RESEARCH ARTICLE

Functional dysconnectivity of the limbic loop of frontostriatal circuits in first-episode, treatment-naïve schizophrenia

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Abstract

Frontostriatal circuits dysfunction has been implicated in the etiology and psychopathology of patients with schizophrenia (SZ). However, few studies have investigated SZ-related functional connectivity (FC) alterations in discrete frontostriatal circuits and their relationship with psychopathology in first-episode schizophrenia (FESZ). The goal of this study was to identify dysfunctions in discrete frontostriatal circuits that are associated with key features of FESZ. To this end, a case-control, cross-sectional study was conducted, wherein resting-state (RS) functional magnetic resonance (fMRI) data were collected from 37 treatment-naïve FESZ patients and 29 healthy control (HC) subjects. Seed-based FC analyses were performed by placing six bilateral pairs of seeds within *a priori* defined subdivisions of the striatum. We observed significantly decreased FC for the FESZ group relative to the HC group [$p < .05$, family-wise error (FWE)-corrected] in the limbic loop, but not in the sensorimotor or associative loops, of frontostriatal circuitry. Moreover, bilaterally decreased inferior ventral striatum/nucleus accumbens (VSI)-dorsal anterior cingulate cortex (dACC) FC within the limbic loop correlated inversely with overall FESZ symptom severity and the disorganization factor score of PANSS. These findings provide new insight into the role of frontostriatal limbic loop hypoconnectivity in early-stage schizophrenia pathology and suggest potential novel therapeutic targets.

KEYWORDS

dorsal anterior cingulate cortex, first-episode schizophrenia, frontostriatal circuits, resting-state functional connectivity, ventral striatum

1 | INTRODUCTION

Over the past 50 years, the striatal dopaminergic dysfunction has come to be recognized as a critical component of the etiology of schizophrenia

(SZ) (Howes & Kapur, 2009). With the conceptualization of SZ as a disorder of disconnectivity becoming widely accepted, modern neuroimaging studies of the striatum have become increasingly focused on the relationship between corticostriatal connections and SZ psychopathology (Jarbo & Verstynen, 2015; Lehericy et al., 2004). Accumulating evidence suggests that discrete channels in frontostriatal circuits

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specializes in the particular neurocognitive domain (Grahn, Parkinson, & Owen, 2008; Simpson, Kellendonk, & Kandel, 2010; Sorg et al., 2013).

The frontostriatal circuits form a looped structure wherein information is delivered directly from the frontal cortex to the striatum while the frontal cortex, in turn, receives information from major outputs of the striatum indirectly via the thalamus (Ferry, Ongur, An, & Price, 2000; Ongur & Price, 2000). The organization of frontal inputs to the striatum in humans and nonhuman primates is highly regular constituting the afferent input-based subdivision of the striatum (Ferry et al., 2000; Haber, 2016; Postuma & Dagher, 2006). Accordingly, frontostriatal circuits can be divided into three functionally distinct and spatially segregated loops, namely the sensorimotor, associative, and limbic loops, which are involved in motor sequence performance and habitual instrumental behavior, executive function and goal-directed behavior, emotion processing, and reinforcement learning, respectively (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986; Delgado, 2007; Haber, 2016). The impairment of any core component of those loops could result in specifically psychopathological and cognitive symptoms (Horga & Abi-Dargham, 2014; Radua et al., 2015).

A convergence of evidence from functional and structural studies has provided substantial support for the notion of frontostriatal loop dysfunction in SZ, as well as potential explanations for clinical and cognitive symptoms of SZ. For instance, positron-emission tomography studies have suggested that excessive dopaminergic activity in associative regions of the striatum during reward tasks is associated with the positive symptoms of SZ, while diminished dopamine release in the ventral striatum has been linked with negative symptoms of SZ (Bruneau, Fecteau, & Suard-Chagny, 2013; Ceccarini et al., 2013; Horga et al., 2016; Howes et al., 2009a, 2009b; Kegeles et al., 2010). Structure brain imaging studies have shown that SZ severity is associated with decrements in gray-matter density and white-matter fractional anisotropy in the frontostriatal loops (Koo et al., 2006; Quan et al., 2013; Stegmayer et al., 2014). Recent functional neuroimaging studies have shown that both aberrant activation and altered functional connectivity (FC) in frontostriatal systems are associated with clinical symptoms of patients with SZ (Kirschner et al., 2016; Morris et al., 2012; Radua et al., 2015; Sorg et al., 2013; Zhang et al., 2016).

Although frontostriatal abnormalities have been associated strongly with SZ, the mode of SZ-related dysfunction is unclear given that both increased (Lancaster et al., 2016; Sorg et al., 2013) and decreased (Grimm et al., 2014; Radua et al., 2015) striatal activity have been reported in patients with psychosis. The discrepancies between the results of different studies could be due to various factors including the lack of a common standard definition of what constitutes the frontostriatal systems, the use of different analysis methods, and differences between study samples, such as sample size, illness stage, medication use, and the heterogeneity in the diagnosis (e.g., psychotic disorder or schizophrenia spectrum disorders). The enrollment of participants with long-term chronic mental illness and medication use could have particularly profound confounding effects (Sarpal et al., 2017). The age of the participants is also a possible factor given that genetic susceptibility to psychosis, psychosis manifestation, and striatal function may evolve over the lifespan (Lancaster et al., 2016).

Additionally, the subtraction analysis used in task-related fMRI studies makes it difficult to judge whether differences in striatal function are related to reduced responses to target cues versus augmented responses to nontarget cues.

Recently, resting-state (RS) functional magnetic resonance (fMRI) has proven to be a useful method for examining the integrity of FC within the frontostriatal loops in patients with SZ (Di Martino et al., 2008; Lynall et al., 2010), including examining FC patterns across all three frontostriatal loops (Dandash et al., 2014; Sarpal et al., 2015). The goal of this study was to investigate whether dysfunction in each particular frontostriatal subdivision loop is present in early-stage SZ. To this end, we examined the RS-fMRI FC patterns of multiple ROIs in drug-naïve young adults with first-episode schizophrenia (FESZ) and explored functional alterations in the three frontostriatal loops relative to a healthy control (HC) group. We hypothesized that characteristic functional alterations in frontostriatal loops would be found to be associated with symptom severity in patients with FESZ.

2 | METHODS

2.1 | Subjects

This study was approved by the Institutional Ethical Committee for clinical research of the Second Xiangya Hospital of Central South University. Written informed consent was obtained from all participants. A total of 41 medication-naïve patients with FESZ (six of them were made provisional diagnosis for schizophreniform disorder at the time of recruitment and be revised for schizophrenia in the follow-up duration) were recruited from the outpatient clinic of the Second Xiangya Hospital. The eligibility criteria included (1) a DSM-IV diagnosis of SZ based on the Chinese version of the Structured Clinical Interview for the DSM-IV (SCID-I; First, Gibbons, Spitzer, & Williams, 1996); (2) age at enrollment of 20–40 years and age at symptom onset 16 years or older; and (3) clinic visit was their first contact with outpatient psychiatric services and the duration of illness was <2 years. The exclusion criteria for the patients included major comorbid conditions (e.g., neurological disorders, mental retardation, alcoholism, or substance abuse), history of head trauma, and history of electroconvulsive therapy. A group of 31 HCs was recruited from the local community with the following exclusion criteria: (1) personal history of psychosis, mood disorder, or substance abuse/dependence as indicated by the Structured Clinical Interview for DSM-IV Non-Patient version (SCID-NP); (2) personal history of organic brain disorder, mental retardation, or severe head trauma; and (3) family history of psychiatric disorders. Two senior clinical psychiatrists performed the clinical-psychometric assessments according to the SCID-I with an interrater reliability >0.9. All patients were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987; Marder, Davis, & Chouinard, 1997) on the day of scanning.

After evaluating the fMRI data quality, six subjects' datasets were excluded for further analysis due to large head motion and low temporal signal-to-noise ratio (tSNR). Finally, there were 37 patients with FESZ and 29 HCs were used for further data analysis. The demographic

TABLE 1 Demographic and clinical characteristics of FESZ and HC groups

Characteristic	FESZ (N = 37)	HC (N = 29)	t/χ^2	P
Age	21.46 ± 5.48	23.07 ± 4.20	1.307	0.196
Gender (male/female)	16/21	14/15	0.469	0.493
Handedness (right/left)	37/0	29/0		
Duration of illness (months)	10.59 ± 7.44			
PANSS total score	81.08 ± 11.72			
5 symptom factors score of PANSS *				
Negative symptoms factor	19.84 ± 7.37			
Positive symptoms	26.76 ± 6.39			
Disorganized thought	16.40 ± 4.60			
Uncontrolled hostility/excitement	9.64 ± 3.70			
Anxiety/depression	8.43 ± 3.08			

Abbreviations: HC, healthy control; FESZ, first-episode, treatment-naïve schizophrenia; PANSS, Positive and Negative Syndrome Scale.

^aThe calculation of five symptom factors score of PANSS is according to the Marder's five factor model of the PANSS (Marder, Davis, & Chouinard, 1997). Two-tailed Fisher exact test was used to compare proportions for categorical variables.

and clinical characteristics of two groups are presented in Table 1. There were no differences between two groups in age, gender distribution, and handedness. All subjects reported that they were of Han ethnicity.

2.2 | MRI data acquisition

MRI was performed on a 3 T MR scanner (Intera Achieva 3.0T X, Philips) with an 8-channel phased-array head coil. For co-registration and volumetric analysis, T1-weighted anatomical data were obtained with an MP-RAGE sequence (echo time = 3.743 ms, repetition time = 8.5 ms, flip angle = 8°, field of view = 256 × 256 mm², matrix = 256 × 256, 180 slices, slice thickness = 1 mm, and 0 mm interslice gap, voxel size = 1 × 1 × 1 mm³). Functional MRI data were obtained with a gradient echo EPI sequence (echo time = 30 ms, repetition time = 2000 ms, flip angle = 90°, field of view = 240 × 240 mm², matrix = 64 × 64, 36 slices, slice thickness = 4 mm, and 0 mm interslice gap, voxel size = 3.75 × 3.75 × 4 mm³; 206 volumes).

2.3 | Definition of ROIs

We analyzed 12 substriatal ROIs (3.5 mm radius, six in each hemisphere) representing the sensorimotor, associative, and limbic loops as defined previously by Di Martino et al. (2008). Specifically, sensorimotor loop ROIs were the dorsal caudal putamen (DCP) ($x = \pm 28$, $y = 1$, $z = 3$) and dorsal rostral putamen (DRP) ($x = \pm 25$, $y = 8$, $z = 6$). The associative loop ROIs were the dorsal caudate (DC) ($x = \pm 13$, $y = 15$, $z = 9$) and the ventral rostral putamen (VRP) ($x = \pm 20$, $y = 12$, $z = -3$). The limbic loop ROIs were the inferior ventral striatum (VSI) ($x = \pm 9$, $y = 9$, $z = -8$), and superior ventral striatum (VSs) ($x = \pm 10$, $y = 15$, $z = 0$). The anatomical locations and Montreal Neurological Institute (MNI) coordinates of all 12 ROIs are shown in Supporting Information, Figure S1.

2.4 | Preprocessing of FC data

First, all fMRI data were preprocessed with a combination of Analysis of Functional NeuroImages (<http://afni.nimh.nih.gov/afni/>) and FMRIB

Software Library (<http://www.fmrib.ox.ac.uk/fsl/>) programs. After the first four images in each participants' series were removed to avoid T1 equilibration effects, the fMRI data were motion corrected by a linear registration algorithm tool and smoothed spatially with a 6-mm full-width half-maximum Gaussian kernel. Then, preprocessing proceeded with the following steps: (1) removal of linear trends; (2) application of a temporal band-pass filter (0.01–0.08 Hz); (3) linear regression was applied to remove spurious data variance produced by body motion (with six rigid body motion correction parameters) and produced by white matter, cerebrospinal fluid, and whole-brain signals.

For controlling the influence of head motion, the framewise displacement (FD) and temporal derivative of the fMRI time series (DVARS) were evaluated by using C-PAC 0.3.9 (<http://fcp-indi.github.io/docs/user/index.html>). Following the previous studies (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012, 2013), we excluded the fMRI time points that exceeded an FD of 0.5 mm and a DVARS of 0.5%, and 1 preceding and 2 subsequent time points of that (for details, see Supporting Information and Table S1). Additionally, we calculated the signal-to-noise ratio (tSNR) of 12 seeds and compared the tSNR values across the HC and FESZ groups for each of the 12 ROIs. Finally, six subjects (2 HC and 4 FESZ) were excluded from data analyses because of excessive head motion (scrubbing bad time points > 20) and low tSNRs (<100). The Kolmogorov–Smirnov test showed no significant differences between the FESZ and HC groups in FD ($p = .8$) and DVARS ($p = .63$, see Supporting Information, Table S1 and Figure S2), and the tSNRs in any ROI (all $p > .05$, see Supporting Information, Figure S3).

2.5 | FC analysis of three frontostriatal loops

For each subject, seed-based whole brain functional connectivity analysis was conducted by extracting the time series from each of 12 striatum regions. The correlation coefficient between each pair of ROI seed time series and those of the entire brain voxels were calculated. FC connectivity maps were further derived by Fisher's r -to- z transformation. For the group-level analysis, one-sample t tests were conducted to detect

TABLE 2 Brain regions showing significantly different connectivity of 12 striatal ROIs between HC and FESZ groups

Seed region	Region of decreased connectivity	BA	MNI coordinates (x, y, z)	Peak t- value	Volume (mm ³)	Cohen's <i>d</i>
LVSi	Right dACC	24/32	6, 11, 37	4.3	1998	1.02
RVSi	Left dACC	24/32	3, 17, 40	3.3	567	0.72
LVSs	Right dACC	24/31	13, -5, 49	4.4	1539	1.10
RVSS	Left dACC	24/32	0, -12, 56	3.5	945	0.87

Abbreviations: BA, Brodmann area; dACC, dorsal anterior cingulate cortex; HC, healthy control; MNI, Montreal Neurological Institute; ROI, region of interest; FESZ, first-episode, treatment-naïve schizophrenia; $p < .05$, corrected.

brain regions with significant FC differences across subjects. Further, group comparisons between patients with FESZ and HCs were then performed with permutation-based nonparametric testing (with 5000 permutations) by the Randomise program in FMRIB Software Library (Nichols & Holmes, 2002). A family-wise error (FWE)-corrected cluster significance threshold of $p < .05$ was used for multiple comparisons with threshold-free cluster enhancement (Smith & Nichols, 2009). To obtain a measure of effect size, we calculated Cohen's *d* for the mean *Z* score within the clusters showing significantly different connectivity of striatal ROIs between HC and FESZ groups.

2.6 | Correlation analyses of FC with clinical variables

Clinical-variable correlation analyses were performed by a robust regression method, which was proved being appropriate for use in multivariate analyses and against univariate outliers in the data (Wager et al., 2005; Wilcox, 1998). Specifically, we used a robust linear model procedure (rlm) of the R statistical language (R Development Core Team, 2009) to reveal the functional consequences of observed FC differences.

3 | RESULTS

3.1 | FC of frontostriatal loops

Functional mappings generated with striatal subregions as the seeds were remarkably consistent with previous studies (Supporting Information, Figures S4–S6). In the FC map of the limbic loop (Supporting Information, Figure S4), the VS showed significant FC with regions within the anterior cingulate cortex (ACC, BA 25/24/32) and orbitofrontal cortex (OFC, BA11). In the FC map of the associative loop (Supporting Information, Figure S5), the DC and VLP regions showed significant FC with the dorsolateral prefrontal cortex (dlPFC (BA 9/46), vlPFC (BA 47), ACC (BA 32), and parietal association areas (inferior parietal lobule, BA 40). In the FC map of the sensorimotor loop, the DCP and DRP regions showed significant FC with the supplementary motor cortex, midcingulate cortex, and primary motor regions (Supporting Information, Figure S6).

Significant FC differences in the frontostriatal loops were found between the FESZ and HC groups ($p < .05$, FWE-corrected). Compared with the HCs, patients with FESZ had reduced FC in limbic loops, including FC between the LVSi and right dorsal ACC (dACC, MIN: 6,11,37), RVSi and left dACC (MIN: 3,17,40), LVSs and right ACC (MIN:

13, -5,49), and RVSS and left ACC (MIN: 0, -12,56) (Table 2 and Figure 1). No significant FC differences were found between the groups in the sensorimotor and associative loops (all $p > .05$, FWE-corrected).

To obtain a measure of effect size, we calculated Cohen's *d* for the mean FC *z*-score between left/right inferior ventral striatum (LVSi and RVSi) and ACC (Table 2). The Cohen's *d* of LVSi-RdACC (1.02), RVSi-LdACC (0.72), LVSS-RACC (1.10), and RVSS-LdACC (0.87), which conventionally interpreted as constituting a relatively large effect size.

3.2 | Correlation of FC with clinical variables

As shown in Figure 2, there was significant negative correlations between the PANSS total score and LVSi-right dACC FC ($r = -.378$, $p = .015$), and the PANSS total score and RVSi-left dACC FC ($r = -.549$, $p = .0004$). In the five symptomatic factors scores, only the disorganized thought factor score were significantly correlated with the FC in limbic frontostriatal loops (LVSi-RdACC: $r = -.35$, $p = .02$; RVSi-LdACC: $r = -.49$, $p = .0017$) of the FESZ group (Figure 3).

4 | DISCUSSION

In this study, we used RS-fMRI to conduct a systematic investigation of FC of the sensorimotor, associative, and limbic loops within frontostriatal circuitry in FESZ patients. We found that the FC of limbic, but not sensorimotor or associative, frontostriatal loops was reduced in the FESZ group relative to that in HC group. Furthermore, decreased FC between the bilateral inferior VS and the dACC within the limbic frontostriatal loops correlated inversely with overall severity of clinical psychotic symptoms in patients with FESZ, and with the disorganized factor score of PANSS, but not other factor scores.

4.1 | Frontostriatal loop dysfunction in FESZ

Although it is well accepted that the frontostriatal circuits play an important role in SZ-associated cellular/molecular-level and neural-system-level alterations (Anticevic & Corlett, 2012; Barnes et al., 2015), the neural mechanism of refined circuit dysfunction underlying SZ pathopsychology has not been clarified. According to the tripartite model of frontostriatal circuits which are defined by their cortical inputs, the sensorimotor loop connects the somatosensory and motor-related cortices with the dorsal caudal putamen and dorsal rostral

FIGURE 1 Group differences in frontostriatal loop FC between HC and FESZ groups in voxel-wise whole brain analysis. Compared to the HC, FESZ patients had reduced FC between the VS and ACC ($p < .05$, FWE corrected) [Color figure can be viewed at wileyonlinelibrary.com]

putamen, associative loop connects the dlPFC with the dorsal caudate and ventral rostral putamen, and the limbic loop connects the ACC, OFC, and ventromedial PFC with the VS (including the nucleus accumbens and ventral parts of the caudate and putamen). Among the above loops, limbic and associative loop dysfunction have been reported frequently in patients with SZ or individuals at a high risk for SZ (Juckel et al., 2012; Lancaster et al., 2016; Rausch et al., 2015; Sarpal et al., 2015, 2017; Sole-Padullés et al., 2016).

In this study, we did not find significant SZ-related alterations in the associative loop as the previous studies report. However, it is notable that although the abnormality of associative striatum have been consistently revealed in previous SZ studies, such as enlarged grey volume (Levitt et al., 2013), reduced fractional anisotropy (Levitt et al., 2017; Quide, Morris, Shepherd, Rowland, & Green, 2013), increased synaptic dopamine function (Horga et al., 2016; Meyer-Lindenberg et al., 2002), increased glutamate levels (de la Fuente-Sandoval et al., 2013), and lower activations or connectivity (Mucci et al., 2015; Peters et al., 2017; Zhou et al., 2007), most of those previous studies recruited chronic patients, or the early-stage SZ patients who had already received the antipsychotic medications. Therefore, the current finding of lacking the associative loop impairment in medication-naïve FESZ suggested that associative loop and their related cognitive function may be progressively present with the development of disease and mainly in the field of active consciousness. In fact, in the few studies which demonstrated the abnormally functional connectivity between the associative striatum and prefrontal subregions, the task-related fMRI studies predominated. For example, a recent study reported significantly decreased performance-related connectivity between the

vIPFC and bilateral putamen during an *n*-back task (Quide et al., 2013). Further researches that overcome the potential confounding factors and include different mental states are needed.

On the other hand, the limbic loop has long been considered playing an important role in the dysfunction of dopaminergic regulation of SZ psychopathology, including impairments in reinforcement learning and reward-based motivational function (Brunelin et al., 2013; Deserno, Schlagenhauf, & Heinz, 2016; Horga & Abi-Dargham, 2014). However, besides the substantial evidences collected by the emotional/reward-related tasks (Deserno et al., 2016; Radua et al., 2015; Rausch et al., 2014), there were few studies examining the functional connectivity between the limbic striatum and prefrontal subregions in directly. The current findings of resting-state hypoconnectivity in the limbic loop of medication-naïve schizophrenia, would add new evidence to the neural mechanism underlying the psychopathology of schizophrenia.

4.2 | Limbic frontostriatal loop dysfunction of connectivity in FESZ

Our findings of patients with FESZ showing reduced FC among all four seeds of VS (LVSi/RVSi and LVSs/RVSs) and dACC (BA24 and BA32), relative to the HC group, complement prior findings of functional and structural abnormalities within these regions in patients with SZ (Esslinger et al., 2012; Juckel et al., 2012; Kirschner et al., 2016; Radua et al., 2015; Stegmayer et al., 2014). The VS has long been considered to play a key role in motivation and reward processing. Blunted VS activation during reward anticipation, which is associated with increased

FIGURE 2 Scatter plots of correlation analysis between VS-ACC connectivity and PANSS total score: (a) Scatterplot of the association between PANSS total score and functional connectivity between the LVSi and RdACC; (b) Scatterplot of the association between PANSS total score and functional connectivity between the RVSi and LdACC [Color figure can be viewed at wileyonlinelibrary.com]

dopamine levels and striatal dopamine synthesis capacity (Bar-Gad, Havazelet-Heimer, Goldberg, Rupp, & Bergman, 2000; Delgado, 2007) has been suggested to underlie the formation of psychotic symptoms in patients with chronic SZ and FESZ, and in individuals at a high risk of developing SZ (de Leeuw, Kahn, & Vink, 2015; van der Meer & Redish, 2011; Ziauddeen & Murray, 2010). However, the exact clinical relevance of altered VS activation in psychosis is unclear and the results of studies examining the potential relationship between VS activation and negative symptoms have been inconsistent (de Leeuw et al., 2015; Gradin et al., 2011; Radua et al., 2015; Roiser, Howes, Chaddock, Joyce, & McGuire, 2013). Alternatively, VS involvement in SZ might be related to its role in salience processing (Blackwood, Howard, Bentall, & Murray, 2001; Zink, Pagnoni, Martin, Dhamala, & Berns, 2003; Zink, Pagnoni, Chappel, Martin-Skurski, & Berns, 2006). Therefore, it is possible that the motivational deficits and the emergence of delusions, hallucinations, and disorganized symptoms in SZ could be both related to aberrant salience attribution due to the limbic frontostriatal loop dysfunction (Kapur, 2003; Murray, 2011; Roiser et al., 2009).

Patients with SZ often show remarkable functional impairments for inappropriate assignment of salience to contextually irrelevant external events and internal mental states. Meanwhile, they often fail to give appropriate attention to the task-relevant stimulus. This “aberrant salience” is considered to be mediated by dysregulation of the VS and mesolimbic dopamine system (Kapur, 2003). To investigate whether there is a common neural basis in midbrain dopaminergic pathways related to aberrant motivation/reward anticipation and salience attribution, Esslinger et al. (2012) combined a monetary reward anticipation task and an implicit nonmonetary salience attribution task and found that those two dysfunctions in FESZ share a common neural mechanism involving the VS. Furthermore, patients with SZ show elevated VS dopamine levels in the absence of incoming stimuli (Howes et al., 2009a, 2009b; Kapur, 2003), which leads to chaotic stress-associated striatal dopamine release (Heinz, 2002; Heinz & Schlagenhauf, 2010) that can hinder phasic dopamine release in response to contextually relevant stimuli (Howes et al., 2009a, 2009b; Kapur, Mizrahi, & Li, 2005). Our current findings of reduced

FIGURE 3 Scatter plots of correlation analysis between VS-ACC connectivity and Disorganized thought (DT) factor score of PANSS

resting-state VS-dACC synchrony correlating with SZ symptom severity, and the relatively large effect size associated with the VS-dACC finding, add new evidence to that frontostriatal hypoconnectivity at rest is a robust physiological mechanism underlies early-stage SZ symptoms. The significant correlation between the abnormality in limbic loop and the disorganized thought factor score suggested that the imbalance of dopaminergic control may influence the automatically link together thought without conscious feedback, control or supervision, a process that may break down in the disorganized thought of FESZ.

It is worthwhile to note that only the bilateral Vsi seeds, but not bilateral Vss seeds showed significant correlation with both PANSS total score and the disorganized thought factor score in current study. According to the original study for functional connectivity of human striatum (Di Martino et al., 2008), following which we defined the striatal subdivisions, there are three seed regions in caudate (VSi, VSSs, and DC), and the superior ventral striatum (VSSs) is the intermediate region along the ventral-dorsal axis. The direct comparison of the significant FC of each seed in whole brain range showed that VSi (ventral caudate/nucleus accumbens) exhibit greater connectivity than VSSs with the brain regions involved affective and reward processing, such as

OFC (BA11/25), ACC and parahippocampal gyrus, while as the superior ventral striatum (VSSs) showed greater connectivity than VSi in the inferior/middle frontal gyrus, and more superior/lateral portions of OFC (BA 10). Meanwhile, the direct comparison of VSi versus DC (dorsal caudate) showed greater correlation of VSi with dACC (BA32/24), insula, and parahippocampal gyrus, and the greater correlation of DC with dlPFC and vlPFC regions. In combination with the above studies, the current finding of unique correlation between bilateral VSi-dACC FC and the symptom severity emphasized the essentiality of comprehensive and precise examination of functional connectivity for striatum, a highly structurally and functionally heterogeneous structure, in the population with psychiatric disorder. That also highlighted that the attenuated coherent patterns of spontaneous activity between bilateral nucleus accumbens and dACC may play a key role in the etiology of SZ. However, it remains to further explore the therapeutic significance of this functional abnormality in limbic frontostriatal loop.

As an important node of salience network, dACC has been described as a connectional intersection of the brain's reward and action networks and associated with a diversity of salience attribution functions, such as inhibitory control, value calculation, decision making,

and emotion regulation (Cardinal, Parkinson, Hall, & Everitt, 2002; Shenhav, Botvinick, & Cohen, 2013). The "hub"-like anatomy of the dACC appears well-suited for these roles (Shenhav et al., 2013). Consistent with its functional characteristics, the projections from dACC to the VS are relative extensive, located between the OFC and dorsal PFC terminal fields (Calzavara, Maily, & Haber, 2007; Haber, 2016; Haber & Knutson, 2010). However, the understanding of the role of the dACC in SZ pathophysiology remains quite limited. Recently, researchers have begun to emphasize a potentially fundamental role of dACC dysfunction in psychosis and expressed the need to elucidate distinctive alterations in the dynamic coordination of the dACC with other brain regions (Goodkind et al., 2015; Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013; van Amelsvoort & Hernaes, 2016). Our finding of abnormal resting-state VS-dACC connectivities are consistent with those of studies reporting functional and structural abnormalities in the ACC, especially in BA24 and BA32, in early SZ (Cui et al., 2015; Fornito et al., 2008; Fusar-Poli, Radua, McGuire, & Borgwardt, 2012; Woodcock, Wadehra, & Diwadkar, 2016).

Given that altered glutamatergic-dopaminergic interactions in the VS have been implicated in SZ pathogenesis (Egerton et al., 2012; Moghaddam & Javitt, 2012; Stone, Morrison, & Pilowsky, 2007), the current finding of symptom severity-related VS-dACC desynchronization in nonmedicated FESZ patients supports the notion that glutamate neurotransmission may be a developmental driver of SZ etiology (Dempster et al., 2015; Moghaddam & Javitt, 2012). Previous studies reported that activation patterns of the dACC and VS were sensitive to SZ treatment with atypical, but not typical antipsychotics (Karch, Pogarell, & Mülert, 2012; Lahti et al., 2004; Schlagenhaut et al., 2008a, 2008b; Snitz et al., 2005), which might due to the particular effects of atypical antipsychotics on prefrontal and striatal brain responses. Furthermore, clinical studies also showed heightened effectiveness of glutamatergic drugs in treatment-resistant patients after failure of traditional tD2 receptor antagonist drugs treatment (Javitt, Duncan, Balla, & Sershen, 2005; Stone, Raffin, Morrison, & McGuire, 2010). Further examination of medical effects on resting-state frontostriatal neural synchronization and tonic neurotransmitter release is needed.

4.3 | Limitations

This study has several limitations. First, we could not eliminate completely the effects of the physiological noise, such as cardiac and respiratory pulsation, from our low-frequency range RS fMRI data (0.01–0.08 Hz). Second, although we excluded the subjects from data analyses who has excessive head motion (scrubbing bad time points > 20) and low tSNR (<100), head motion, and physiological noise would have an impact on the data analysis of functional connectivity. Third, the relatively small sample sizes may increase the risk of false negatives and effect-size inflation in FC analysis, and reduce the power for detecting the correlation of clinical symptoms and the abnormal FC in frontostriatal circuits. Finally, although the role of frontostriatal circuitry in SZ pathopsychology may evolve over a patient's lifespan, the present study focused on the first-episode SZ. Further studies should examine

individuals involving different SZ stages (e.g., high risk of psychosis and chronic SZ).

5 | CONCLUSIONS

In this study, we found reduced FC between the VS and dACC within the limbic loop of frontostriatal circuitry in patients with FESZ and an inverse correlation between VS-dACC connectivity and overall symptom severity. The current findings indicate that FC impairment in the limbic loop specifically may play a key role in the pathology at early-stage SZ and thus provide novel insights for SZ treatment development. Future researches for pharmacological manipulations of dopamine and glutamine would provide important insights into how biochemical transmission deficits in patients with FESZ impact FC and overall circuit function.

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CONFLICT OF INTEREST

Dost Öngür served on a scientific advisory board for Neurocrine Inc. in 2016. Dr Kirkpatrick has received licensing royalties and travel support from ProPhase for use of the Brief Negative Symptom Scale (BNSS) by for-profit groups; these fees are donated the Brain and Behavior Research Foundation. He has also received consulting fees and travel support from Genentech/Roche, Minerva Neurosciences, and ProPhase LLC, consulting fees from anonymized pharmaceutical companies through Decision Resources, Inc. and L.E.K. Consulting, and from an investment capital company through Guideposts. He has also consulted with Sterne Kessler, a law firm, about a pharmaceutical litigation issue. Dr Kirkpatrick also receives fees from Walsh Medical Media for editorial services, and received fees for editorial services from Physicians Postgraduate Press, Inc. All the other authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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