Title Page

Title:

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

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Abstract

Frontostriatal circuit 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 pathopsychology 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 35 treatment-naïve FESZ patients and 27 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 [$p < 0.05$, family-wise error (FWE)-corrected] in the limbic loop, but not in the sensorimotor or associative loops, of frontostriatal circuitry. Moreover, bilaterally decreased ventral striatum (VS)-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.

Key words: First-episode schizophrenia; Frontostriatal circuit; Resting-state functional connectivity; Ventral striatum; Dorsal anterior cingulate cortex

Corresponding author: Xiang Wang

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 and 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 and Verstynen, 2015; Lehericy, et al., 2004). Accumulating evidence suggests that discrete channels in frontostriatal circuits are related with abnormalities in movement planning and execution, motivation and reinforcement learning, cognition, and goal-directed behavior in patients with SZ (Csernansky and Bardgett, 1998; Horga and Abi-Dargham, 2014; Simpson, et al., 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, et al., 2000; Ongur and 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 and Dagher, 2006). Accordingly, frontostriatal circuits can be divided into three functionally distinct and spatially segregated loops, namely the sensorimotor, associative, and limbic loops, each of which specializes in a particular neurocognitive domain(Alexander and Crutcher, 1990; Di Martino, et al., 2008; Haber, 2016). Specifically, the sensorimotor loop connects the somatosensory and motor-related cortices (supplementary motor area, primary motor cortex, and midcingulate motor cortex) with the dorsal caudal putamen and dorsal rostral putamen, which have been shown to be involved in motor sequence acquisition and performance as well as habitual instrumental behavior

Corresponding author: Xiang Wang

(Bhatia and Marsden, 1994). The associative loop, which connects the dorsolateral prefrontal cortex (dlPFC) with the dorsal caudate and ventral rostral putamen, has been associated with executive function and goal-directed behavior. The limbic loop, which connects the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and limbic structures with the ventral striatum (VS, including the nucleus accumbens and ventral parts of the caudate and putamen), has been implicated in emotion processing, motivational function, and reinforcement learning (Bar-Gad, et al., 2000; Delgado, 2007). The impairment of any core component of those loops could alter cognitive, affective, or sensorimotor function directly and could, ultimately, result in psychopathological and cognitive symptoms (Horga and 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 and limbic regions of the striatum is associated with the positive symptoms of SZ, while diminished dopamine release in the ventral striatum has been linked with negative symptoms of SZ (Brunelin, et al., 2013; Ceccarini, et al., 2013; Horga, et al., 2016; Howes, et al., 2009a; Howes, et al., 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 frontalstriatal loops (Koo, et al., 2006; Quan, et al., 2013; Stegmayer, et al., 2014). Recent functional neuroimaing studies have shown that both aberrant activation and altered functional connectivity (FC) in frontostriatal systems are associated with clinical symptoms of patients with SZ (Arrondo, et al., 2015; Kirschner, et al., 2016; Morris, et al., 2012; Radua, et al., 2015; Rausch, et al., 2014; Roth, et al., 2016; Sorg, et al., 2013; Zhang, et al.,

Corresponding author: Xiang Wang

2015). Moving forward, higher resolution findings based on systemic and refined analyses of striatal subdivisions defined according to their frontal cortex inputs can advance our understanding of frontostriatal circuitry in SZ beyond what we have learned from coarse whole striatum or striatal region of interest (ROI) findings.

Although frontalstiatal 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, and medication use. The enrollment of participants with long-term chronic mental illness and medication use could have particularly profound confounding effects. 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 (Bossong and Kahn, 2016; 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 non-target 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,

Corresponding author: Xiang Wang

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.

Methods

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 35 medication-naïve patients with FESZ were recruited from the outpatient clinic of the Second Xiangya Hospital. The eligibility criteria included: 1) a DSM-IVdiagnosis of SZ based on the Chinese version of the Structured Clinical Interview for the DSM-IV (SCID-I) (First, et al., 1996); 2) age at enrollment of 20–40 years and age at symptom onset 16 years or older; 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, history of electroconvulsive therapy. A group of 27 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

Corresponding author: Xiang Wang

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, et al., 1987; Marder, et al., 1997) on the day of scanning.

The demographic and, for the FESZ group, clinical characteristics of the groups are presented in Table 1. The two groups were similar with respect to age, gender distribution, and handedness. All subjects reported that they were of Han ethnicity.

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 mm^2, matrix = 256 × 256, 180 slices, slice thickness = 1 mm, and 0 mm interslice gap, voxel size = 1 × 1 × 1 mm^3). 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 mm^2, matrix = 64 × 64, 36 slices, slice thickness = 4 mm, and 0 mm interslice gap, voxel size = 3.75 × 3.75 × 4 mm^3; 206 volumes).

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 and collegues (Di Martino, et al., 2008). Specifically, sensorimotor loop ROIs were the dorsal caudal putamen (DCP) (x = ±28, y = 1, z = 3) and dorsal rostral putamen (DRP) (x = ±25, y = 8, z = 6). The associative loop

Corresponding author: Xiang Wang

ROIs were the dorsal caudate (DC) (x = ±13, y = 15, z = 9) and the ventral rostral putamen (VRP) (x = ±20, y = 12, z = −3). The limbic loop ROIs were the inferior ventral striatum (VSi) (x = ±9, y = 9, z = -8), and superior ventral striatum (VSs) (x = ±10, y = 15, z = 0). The anatomical locations and Montreal Neurological Institute (MNI) coordinates of all 12 ROIs are shown in supplemental figures S1.

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 Hz-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.

The head motion artifacts would impact on resting state fMRI functional connectivity (Power, et al., 2012; Power, et al., 2013). The previous studies (Power et al., 2012) suggest that Framewise Displacement (FD)>0.5mm and temporal derivative of the fMRI time series (DVARS) >0.5% values were used to identify bad volumes in the fMRI time data. First, using C-PAC 0.3.9 (http://fcp-indi.github.io/docs/user/index.html),we evaluated whether the head motion parameters (FD and DVARS) show significant differences between the FESZ and HC. We used Kolmogorov-Smirnov

Corresponding author: Xiang Wang

tests to compare head motion parameters (FD and DVARS) between two groups. There were no significant differences between two groups (FD: $p = 0.8$; DVARS: $p = 0.63$; supplementary Figure S2 and Table S1). Second, to minimize the head motion artifacts impact, we excluded fMRI time points for which FD> 0.5mm and DVARS> 0.5% signal change (as well as 1 preceding fMRI time point and 2 subsequent fMRI time points). The each group left fMRI time points were reported in supplementary Table S1. A detailed description of head motion can be found in the supplementary document and supplementary Figure S3-S4 and Table S1.To further assess whether the striatum sub-region temporal signal-to-noise ratio (tSNR) have significant difference between two groups, we calculated the tSNR of 12 seeds and compared these tSNR values across the HC and FESZ groups for each of the 12 ROIs using Kolmogorov-Smirnov tests. There were no significant group differences between HC and FESZ participants in tSNR in any ROI ($p>0.05$, supplementary Figure S5).

FC analysis of three frontostriatal loops

For each subject, seed-based FC 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 brain regions with significant FC differences across subjects. Further, group comparisons between patients with FESZ and HCs were then performed with permutation-based non-parametric testing (with 5000 permutations) by the Randomise program in FMRIB Software Library (Nichols and Holmes, 2002). A family-wise error (FWE)-corrected cluster significance threshold of $p < 0.05$ was used for multiple comparisons with Threshold-Free Cluster Enhancement (Smith and Nichols, 2009). To obtain a

Corresponding author: Xiang Wang

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.

Correlation analyses of FC with clinical variables

Clinical-variable correlation analyses were performed to reveal the functional consequences of observed FC differences. The threshold for significance was $p < 0.05$ (FWE corrected). To assess the correlation between PANSS scores and FC for regions whose FC values differed between the groups. Here, we used a regression method that is robust against univariate outliers in the data, as implemented using a robust linear model procedure (rlm) of the R statistical language (R Development Core Team 2009). Such robust regression methods have been proposed for analysis of both behavioral data (Wilcox 1998).

Results

FC of frontostriatal loops

Functional mappings generated with striatal subregions as the seeds were remarkably consistent with previous studies (supplementary figures S6-8). In the FC map of the limbic loop (supplementary figures S6), the VS showed significant FC with regions within the ACC (BA 25/24/32) and OFC (BA11). In the FC map of the associate loop (supplementary figures S7), the DC and VRP regions showed significant FC with the 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 (supplementary figures S8).

Significant FC differences in the frontostriatal loops were found between the FESZ and HC groups

Corresponding author: Xiang Wang

($p < 0.05$, 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), between the RVSi and left dACC (MIN: 3,17,40), between the LVSs and right ACC (MIN: 13,-5,49), and between the RVSs and left ACC (MIN: 0, -12,56) (Table 2 and Fig. 1). No significant FC differences were found between the groups in the sensorimotor and associative loops (all $p > 0.05$, 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 large effect size.

Correlation of FC with clinical variables

As shown in Fig. 2, we found a significant negative correlation between PANSS total scores and LVSi -right dACC FC ($p = 0.015$, $r = -0.378$). Additionally, we observed a significant negative correlation between PANSS total scores and RVSi-left dACC FC ($p = 0.0004$, $r = -0.549$). In the 5 symptom factors scores, only the Disorganized thought factor score was significant correlated with the FC in limbic frontostriatal loops (LVsi-RdACC: $p = 0.02$, $r = -0.35$; RVSi-LdACC: $p = 0.0017$, $r = -0.49$) of the FESZ group (Fig. 3).

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

Corresponding author: Xiang Wang

relative to that in HCs. 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.

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 and Corlett, 2012; Barnes, et al., 2015), the neural mechanism of refined circuit dysfunction underlying SZ pathopsychology has not been clarified. More accurate representations of frontostriatal neural processing are needed, particularly with respect to early-stage patients early who have not yet taken any antipsychotic medicines (Bossong and Kahn, 2016; Deutch, 2016; Gong, et al., 2016; Haber, 2016; Sarpal, et al., 2016). Previously, in the tripartite model of frontostriatal circuits, limbic and associative loop dysfunction have been reported frequently in patients with FESZ or individuals at a high risk for SZ (Esslinger, et al., 2012; Horga, et al., 2016; Juckel, et al., 2012; Lancaster, et al., 2016; Rausch, et al., 2015; Sarpal, et al., 2015; Sole-Padulles, et al., 2016) .

Although enlarged grey volume (Levitt, et al., 2013), increased synaptic dopamine function (Kegeles, et al., 2010), and increased glutamate levels (de la Fuente-Sandoval, et al., 2011) in the associative striatum have been reported in SZ studies, few studies have examined the functional or structural connectivity between the associative striatum and prefrontal subregions directly. One RS-fMRI study reported that the bilateral dlPFC showed reduced FC with the striatum in FESZ patients (Zhou, et al., 2007). Additionally, a task-related frontostriatal FC study showed significantly decreased

Corresponding author: Xiang Wang

performance-related connectivity between the vlPFC and bilateral putamen during performance of the n-back working memory task (Quide, et al., 2013). A recent structural MRI study reported findings of white matter tract abnormalities of the associative loop in FESZ (Quan, et al., 2013). Specifically, patients with FESZ were found to have bilaterally reduced fractional anisotropy in the rostral middle frontal gyrus-striatum tract and inferior frontal gyrus-striatum tract, but neither reduction correlated with clinical characteristics as rated on the Brief Psychiatric Rating Scale. Further research that overcomes the incongruences, limitations, and potential confounding factors of previous studies is needed to explore the underlying mechanisms of associative loop alterations in SZ.

Because the limbic frontostriatal loop is a major pathway for dopamine, it has been suggested that dysfunction of dopaminergic regulation of the limbic loop may play an important role in SZ psychopathology, including impairments in reinforcement learning and reward-based motivational function (Brunelin, et al., 2013; Deserno, et al., 2016; Horga and Abi-Dargham, 2014). Our findings, together with those of recent studies across multiple modalities demonstrating altered FC within the limbic loop in early-stage SZ (Brunelin, et al., 2013; Deserno, et al., 2016; Horga and Abi-Dargham, 2014; Radua, et al., 2015; Rausch, et al., 2014), are consistent with this view. On the other hand, it is notable that prior reports of significant SZ-related alterations in the associative loop were not supported by the current results.

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

Corresponding author: Xiang Wang

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 dopamine levels and striatal dopamine synthesis capacity (Bar-Gad, et al., 2000; Delgado, 2007) has been suggested to underlie the formation of psychotic symptoms in patients with chronic SZ and FESZ, as well as in individuals at a high risk of developing SZ (de Leeuw, et al., 2015; van der Meer and Redish, 2011; Ziauddeen and 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, et al., 2013). Alternatively, VS involvement in SZ might be related to its role in salience processing (Blackwood, et al., 2001; Zink, et al., 2006; Zink, et al., 2003). That is, 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 non-monetary salience attribution task and found

Corresponding author: Xiang Wang

the 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; Kapur, 2003), which leads to chaotic stress-associated striatal dopamine release (Heinz, 2002; Heinz and Schlagenhauf, 2010) that can hinder phasic dopamine release in response to contextually relevant stimuli (Howes, et al., 2009a; Kapur, et al., 2005). Our current findings of reduced 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. However, it remains to further explore the therapeutic significance of this functional abnormality in limbic frontolstriatal 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, et al., 2002; Shenhav, et al., 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, et al., 2007; Haber, 2016; Haber and 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

Corresponding author: Xiang Wang

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, et al., 2013; van Amelsvoort and Hernaus, 2016). The present finding of bilateral VS-dACC connectivities correlating with symptom severity suggest that ACC-VS disconnection within limbic circuit may be a key element of early-stage SZ, and may, ultimately, underlie diverse cognitive and emotive impairments. Our results are consistent with those of studies reporting functional and structural abnormalities in the ACC, especially in BA24 and BA32, in early SZ (Chan, et al., 2011; Cui, et al., 2015; Fornito, et al., 2008; Fusar-Poli, et al., 2012; Woodcock, et al., 2016).

Given that altered glutamatergic-dopaminergic interactions in the VS have been implicated in SZ pathogenesis (Egerton, et al., 2012; Moghaddam and Javitt, 2012; Stone, et al., 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 and Javitt, 2012). Although the associative striatum has also been implicated in some studies (de la Fuente-Sandoval, et al., 2013; Esslinger, et al., 2012), activation patterns of the dACC and VS have been shown consistently to be sensitive to SZ treatment (Karch, et al., 2012; Sarpal, et al., 2015). Interestingly, they are normalized by atypical, but not typical, antipsychotics (Karch, et al., 2012; Lahti, et al., 2004; Schlagenhauf, et al., 2008a; Schlagenhauf, et al., 2008b; Snitz, et al., 2005), perhaps due to the particular effects of atypical antipsychotics on prefrontal and striatal brain responses. Indeed, clinical studies have shown heightened effectiveness of glutamatergic drugs in treatment-resistant patients after failure of traditional tD2 receptor antagonist drugs treatment (Javitt, et al., 2005; Stone, et al., 2010). Nevertheless, most previous studies investigated the relationship between posttreatment symptom

Corresponding author: Xiang Wang

improvement and brain activation pattern changes during the performance of a task. Further examination of medical effects on RS frontostriatal neural synchronization and tonic neurotransmitter release is needed.

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, resting state fMRI functional connectivity is widely used to characterize patients and control differences in functional connectivity. Head motion would impact on functional connectivity different analysis (Power, et al., 2012). In particularly, some patient participants may be more prone to have head movement in the MRI scanner. So, we were very careful to remove effects from head movements during scanning from the fMRI data. This head motion parameters evaluation ensured that our findings were not attributable to group differences in head motion. In addition, tSNR gives very important information on the data quality of fMRI time series. Low tSNR dataset would induce spurious differences in functional connectivity between groups. We excluded participants who have low tSNR. So, better data quality control procedure can significant improve the results reliable and replicable. Third, although the current study demonstrated altered RS-FC in the limbic loop and its relationship with SZ symptom severity, future studies should employ targeted behavioral tasks to gain a better understanding of the clinical relevance of the present findings. Fourth, the relatively small sample sizes may 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 studied focused on early-stage SZ. Further studies should examine individuals at different SZ

Corresponding author: Xiang Wang

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

Conclusions

In the present 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.

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 no conflict of interest.

Corresponding author: Xiang Wang

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Corresponding author: Xiang Wang

Table 1. Demographic and clinical characteristics of FESZ and HC groups.

Characteristic	FESZ (N = 35)	HC (N = 27)	t/χ2	*P*
Age	20.74 ± 5.24	22.56 ± 3.25	1.576	0.120
Gender (male/female)	16/19	15/15	1.032	0.310
Handedness (right/left)	35/0	27/0		
Duration of illness (months)	9.51 ± 7.98			
PANSS total score	82.20 ± 12.04			
5 symptom factors score of PANSS *				
Negative symptoms factor	20.34 ± 6.98			
Positive symptoms	26.37 ± 6.00			
Disorganized thought	17.29 ± 5.06			
Uncontrolled hostility/excitement	9.63 ± 3.73			
Anxiety/depression	8.57 ± 3.25			

Two-tailed Fisher exact test was used to compare proportions for categorical variables.

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

* the calculation of five symptom factors score of PANSS is according to the Marder's five factor model of the PANSS (Marder SR, 1997)

Corresponding author: Xiang Wang

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' d
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

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; $p < 0.05$, corrected

Corresponding author: Xiang Wang

Fig. 1 Group differences in frontostriatal loop FC between HC and FESZ groups in voxel-wise brain analysis. Compared to the HCs, FESZ patients had reduced FC between the VS and ACC ($p < 0.05$, FWE corrected).

Fig. 2 Scatter plots of correlation analysis between VS - ACC connectivity and PANSS Total score.

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

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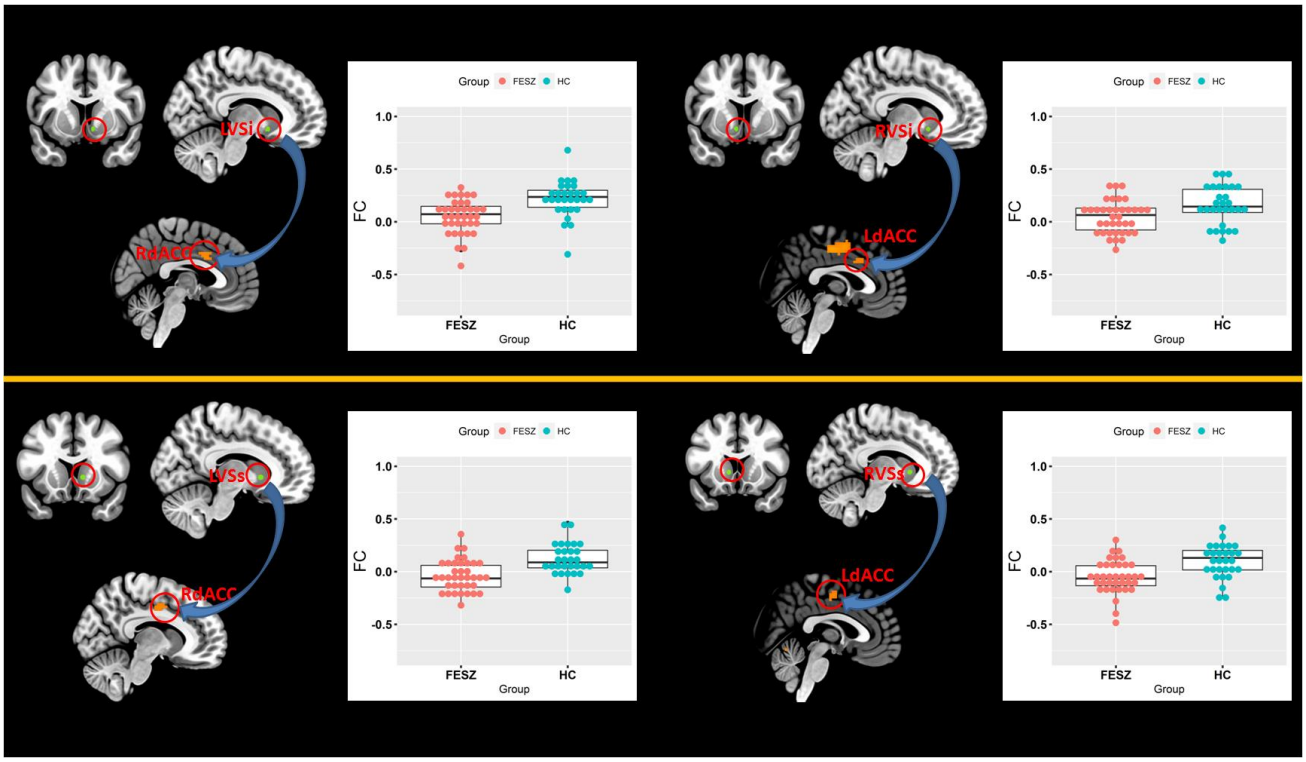

Fig. 1 Group differences in frontostriatal loop FC between HC and FESZ groups in voxel-wise whole brain analysis. Compared to the HCs, FESZ patients had reduced FC between the VS and ACC ($p < 0.05$, FWE corrected).

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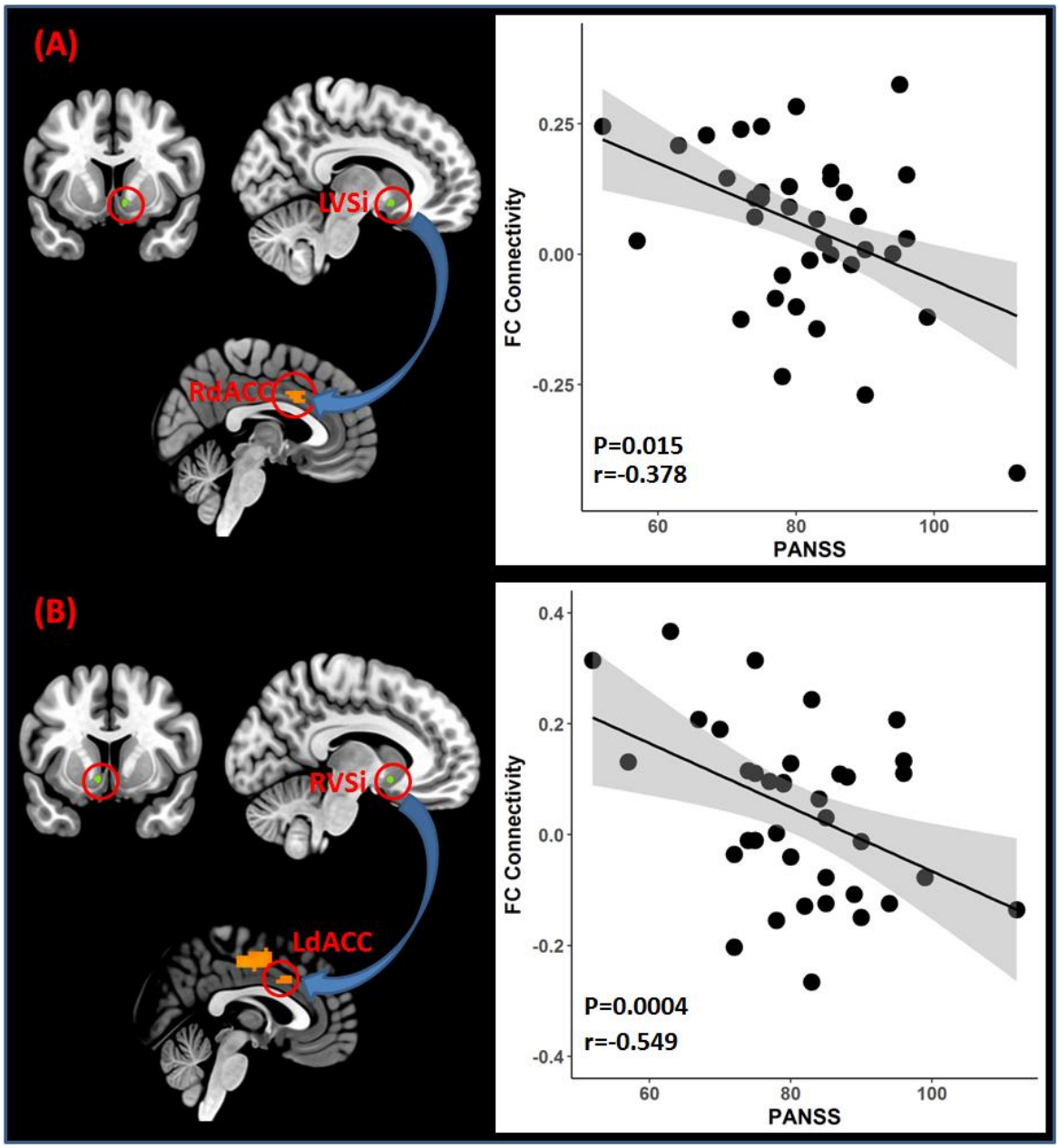

Fig. 2 Scatter plots of correlation analysis between VS - ACC connectivity and PANSS Total score. (A) Scatterplot of the association between PANSS Total score and functional connectivity between the LVSi and RdACC (B) Scatterplot of the association between PANSS Total score and functional connectivity between the RVSi and LdACC.

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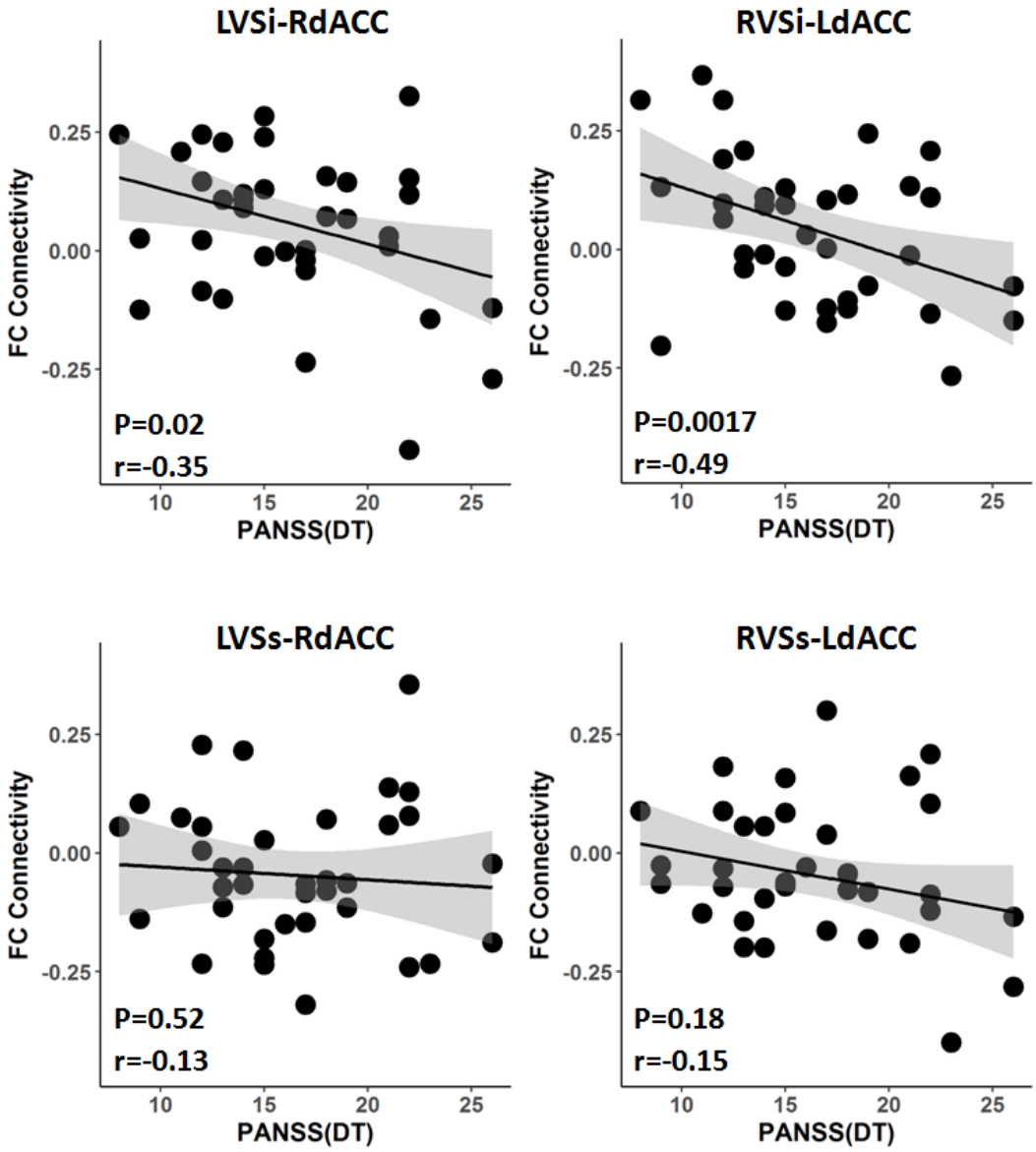

Fig. 3 Scatter plots of correlation analysis between VS - ACC connectivity and PANSS Disorganized thought (DT) factor score.

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Supplementary Materials

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

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Substriatal ROIs definitions

12 substriatal ROIs (3.5 mm radius, six in each hemisphere) representing the sensorimotor, associative, and limbic loops as defined previously by Di Martino and collegues. 12 substriatal ROIs are displayed in Supplementary Figure S1.

Evaluation of head motion artifacts

The head motion would impact on resting state fMRI functional connectivity (Power, et al., 2012; Power, et al., 2013). The previous studies (Power et al., 2012) had suggested that FD>0.5 mm and DVARS>0.5% signal change should be excluded after scrubbing bad time points. In addition, the offending time points(one before and two after) need to been excluded. First, we evaluated whether the head motion(FD and DVARS) differences between the patient and control patients. We used Kolmogorov-Smirnov tests to compare head motion parameters (FD and DVARS) between two groups. There were no significant differences between two groups. The mean FD values and DVARS values of HC and FESZ see supplementary Figure S2 and Table S1. Second, to minimize the head motion impact, we excluded fMRI time points for which FD was greater than 0.5mm and DVARS was greater than 0.5% signal change (as well as 1 time point before and 2 time points after). The each group left fMRI time points were reported in supplementary Table S1. Third, head motion during the scanning would

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influence measures of functional connectivity. Whether head motion parameters (FD) was correlated with FC. We calculated the correlation between FD and FC between VSi/VSs and dACC. There was no relationship between head motion (FD) and FC ($p > 0.05$) (see supplementary Figure S3). Furthermore, we further investigated whether the head motion correlated with clinical symptoms, we calculated the correlation between FD and clinical symptoms (PANSS and PANSS(DT)). There was no relationship between head motion (FD) and clinical symptoms ($p > 0.05$) (see supplementary Figure S4).

Evaluation of group differences in striatum sub-region tSNR

For the extraction of ROI-based temporal signal-to-noise ratio (tSNR) values, we used the prior define 12 substriatal ROIs. tSNR was calculated by dividing each ROI voxel's mean signal intensity by the standard deviation of the time-course. I had calculated the tSNR of 12 seeds, the results are reported in supplementary Figure S5. We further compared these tSNR values across the HC and FESZ groups for each of the 12 ROIs using Kolmogorov-Smirnov tests. There were no significant group differences between HC and FESZ participants in tSNR in any ROI ($p>0.05$). The subject who has low TSNR (<50) in those seed region have been excluded for further analysis.

Supplementary References

Di Martino A, Scheres A, Margulies DS, et al. Functional connectivity of human striatum: a resting state FMRI study. Cereb Cortex Dec 2008;18(12):2735-2747.

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

Supplementary Table S1 Comparison of head motion parameters between HC and FESZ

Assessment	HC	FESZ	Group Differences(p values)

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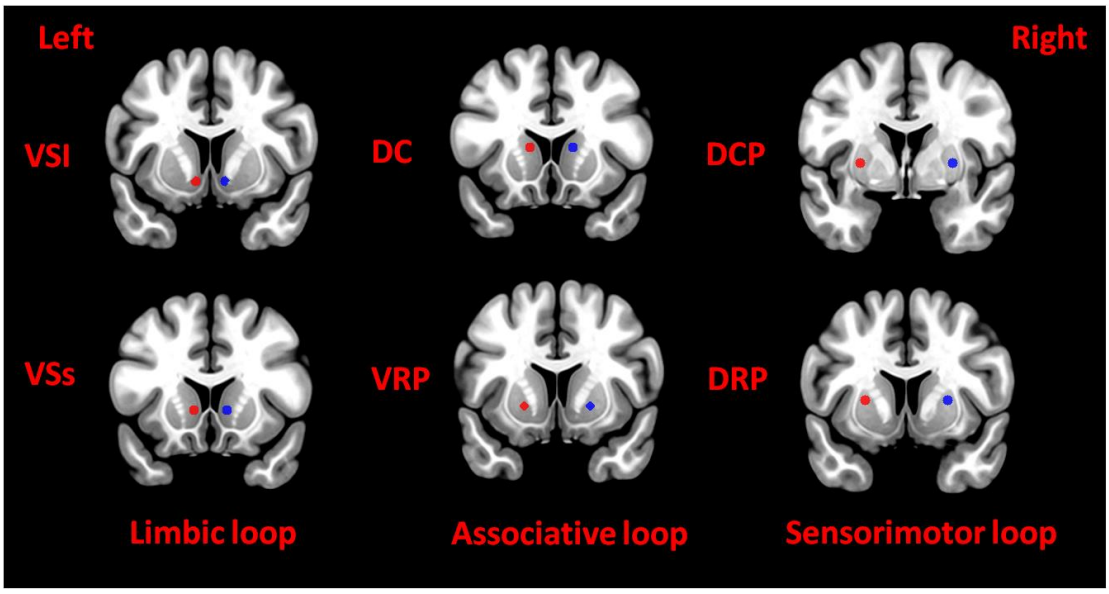
FD (mean±SD)	0.13±0.05	0.138±0.06	0.80
DVARS (mean±SD)	0.152±0.04	0.158±0.05	0.63
fMRI time points Left (mean)	199	200	0.98
fMRI time points Left (min)	186	187	na
fMRI time points Left (max)	202	202	na



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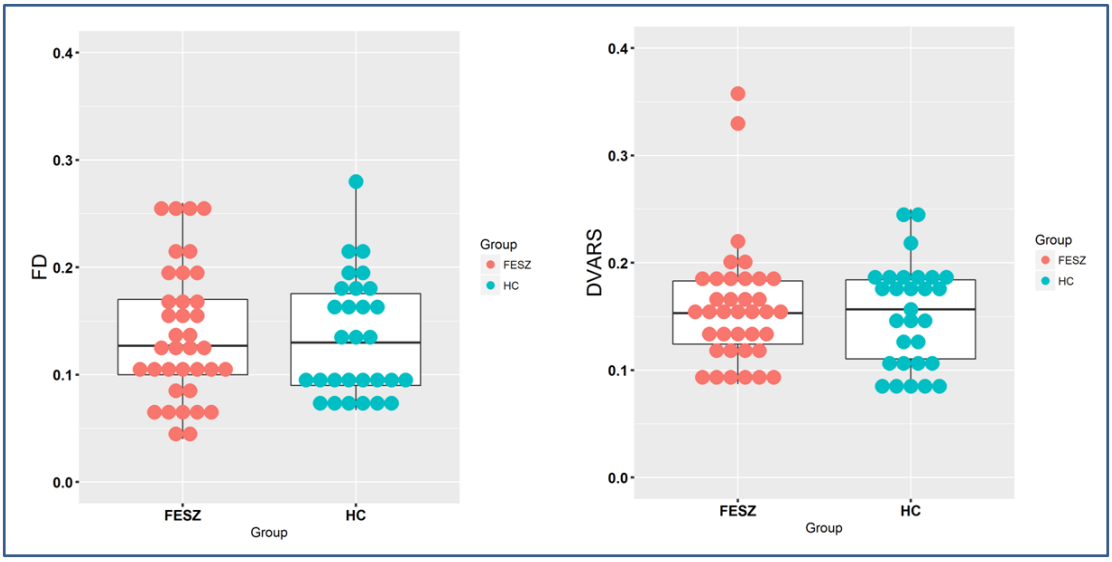
Supplementary Figure S1. Substriatal regions-of-interest definitions. The limbic loop ROIs were the inferior ventral striatum (VSi) (x = ±9, y = 9, z = -8), and superior ventral striatum (VSs) (MNI:x = ±10, y = 15, z = 0). The associative loop ROIs were the dorsal caudate (DC) (MNI:x = ±13, y = 15, z = 9) and the ventral rostral putamen (VRP) (MNI:x = ±20, y = 12, z = −3). The sensorimotor loop ROIs were the dorsal caudal putamen (DCP) (MNI:x = ±28, y = 1, z = 3) and dorsal rostral putamen (DRP) (MNI:x = ±25, y = 8, z = 6).Red color represent Left ROIs, Blue color represent Right ROIs, Coordinates are in Montreal Neurological Institute (MNI). VSI= inferior ventral striatum; VSs= superior ventral striatum; DC= dorsal caudate; VRP = ventral rostral putamen; DCP= dorsal caudal putamen; DRP= dorsal rostral putamen.



Supplementary Figure S2. Head motion parameters between two groups. Mean FD <0.5mm and DVARS<0.5% did not differ between two groups (p>0.05,Kolmogorov-Smirnov tests).

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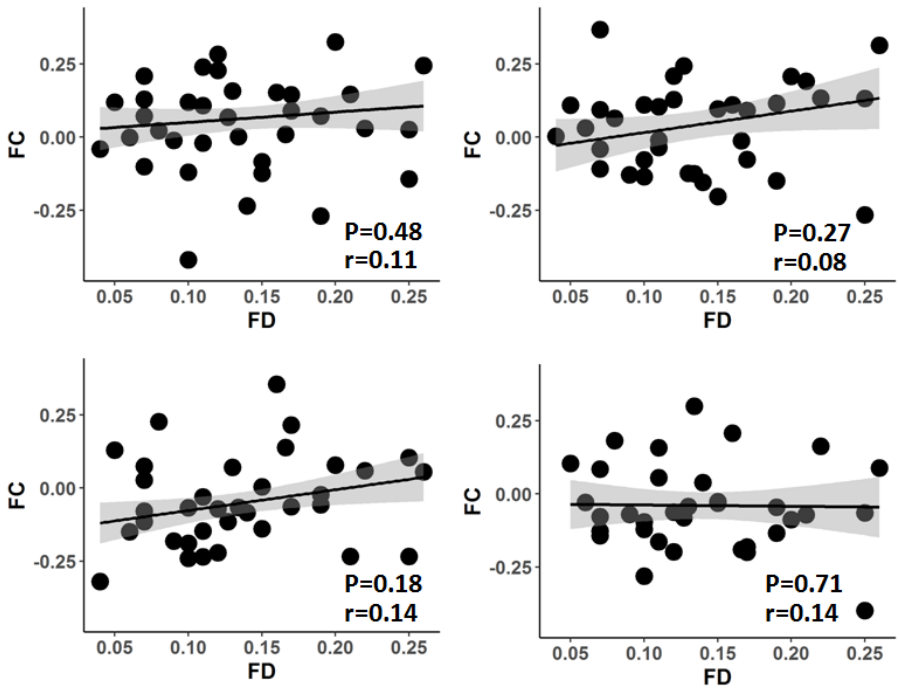

Supplementary Figure S3. The relationship between FD and functional connectivity

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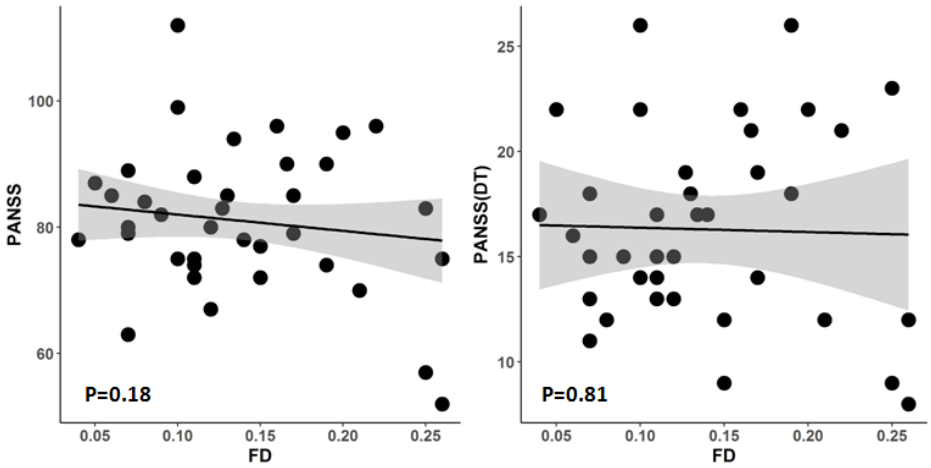

Supplementary Figure S4. The relationship between FD and clinical symptoms

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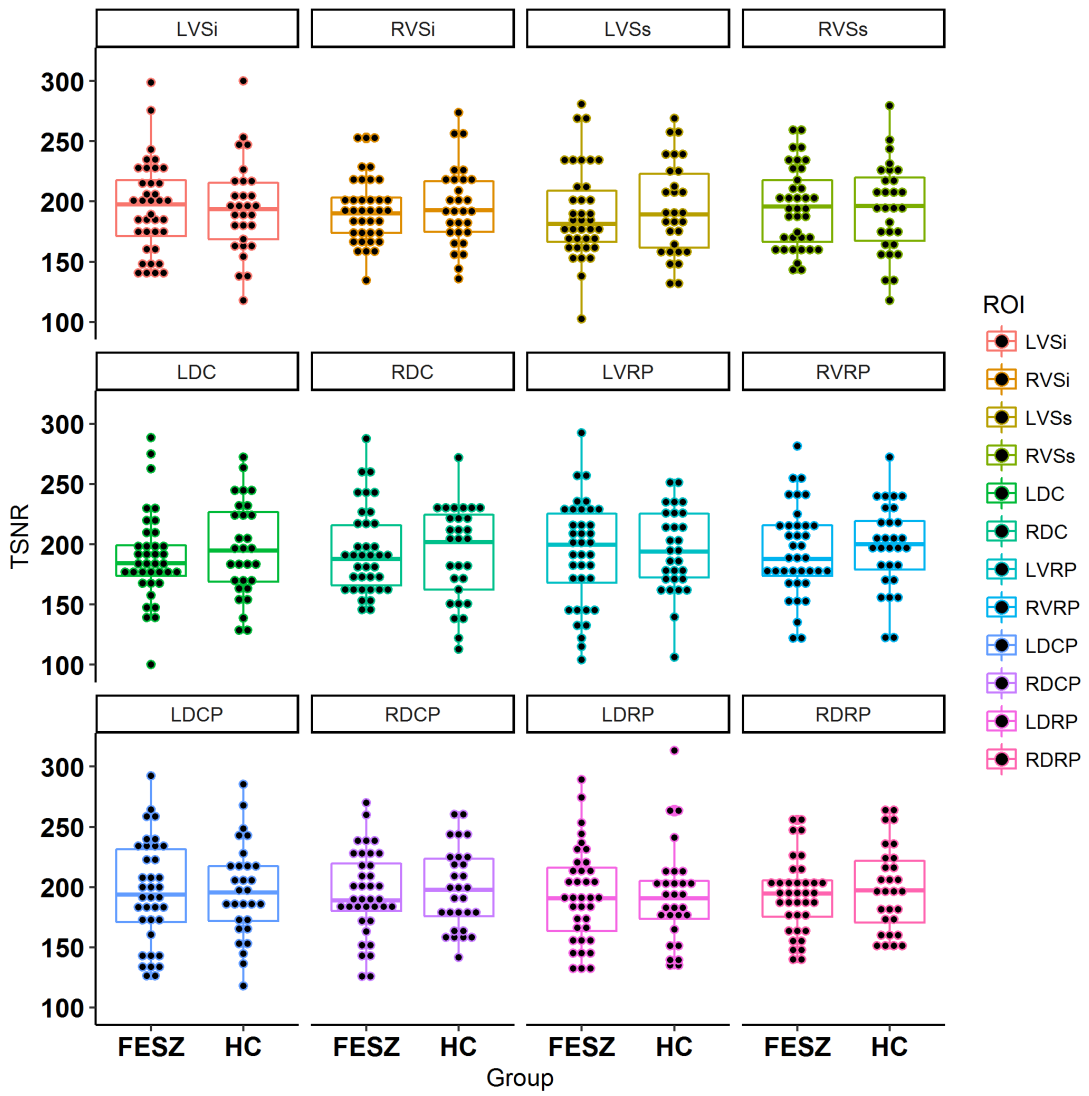

Supplementary Figure S5. Temporal Signal-to-Noise Ratio (tSNR) of 12 ROIs. Plots depict the distribution of individual tSNR values for each ROI.

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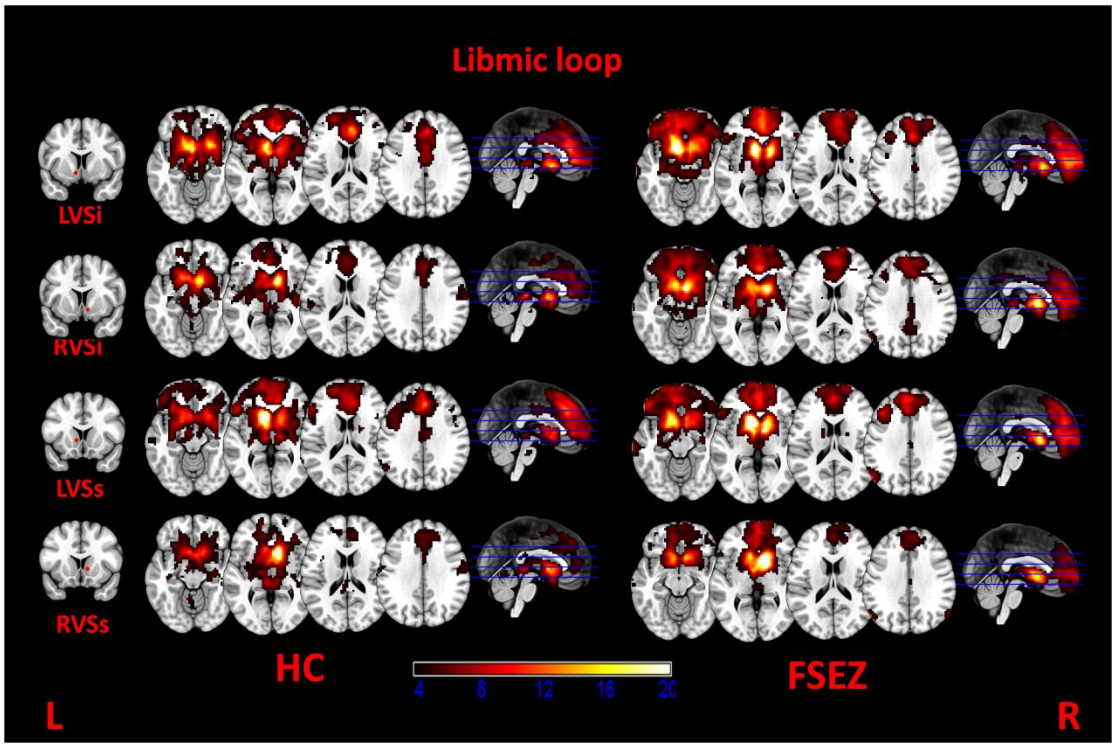

Supplementary Figure S6. Functional connectivity maps of the Libmic loop. The limbic loop ROIs were the inferior ventral striatum (VSi) (MNI:x = ±9, y = 9, z = -8), and superior ventral striatum (VSs) (MNI:x = ±10, y = 15, z = 0).. Results are displayed at P < .05 (false discovery rate) corrected. R, right hemisphere; L, left hemisphere ;MNI,Montreal Neurological Institute (MNI).

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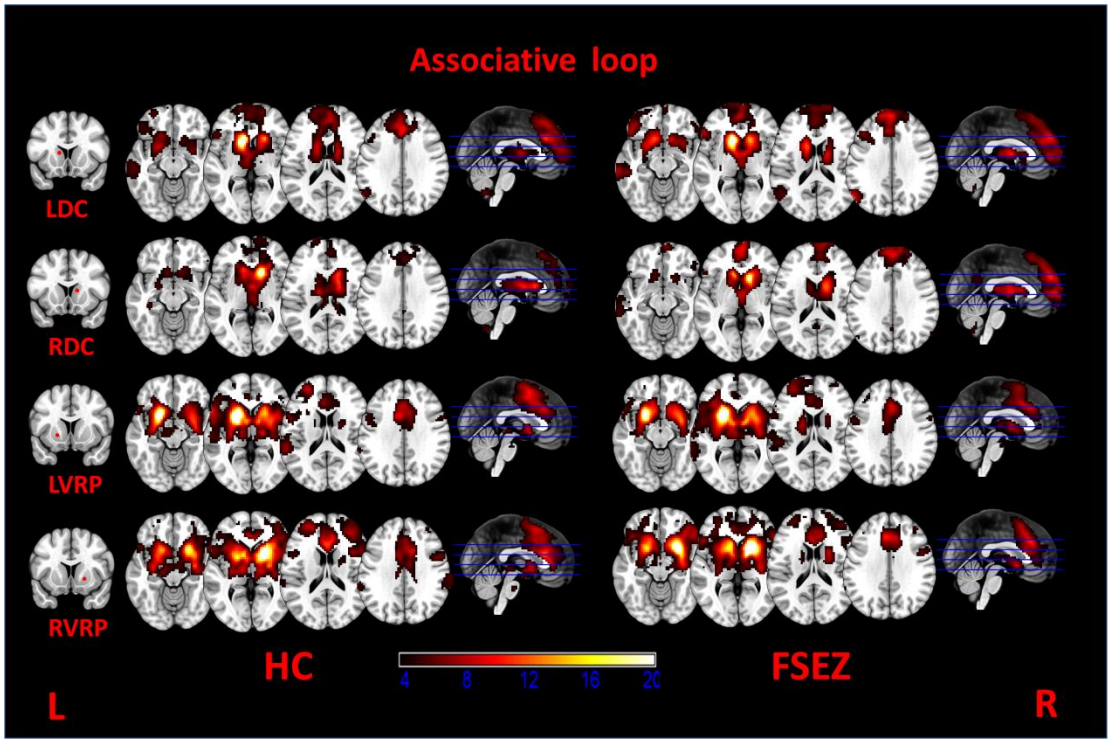

Supplementary Figure S7. Functional connectivity maps of the associative loop. The associative loop ROIs were the dorsal caudate (DC) (MNI:x = ±13, y = 15, z = 9) and the ventral rostral putamen (VRP) (MNI:x = ±20, y = 12, z = −3). Results are displayed at P < .05 (false discovery rate) corrected. R, right hemisphere; L, left hemisphere; MNI,Montreal Neurological Institute (MNI).

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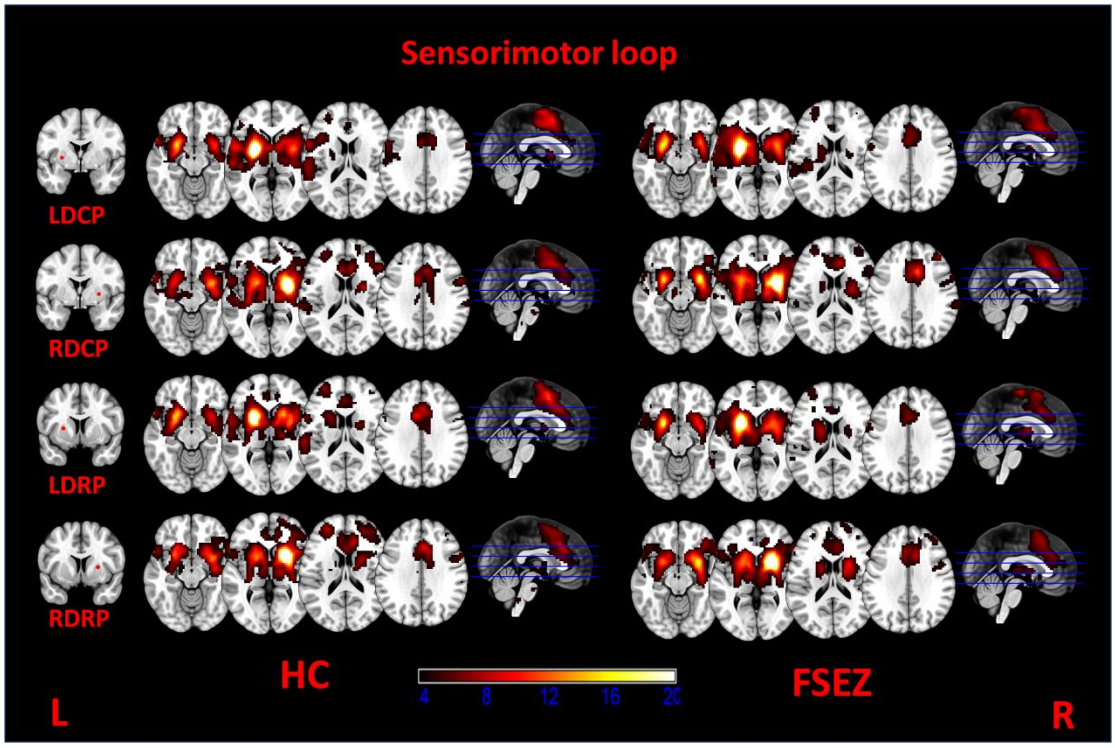

Supplementary Figure S8. Functional connectivity maps of the sensorimotor loop. The sensorimotor loop ROIs were the dorsal caudal putamen (DCP) (MNI:x = ±28, y = 1, z = 3) and dorsal rostral putamen (DRP) (MNI:x = ±25, y = 8, z = 6). Results are displayed at $P < .05$ (false discovery rate) corrected. R, right hemisphere; L, left hemisphere.

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