statement

Changyue Hou (Formal analysis, Methodology, Software, Visualization, Writing—original draft, Writing—review & editing), Sisi Jiang (Formal analysis, Validation), Mei Liu (Data curation, Investigation, Resources), Hechun Li (Methodology, Software), Lang Zhang (Investigation, Resources), Mingjun Duan (Methodology, Resources), Gang Yao (Investigation, Resources), Hui He (Investigation, Methodology), Dezhong Yao (Project administration, Supervision), Cheng Luo (Conceptualization, Funding acquisition, Project administration, Supervision)

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

Funding

This work was partly supported by grants from the National Natural Science Foundation of China (grant number: U2033217, 61933003, 81960249, and 82101620), the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2019-I2M-5-039), Project of Science and Technology Department of Hainan Province (Grant number: ZDYF2021SHFZ095), the Natural Science Foundation of Sichuan (23NSFSC0016, 22NSFSC0530), and the Sichuan Provincial Program of Traditional Chinese Medicine (2021ZD017).

Conflict of interest statement: The authors declare no competing interests.

Data and code availability

The codes, imaging and behavioral data are available from the corresponding author (Cheng Luo) upon reasonable request.

References

Allen P, Laroi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav R*. 2008:32:175–191.

Allen P, Modinos G, Hubl D, Shields G, Cachia A, Jardri R, Thomas P, Woodward T, Shotbolt P, Plaze M, et al. Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. *Schizophr Bull*. 2012:38:695–703.

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

Ashok AH, Myers J, Reis Marques T, Rabiner EA, Howes OD. Reduced mu opioid receptor availability in schizophrenia revealed with [(11)C]-carfentanil positron emission tomographic imaging. *Nat Commun*. 2019:10:4493.

Avena-Koenigsberger A, Misic B, Sporns O. Communication dynamics in complex brain networks. *Nat Rev Neurosci*. 2017:19:17–33.

Bell PT, Shine JM. Subcortical contributions to large-scale network communication. *Neurosci Biobehav Rev*. 2016:71:313–322.

Blokhin IO, Khorkova O, Saveanu RV, Wahlestedt C. Molecular mechanisms of psychiatric diseases. *Neurobiol Dis*. 2020:146:105136.

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

Catani M, Dell'acqua F, Thiebaut de Schotten M. A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev*. 2013:37:1724–1737.

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

Chen J, Muller VI, Dukart J, Hoffstaedter F, Baker JT, Holmes AJ, Vatansever D, Nickl-Jockschat T, Liu X, Derntl B, et al. Intrinsic connectivity patterns of task-defined brain networks allow individual prediction of cognitive symptom dimension of schizophrenia and are linked to molecular architecture. *Biol Psychiatry*. 2021:89:308–319.

Cobia D, Rich C, Smith MJ, Mamah D, Csernansky JG, Wang L. Basal ganglia shape features differentiate schizoaffective disorder from schizophrenia. *Psychiatry Res Neuroimaging*. 2021:317:111352.

Conio B, Martino M, Magioncalda P, Escelsior A, Inglese M, Amore M, Northoff G. Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders. *Mol Psychiatry*. 2020:25:82–93.

de Bartolomeis A, Buonaguro EF, Iasevoli F. Serotonin-glutamate and serotonin-dopamine reciprocal interactions as putative molecular targets for novel antipsychotic treatments: from receptor heterodimers to postsynaptic scaffolding and effector proteins. *Psychopharmacology*. 2013:225:1–19.

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

Dong L, Luo C, Liu XB, Jiang SS, Li FL, Feng HS, Li JF, Gong DK, Yao DZ. Neuroscience information toolbox: an open source toolbox for EEG-fMRI multimodal fusion analysis. *Front Neuroinform*. 2018b:12:56.

Dong D, Duan M, Wang Y, Zhang X, Jia X, Li Y, Xin F, Yao D, Luo C. Reconfiguration of dynamic functional connectivity in sensory and perceptual system in schizophrenia. *Cereb Cortex*. 2019:29:3577–3589.

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

Dukart J, Holiga S, Rullmann M, Lanzenberger R, Hawkins PCT, Mehta MA, Hesse S, Barthel H, Sabri O, Jech R, et al. JuSpace: a tool for spatial correlation analyses of magnetic resonance imaging data with nuclear imaging derived neurotransmitter maps. *Hum Brain Mapp*. 2021:42:555–566.

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

Fan L, Yu M, Pinkham A, Zhu Y, Tang X, Wang X, Zhang X, Ma J, Zhang J, Zhang X, et al. Aberrant large-scale brain modules in deficit and non-deficit schizophrenia. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2022:113:110461.

Gong J, Luo C, Li X, Jiang S, Khundrakpam BS, Duan M, Chen X, Yao D. Evaluation of functional connectivity in subdivisions of the thalamus in schizophrenia. *Br J Psychiatry*. 2019:214:288–296.

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

He H, Luo C, Li N, Li Z, Duan M, Yao G, Wang H, He M, Yao D. Altered asymmetries of diffusion and volumetry in basal ganglia of schizophrenia. *Brain Imaging Behav*. 2021:15:782–787.

Hirjak D, Wolf RC, Wilder-Smith EP, Kubera KM, Thomann PA. Motor abnormalities and basal ganglia in schizophrenia: evidence from structural magnetic resonance imaging. *Brain Topogr*. 2015:28:135–152.

Hua M, Peng Y, Zhou Y, Qin W, Yu C, Liang M. Disrupted pathways from limbic areas to thalamus in schizophrenia highlighted by whole-brain resting-state effective connectivity analysis. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2020:99:109837.

Iraji A, Deramus TP, Lewis N, Yaesoubi M, Stephen JM, Erhardt E, Belger A, Ford JM, McEwen S, Mathalon DH, et al. The spatial chronnectome reveals a dynamic interplay between functional segregation and integration. *Hum Brain Mapp*. 2019:40:3058–3077.

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

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

Jiang S, Pei H, Huang Y, Chen Y, Liu L, Li J, He H, Yao D, Luo C. Dynamic Temporospatial patterns of functional connectivity and alterations in idiopathic generalized epilepsy. *Int J Neural Syst*. 2020a:30:2050065.

Jiang Y, Yao D, Zhou J, Tan Y, Huang H, Wang M, Chang X, Duan M, Luo C. Characteristics of disrupted topological organization in white matter functional connectome in schizophrenia. *Psychol Med*. 2020b:52:1333–1343.

Jiang S, Li H, Pei H, Liu L, Li Z, Chen Y, Li X, Li Q, Yao D, Luo C. Connective profiles and antagonism between dynamic and static connectivity underlying generalized epilepsy. *Brain Struct Funct*. 2021:226:1423–1435.

Kahn RS, Keefe RSE. Schizophrenia is a cognitive illness time for a change in focus. *Jama Psychiat*. 2013:70:1107–1112.

Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, O'Donovan M, Correll CU, Kane JM, van Os J, et al. Schizophrenia. *Nat Rev Dis Primers*. 2015:1:15067.

Li Q, Liu S, Guo M, Yang CX, Xu Y. The principles of electroconvulsive therapy based on correlations of schizophrenia and epilepsy: a view from brain networks. *Front Neurol*. 2019:10:688.

Limongi R, Jeon P, Mackinley M, Das T, Dempster K, Theberge J, Bartha R, Wong D, Palaniyappan L. Glutamate and Dysconnection in the salience network: neurochemical, effective connectivity, and computational evidence in schizophrenia. *Biol Psychiatry*. 2020:88:273–281.

Liu F, Wang Y, Li M, Wang W, Li R, Zhang Z, Lu G, Chen H. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. *Hum Brain Mapp*. 2017:38:957–973.

Luo Y, He H, Duan M, Huang H, Hu Z, Wang H, Yao G, Yao D, Li J, Luo C. Dynamic functional connectivity strength within different frequency-band in schizophrenia. *Front Psychiatry*. 2019:10:995.

Marder SR, Cannon TD. Schizophrenia. *N Engl J Med*. 2019:381(18):1753–1761.

Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. *Science*. 2007:315:393–395.

Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct*. 2010:214:655–667.

Mueser KT, McGurk SR. Schizophrenia. *Lancet*. 2004:363:2063–2072.

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

Preti MG, Bolton TA, Van De Ville D. The dynamic functional connectome: state-of-the-art and perspectives. *NeuroImage*. 2017:160:41–54.

Ray KL, Lesh TA, Howell AM, Salo TP, Ragland JD, MacDonald AW, Gold JM, Silverstein SM, Barch DM, Carter CS. Functional network changes and cognitive control in schizophrenia. *Neuroimage Clin*. 2017:15:161–170.

Smallwood J, Brown K, Baird B, Schooler JW. Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought. *Brain Res*. 2012:1428:60–70.

Stahl SM. Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS spectrums*. 2018:23:187–191.

Tomasi D, Volkow ND. Functional connectivity density mapping. *P Natl Acad Sci USA*. 2010:107:9885–9890.

Tseng HH, Bossong MG, Modinos G, Chen KM, McGuire P, Allen P. A systematic review of multisensory cognitive-affective integration in schizophrenia. *Neurosci Biobehav Rev*. 2015:55: 444–452.

Uddin LQ. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci*. 2015:16:55–61.

White T, Cullen K, Rohrer LM, Karatekin C, Luciana M, Schmidt M, Hongwanishkul D, Kumra S, Charles Schulz S, Lim KO. Limbic structures and networks in children and adolescents with schizophrenia. *Schizophr Bull*. 2008:34:18–29.

Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol*. 2012:8: 49–76.

Wylie KP, Tregellas JR. The role of the insula in schizophrenia. *Schizophr Res*. 2010:123:93–104.

Xue K, Liang S, Yang B, Zhu D, Xie Y, Qin W, Liu F, Zhang Y, Yu C. Local dynamic spontaneous brain activity changes in first-episode, treatment-naive patients with major depressive disorder and their associated gene expression profiles. *Psychol Med*. 2022:52: 2052–2061.

Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011:106:1125–1165.

Zhou L, Pu W, Wang J, Liu H, Wu G, Liu C, Mwansisya TE, Tao H, Chen X, Huang X, et al. Inefficient DMN suppression in schizophrenia patients with impaired cognitive function but not patients with preserved cognitive function. *Sci Rep*. 2016:6:21657.