Functional Connectivity of the Fronto-striato-thalamic Circuit Correlates with Positive Symptoms in Schizophrenia

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【Abstract】 Objective: To explore the relationship between the functional connectivity of the striatum and clinical symptoms of schizophrenia. Methods: Voxel-based resting-state functional connectivity analyses were performed to identify the functional connectivity of the striatal regions in whole brain in 70 schizophrenia patients and 60 age- and sex-matched healthy controls. Results: We found the functional connectivity between the left caudate(CAU) and left middle frontal gyrus (MFG), left superior frontal gyrus(SFG) and left thalamus(THA), right CAU and right MFG, left THA and right THA, and right putamen(PUT) and right cuneus(CUN) to be significantly decreased in the schizophrenia patient group compared to the healthy controls. Moreover, the functional connectivity between the left CAU and MFG was found to be negatively associated with hallucinations in patient group. Moreover, a positive correlation was found between bizarre behavior and the functional connectivity of the CAU with THA. Conclusion: These findings demonstrate resting-state functional abnormalities of the frontal-striatal-thalamic(FST) circuit in schizophrenia. Moreover, the significantly altered functional connectivity between the left CAU and left MFG and between the right CAU and right THA in the FST circuit may be the underlying neuro-substrates, respectively, for the hallucinations and bizarre behaviors observed in schizophrenia patients.

【Key words】 Functional connectivity analysis; Positive symptoms; Resting-state; Schizophrenia; Striatum

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额叶-纹状体-丘脑神经环路功能连接与精神分裂症患者阳性症状的相关

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【摘要】 **目的：**探讨纹状体的功能连接和精神分裂症临床症状的关系。**方法：**运用基于体素的功能连接分析法来识别精神分裂症患者纹状体与其他脑区功能连接的异常，入组对象为70位精神分裂症患者和60位年龄、性别相匹配的健康对照。**结果：**与健康对照比较，我们发现患者的左侧尾状核与左侧额中回、左侧额上回以及左侧丘脑，右侧尾状核与右侧额中回、左右两侧丘脑，右侧壳核与右侧楔叶均表现为功能连接减弱。相关分析发现，左侧尾状核和左侧额中回的功能连接强度与患者阳性症状量表的幻觉评分成负相关，右侧尾状核与右侧丘脑的功能连接强度与患者阳性症状量表的怪异行为呈正相关。**结论：**结果显示精神分裂症患者额叶-纹状体-丘脑环路静息态功能连接存在异常。并且此环路中的左侧尾状核与左侧额中回以及右侧尾状核与右侧丘脑的功能连接异常可能分别为精神分裂症患者幻觉和怪异行为的神经生物学基础。

【关键词】 功能连接分析；阳性症状；静息态；精神分裂症；纹状体

1 Introduction

Schizophrenia patients have often been found with increased dopamine in the striatum, and interventions in the dopaminergic system have been reported to be successful in treating positive symptoms of schizophrenia[1,2], suggesting that the striatum may play a key role in the pathophysiology of schizophrenia. However, the

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striatum's functional connectivity with other brain regions and its relationship to clinical symptoms remain unclear. The emergence of resting-state magnetic resonance imaging(fMRI) techniques has enabled scholars to observe the low-frequency spontaneous fluctuations of blood oxygenation level-dependent signals, striatum impairment, and functional connectivity of the striatum with other brain regions in humans[3-5]. Moreover, the interaction between brain regions can be assessed using functional connectivity analysis, which is a method for estimating correlations between brain activities in different regions.

The striatum mainly comprises the caudate nucleus and the putamen and has traditionally associated with the control of motor movement[6], motivation to reward values[7], and cognitive control[8]. The striatum is activated by events essential to the survival of the species, such as those related to food, sexuality, or important social interactions[9-11], the responses to which are often reported to be impaired in schizophrenia patients. Neurodegenerative disorders known to affect the striatum, such as Parkinson's, Huntington's, and Wilson's disorders shave been found to affect motor control and produce clinical symptoms that are fundamentally similar to those of schizophrenia[12, 13]. Moreover, drugs that are presumed to act in the striatum to treat hypokinetic movement disorders such as dopaminergic agonists or muscarinic cholinergic antagonists have been reported to precipitate psychotic symptoms, including hallucinations and delusions[14, 15]. Thus, there is considerable interest in investigating the role of the striatum in schizophrenia pathophysiology.

The striatum, though mostly associated with positive symptoms of schizophrenia has also been implicated in negative symptoms of schizophrenia. For example, anhedonia and other predominantly negative affective symptoms have been associated with the dysfunction of dopaminergic neurons in the ventral striatum, including the nucleus accumbens, a core region of the brain reward system[4]. The occurrence of these symptoms has been associated with primary disconnection between the prefrontal and temporolimbic cortices[16, 17]. Ventral striatal activity has been associated with pleasant emotions of anticipation[9], and ventral striatal dysfunction has long been associated with reduced motivation or anhedonia[11, 18]. Taken together, this evidence suggests that the striatum may play a key role in cognitive impairment, including both negative and positive symptoms of schizophrenia. However, most of previous resting-state fMRI studies investigating functional connectivity in schizophrenia have focused on the prefrontal and temporal lobes. The functional connectivity of the striatum and its associated clinical symptoms remain unknown.

Resting-state functional connectivity analysis has been widely used to study the abnormalities of psychiatric diseases[19], as it can capture the natural mental state of participants without producing task-induced biases, allowing patients representing abroad range of illness severity to be included in the study population[20]. Functional connectivity analysis also allows multiple cortical systems to be studied using the same fMRI data set, providing a better signal to noise ratio and facilitating the investigation of neural plasticity after long disease durations[20]. Resting state fMRI has illuminated the potential valume of investigating the functional connectivity of deeper brain regions that are thought to play a crucial role in the pathophysiology of schizophrenia, but the striatum has received less attention.

In this study, we aimed to characterize abnormal functional connectivity of the striatal regions with other brain regions and subsequently examine correlations to clinical symptoms. To determine striatal functional connectivity, we use the automated anatomical labeling (AAL) template[21] in our resting-state data to select the putamen and caudate bilaterally(left and right) as seeds of regions of interest(ROIs) and subsequently compare the functional connectivity of these seed ROIs between schizophrenia patients and healthy controls.

2 Methods and materials

2.1 Participants

Seventy schizophrenia patients were recruited from the Department of Psychiatry, Second Xiangya Hospital of Central South University, Changsha, China. All patients were assessed with the Structured Clinical

Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P)[22]. The diagnosis and symptom ratings of schizophrenia were made independently by two experienced psychiatrists and the inter-rater reliability level was $k \geqslant 0.80$. Patients met the following inclusion criteria: ①18-45 years of age; ②Han Chinese ethnicity; ③completed nine or more years of education; ④right-handedness determined by the Annett Hand Preference Questionnaire[23]; and ⑤met the DSM-IV diagnostic criteria for schizophrenia. Participants were excluded if they had: ①a history of neurological disorder or other serious physical illness; ②a history of severe medical disorder or substance abuse as reported by participants and confirmed with collateral sources such as medical records and close relatives; ③a contraindication for MRI; or ④a history of electroconvulsive therapy. For all schizophrenia patients, positive and negative symptoms were assessed with the Scale for the Assessment of Positive Symptoms(SAPS)[24] and the Scale for the Assessment of Negative Symptoms(SANS)[25, 26], respectively. Of these patients, 65 were receiving atypical antipsychotics(clozapine, risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone), 1 typical antipsychotics(sulpiride), and 4 combined typical and atypical antipsychotics.

Sixty healthy controls were recruited from the Changsha city area. The inclusion and exclusion criteria were the same as those for the patients, except that the healthy controls did not meet the DSM-IV criteria for any Axis-I psychiatric disorders. Individuals with a family history of psychiatric illness among their first-degree relatives were excluded from the healthy controls group.

All participants gave written informed consent to participate in the study after the risks and benefits of the study were discussed in detail. The study was approved by the ethics committee of the Second Xiangya Hospital, Central South University.

2.2 Image Acquisition

MR images were acquired on a 3.0 T MR scanner (Philips Achieva XT). A standard head coil was used for radio frequency transmission and reception of magnetic resonance signals. Foam pads and ear plugs were used to minimize head motion and scanner noise. Subjects were instructed to keep their eyes closed, avoid specific thoughts and minimize movement. fMRI images were collected in the axial location, using a gradient-echo echo-planar imaging[27] sequence: repetition time(TR)=2000 ms, echo time(TE)=30 ms, flip angle (FA)=90°, matrix=64×64, field of view=240×240 mm^2, slice thickness=4 mm, gap=0 mm, slices=36.

2.3 Functional MRI Image Preprocessing and Statistical Analysis

All functional images were processed on Statistical Parametric Mapping 8(SPM8; http//www.fil.ion.ucl.ac.uk/spm). For each participant, the first 10 volumes of scanned data were discarded because of signal equilibrium and participants' adaptation to the scanning noise. The 240 volumes of each subject were preprocessed. Slice timing was used to correct differences in slice acquisition times. Temporal processed images were realigned to the first volume for correcting head motion and a mean functional image was correspondingly obtained. The participants needed to meet the criteria that there was less than 1.5 mm of translation and 1.5° of rotation in x-, y-, or z- axis. Further preprocessing procedures included spatial normalizing(resampling to 3×3×3 mm^3) and spatial smoothing(full-width at half maximum=4 mm). To further reduce the effects of confounders, six motion parameters, linear drift, and the mean time series of all voxels in the whole brain were regressed out after the images were smoothed. The fMRI data were then band-pass filtered(0.01-0.08 Hz) using REST software(http://restfmri.net/). In accordance with the hypothesis, each of the sub-regions of the striatum, including the bilateral caudate and putamen, was defined as a seed for functional connectivity analysis. Four correlation analyses were performed between the seed and the rest of the brain in a voxel-wise manner. Finally, the correlation coefficients in each voxel were transformed to z-values using the Fisher r-to-z transformation to improve normality.

Voxel-based comparison of z-value functional connectivity maps between healthy controls and schizophrenia patients was performed using analysis of covariance(ANCOVA) with years of education as covariates

at a significance threshold $P<0.05$, FDR corrected, cluster≥20. The brain regions indicating obvious functional connectivity differences between healthy controls and schizophrenia patients were regarded as the ROIs. We extracted the ROIs as mask for calculating their mean functional connectivity in all schizophrenia patients. The relationships between clinical variables and functional connectivity, which differ significantly between the healthy controls and schizophrenia patients were examined in the schizophrenia patients through correlation analyses using the Spearman correlation coefficient(rho) in SPSS(significance threshold $P<0.05$).

Group differences in demographic and clinical factors were analyzed with t-test or Chi-square test (significance threshold $P<0.05$) using SPSS 19.0 for Windows(SPSS, Chicago, IL, USA).

3 Results

3.1 Demographic and clinical characteristics

The demographic and clinical characteristics of participants are shown in the Table 1. No significant differences were observed between the healthy controls and schizophrenia patients in age or gender, but there was a significant difference between the groups in years of education.

Table 1　Demographic and clinical variables of healthy controls and schizophrenia patients

	Healthy controls(n=60)	Schizophrenia patients(n=70)	Statistical test	
			t or χ^2	P
Sex(male/female)	29/31	45/25	3.35	0.06
Age(SD), years	24.48(5.44)	24.50(5.59)	0.02	0.99
Education(SD), years	13.67(2.18)	12.14(2.27)	−3.90	0.00
Duration of illness(SD), months	−	24.11(32.17)	−	−
Chlorpromazine equivalents(SD)mg	−	231.07(150.21)	−	−
SAPS sum-score(SD)	−	19.39(15.24)	−	−
SAPS hallucinations(SD)	−	1.21(1.72)	−	−
SAPS delusions(SD)	−	2.06(1.62)	−	−
SAPS bizarre behavior(SD)	−	1.07(1.29)	−	−
SAPS positive formal thought disorder(SD)	−	0.79(1.14)	−	−
SANS sum-score(SD)	−	28.97(25.67)	−	−
SANS affective blunting(SD)	−	1.27(1.36)	−	−
SANS alogia(SD)	−	1.26(1.38)	−	−
SANS avolition/apaphy(SD)	−	1.66(1.58)	−	−
SANS anhedonia(SD)	−	1.94(1.61)	−	−
SANS inappropriate atention(SD)	−	1.20(1.35)	−	−

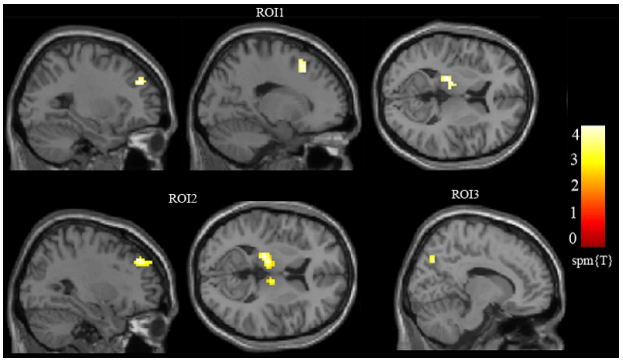
Note: SAPS and SANS=Scales for Assessed Positive and Negative Symptoms, SD=standard deviations

3.2 Functional connectivity analysis

When the seed was located in the left caudate (CAU), significantly decreased functional connectivity of the left CAU with the left middle frontal gyrus (MFG), left superior frontal gyrus(SFG) and left thalamus(THA) (fig. 1) was found in the schizophrenia patients group compared to the healthy controls group($P<0.05$, FDR corrected). When the seed was located in the right CAU, significantly decreased functional connectivity with the right MFG, left THA and right THA (fig. 1) was found in the schizophrenia patients group ($P<0.05$, FDR corrected). When the seed was located in the left putamen(PUT), there was no significantly altered functional connectivity with this region. When the seed was located in the right PUT, significantly decreased functional connectivity with the right cuneus (CUN) (fig. 1) was found in the schizophrenia patients group($P<0.05$, FDR corrected).

In the subsequent regression analyses for the schizophrenia patients group, the functional connectivity strength between the left CAU and left MFG, found to be reduced in the patients, was negatively associated with SAPS-hallucinations scores($r=-0.30$, $P=0.012$). A significantly positive association was found between SAPS-bizarre behavior scores and the functional connectivity strength between right CAU and right THA,

which was also reduced in the patients(t=0.273, P=0.022).



Note: Abnormal functional connectivity of striatal regions with other brain regions. When the seed was located in the left caudate(ROI 1), significantly decreased functional connectivity with the left middle frontal gyrus, left superior frontal gyrus and left thalamus was found. When the seed was located in the right caudate(ROI 2), significantly decreased functional connectivity with the right middle frontal gyrus, bilateral thalamus was found. When the seed was located in the right putamen(ROI 3), significantly decreased functional connectivity with the right cuneus was found. Statistically significant differences in functional connectivity were defined as P<0.05, FDR corrected. The color bar represents the range of T values.

Figure 1

4 Discussion

The aim of this study was to determine the functional connectivity of the striatum and its associated clinical relevance. Thus, we selected the bilateral caudate and putamen as seeds of ROIs and subsequently compared the functional connectivity of these seed ROIs between schizophrenia patients and healthy controls. When the seed was located in the left CAU, we found significantly decreased functional connectivity between the left CAU and left MFG and between the left SFG and left THA in schizophrenia patients compared to healthy controls, and when the seed was located in the right CAU, we found significantly decreased functional connectivity between the right CAU and the right MFG and bilateral THA in schizophrenia patients. Similarly, when the seed was located in the right PUT, we found significantly decreased functional connectivity between the PUT and right CUN in schizophrenia patients. The functional connectivity between the left CAU and left MFG was found to be negatively correlated with SAPS- hallucination scores and the functional connectivity between the right CAU and the right THA was positively correlated with SAPS-bizarre behavior scores. These findings are consistent with other studies that report the striatum playing a key role in schizophrenia psychopathology[1,2]. Therefore, this study demonstrates that the FST circuit maybe the underlying neuro-substrate for the hallucinations and bizarre behaviors observed in schizophrenia patients.

We used resting-state functional connectivity analysis, which has been widely used to study the functional connectivity in schizophrenia and other psychiatric diseases[28,29], to characterize the abnormal functional connectivity of the striatum regions with other brain regions and its associated clinical symptoms. This approach helped us find the reduced functional connectivity between the CAU and MFG and between the CAU and THA to be significantly correlated with positive symptoms. Specifically, we found that the functional connectivity between the left CAU and left MFG was negatively correlated with severity of hallucinations, and the functional connectivity between the right CAU and the right THA was positively correlated with severity of bizarre behavior. Investigators using resting-state MRI techniques have been challenged to understand what the brain is doing during resting- state scans[30]. The resting- state functional connectivity analysis has an advantage as it enables the investigator to study the natural mental state without producing task- induced biases and can facilitate investigation of neural plasticity after long disease durations[28, 29]. The resting state functional connectivity analysis approach may help provide reliable information relevant to the neuro- correlates of schizophrenia.

In this study, we found the functional connectivity between the left CAU and left MFG to be negatively correlated with severity of hallucinations. These findings are consistent with other studies that reported cortico-striatal circuitry dysfunction to be a fundamental element of schizophrenia[31]. For instance, an increase in dopamine transmission in the striatum, particularly in the caudate nucleus[32], has been associated with severity of positive symptoms[33, 34] and alteration of prefrontal function. Antidopaminergic drugs have been

found to reduce these symptoms in most patients with schizophrenia[35]. The altered functional connectivity between the striatum and the prefrontal cortex has also been reported in individuals at risk for mental state psychosis[36] or with other psychotic disorders such as bipolar disorder[37], giving an indication of its stability and genetic link. Abnormalities in resting-state connectivity in the cortico-striatal region have been associated with the disruption of the integrity of structural fiber connecting these two regions[38, 39]. Thus, the findings of this study add to the body of knowledge regarding the role that reduced functional connectivity between the left CAU in the striatum and the left MFG in the prefrontal cortex may play a key role in positive symptoms of schizophrenia, particularly in hallucinations and bizarre behavior.

The altered functional connectivity in the right hemisphere of the CAU and THA which was also associated with bizarre behavior is of particular interest. Previous studies have suggested that the disinhibition of subcortical dopamine increases the flow of sensory information to the thalamus, which in turn results into a failure of the THA to "filter out" irrelevant stimuli before they reach the cortex, thereby predisposing an individual to psychotic symptoms[40]. Patients with schizophrenia may present with bizarre behavior, including odd mental and emotional behaviors, indicating impairment of ability to control responses to irrelevant stimuli. Therefore, this evidence suggests that the impaired functional connectivity in the striato-thalamic circuit may be the underlying neuro-correlate for the bizarre behaviors observed in individuals with schizophrenia.

The mechanism underlying these findings remains unclear. Anatomically, the striatum comprises the CAU and PUT and receives its inputs from the cortex, the THA, the hippocampus and the amygdala, and it is an input component of the basal ganglia. The basal ganglia mainly project to the THA and the THA projects back to the cortex, completing a loop that involves the cortex, striatum, pallidum and THA(CSPT)[41]. The striatum has been implicated in the pathophysiology of positive symptoms in schizophrenia[42, 43]. The involvement of the striatal region in positive symptoms has been postulated to result from an increase in dopamine, and to be related to dopamine receptors and effectiveness of antipsychotic medications in reducing striatal dopamine. These hypotheses are consistent with the original version of the dopamine hypothesis, which viewed schizophrenia as a general dopamine hyperfunction syndrome. In this study, we observed the abnormal functional connectivity within the cortico-striato-thalamic neural loops, in which the striatum served as a center for the integration and modulation of many high-level cognitive, motor, and limbic processes[44-46], and its dysregulation has been reported to contribute to the psychotic symptoms of schizophrenia spectrum disorders[47]. Therefore, the severity of positive symptoms may result from a dysfunction of dopaminergic neurons in the nucleus of the striatum, which is a core region of the brain reward system[4], causing disconnection of the FST circuit which is a portion of CSPT loop.

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