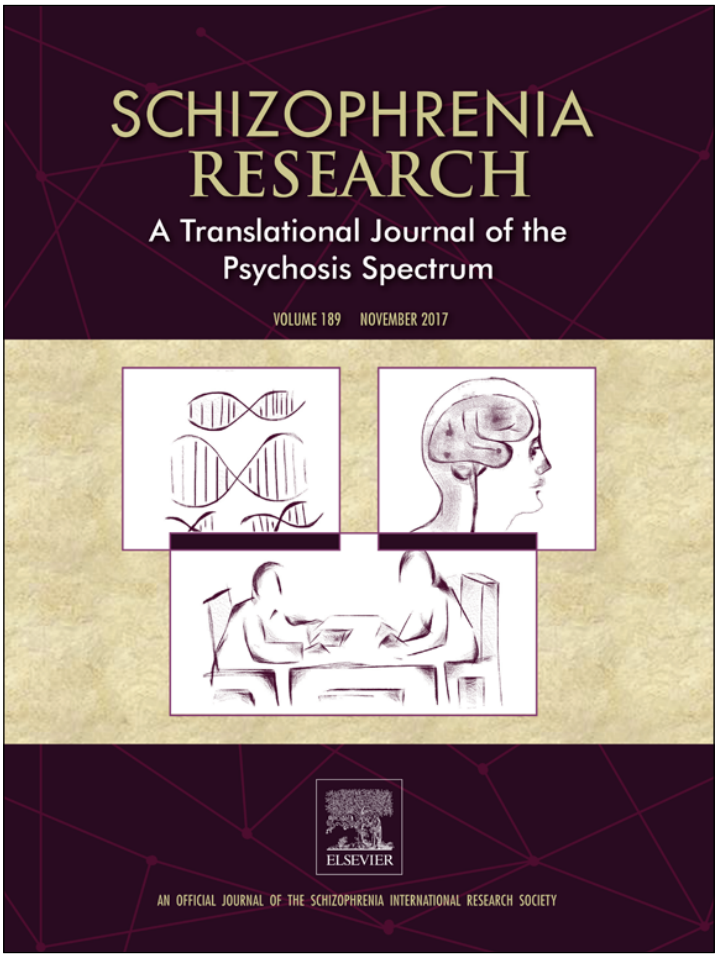

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# Frequency-selective alteration in the resting-state corticostriatal-thalamo-cortical circuit correlates with symptoms severity in first-episode drug-naive patients with schizophrenia

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ABSTRACT

Schizophrenia is a prototypical disorder of brain connectivity with altered neural activity in regions extending throughout the brain. Regions, including the subcortex and cortex, present activity mainly within a specific frequency band in resting-state. Whether these altered resting-state functional connections also present frequency specificity is unknown. In the present study, empirical mode decomposition, which is a pure data-driven method suitable for nonlinear and nonstationary signals, was used to decompose blood-oxygen-level-dependent (BOLD) signals into different intrinsic frequency bands. Our study included 42 first-episode drug-naive patients with schizophrenia and 38 controls. Significant aberration in functional connectivity was observed only at a higher frequency range (the peak spectral density power was 0.06 Hz). In this frequency band, patients with schizophrenia showed significantly increased functional connections between the bilateral cuneus and right supplementary motor area, reduced connections within the basal ganglia, and reduced connections between the dorsal striatum and left supplementary motor area. The dysfunction of the frontal gyrus significantly correlated with the dysfunction of the basal ganglia. Notably, these altered connections were significantly correlated with symptom severity. Our results demonstrate that frequency-selective altered corticostriatal-thalamo-cortical circuits in patients with schizophrenia are associated with symptoms severity.



## 1. Introduction

Patients with schizophrenia show a lack of integration between thought, emotion, and behavior, cognitive and affective deficits, positive symptoms such as delusions, hallucinations and thought disorder, and negative symptoms such as a flattened affect and volitional disturbances (Camchong et al., 2011; Fornito et al., 2012). The fundamental mechanism of schizophrenia is unclear. In patients with schizophrenia, altered resting-state brain activity has been found extending in regions throughout the brain (Lencz et al., 2003; Shenton et al., 2001). For example, the dopamine (DA) hypothesis of schizophrenia has received the most attention and is thought to be central to the fundamental mechanism (Abi-Dargham and Rodenhiser, 2000; Carlsson and Lindqvist, 1962; Carter and Pycock, 1980; Heinz et al., 1999; Saunders et al., 1998; Weinberger, 1987). Schizophrenia, as a prototypical disorder of brain connectivity, may be the result of hyperactive subcortical and hypoactive cortical DA metabolism (Catani and Mesulam, 2008; Friston and Frith, 1995; Howes and Kapur, 2009; Howes et al., 2009; Volkow et al., 1988).

The physiopathological mechanism of schizophrenia may be frequency-specific. The frequency-specific physiological functions of the human brain occur in the low-frequency range (Buzsaki and Draguhn, 2004; Buzsaki et al., 2013). Distinct oscillations with specific properties and physiological functions generate independent frequency bands (Buzsaki and Draguhn, 2004; Buzsaki et al., 2013). Electroencephalogram (EEG), studies suggest that altered oscillatory neuronal synchronization in the gamma band reflect core neural circuit abnormalities and cognitive deficits in schizophrenia (Cunningham et al., 2006; Spencer et al., 2008; Symond et al., 2005). In addition, review of electrophysiological studies of schizophrenia noted the importance of investigating frequency band abnormalities and interactions in schizophrenia

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(Moran and Hong, 2011). In this regard, resting-state functional magnetic resonance imaging (fMRI) may be useful, as frequency-specific characteristics in resting-state BOLD signals show an anatomically constrained spatial distribution (Baria et al., 2011). For example, subcortical regions such as the basal ganglia and thalamus show prominent slow-4 (0.027–0.073 Hz) frequencies, while other cortical regions show mainly slow-5 (0.013–0.027 Hz) frequencies (Zuo et al., 2010a). Notable, the basal ganglia and prefrontal cortex have critical roles in the physiopathology of schizophrenia (Howes and Kapur, 2009).

Studies have shown that alteration can vary for different frequency bands. For example, a wavelet transform to decompose fMRI time series into many frequency intervals revealed significantly altered global functional connectivity only in the frequency interval of 0.06–0.125 Hz (Lynall et al., 2010). Moreover, regional homogeneity (ReHo) changes in schizophrenia are widespread and frequency dependent (Yu et al., 2013). Furthermore, alterations of the amplitude of low-frequency fluctuations (ALFF) in schizophrenia vary with different frequency bands (Yu et al., 2014). These studies suggest that the physiological mechanism of schizophrenia may be frequency-specific. Exploring frequency-specific abnormality may provide novel insight in the study of schizophrenia.

Here, we used empirical mode decomposition (EMD) to explore frequency-specific dysfunction of functional connectivity in first-episode drugs-naive patients with schizophrenia. EMD is a pure data-driven method that can divide nonlinear and nonstationary brain signals into different intrinsic frequency bands (Huang et al., 1998). The advantage of EMD is that it avoids the arbitrary selection of a frequency band, as such as an approach may present two limitations, namely the loss of other frequency realms and physiological fluctuations confounding potentially specific frequencies (Wang et al., 2014b). Previous studies have used EMD to analyze fMRI data (Al-Subari et al., 2015; Song et al., 2014; Wang et al., 2014a). In our study, EMD was used to decompose BOLD signals into different intrinsic frequency bands. We hypothesized that frequency-specific altered functional connectivity is a fundamental mechanism of schizophrenia.

## 2. Materials and methods

### 2.1. Participants

The Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University approved the study and all patients provided written informed consent for their participation in this study. In the present study, 42 antipsychotic-naive patients with first-episode schizophrenia were recruited during consecutive admission at the Second Affiliated Hospital of Xinxiang Medical University. Participants were right-handed and of Han Chinese ethnicity (patient details are summarized in Table 1). The participants also fulfilled the following additional inclusion criteria: (1) Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for schizophrenia and (2) no comorbid Axis I diagnosis. Using the Structured Clinical Interview for the DSM-IV-TR, patient version (SCID-I/P), two well-trained psychiatrists independently diagnosed schizophrenia Patients were interviewed again after six months for a final diagnosis of schizophrenia. Psychiatric symptomatology was evaluated using the Positive and Negative Syndrome Scale (PANSS). Some subjects were excluded because translational and rotational displacement exceeded 2.0 mm or 2.0°. A total of 41 patients (mean age, 24.98; age range, 18–37; male, 26; female, 15) and 34 age-, gender-, and education-matched healthy controls (mean age, 25.12; age range, 18–32; male, 21; female, 13) were included in this study. Control participants were recruited from the local community using advertisements and further screened via structured interviews based on the Chinese version of SCID to rule out individuals who presented any history of psychiatric or medical conditions. All participants were excluded if they met any of the following criterions: (1) a history of neurological disorders or family history of hereditary neurological disorders; (2) a head injury resulting in the loss of consciousness; (3) alcohol or substance abuse; and (4) any metallic objects in their body (exclusion criterion for magnetic resonance imaging [MRI]).

**Table 1**
Characteristics of schizophrenia patients (Sch) and healthy controls (HC).

| | Sch ($n = 41$) | HC ($n = 34$) | $p$ |
|---|---|---|---|
| Age (years), mean ± SD | 24.98 ± 4.79 | 25.12 ± 4.58 | 0.90[a] |
| Gender, male: female | 26:15 | 21:13 | 0.94[b] |
| Duration of illness (months), mean ± SD | 8.29 ± 2.58 | | – |
| Alcohol, yes/no | 6/35 | 7/27 | 0.40[a] |
| Cigarette, yes/no | 9/32 | 8/26 | 0.86[a] |
| Years of education, mean ± SD | 10.4 ± 2.8 | 11.12 ± 2.8 | 0.25[b] |
| Handness, right/left | 41/0 | 34/0 | – |
| PANSS positive score | 25.78 ± 3.60 | – | – |
| PANSS negative score | 18.32 ± 5.18 | – | – |
| PANSS general score | 48.29 ± 6.47 | – | – |
| PANSS total score | 92.39 ± 10.92 | – | – |

[a] $P$-value was obtained by two-sample $t$-test.
[b] $P$-value was obtained by $\chi^2$ two-tailed test.

### 2.2. Data acquisition

All fMRI data were collected using a Siemens 3T Trio scanner (Siemens Medical Systems, Erlangen, Germany) with an eight-channel phased array head coil in the Second Affiliated Hospital of Xinxiang Medical University. Scanning was conducted following clinical assessment on the same day. Functional images were acquired using an echo-planar imaging sequence (EPI) with the following parameters: TR/TE = 2000/30 ms, 33 slices, 64 × 64 matrix, 90° flip angle, field of view = 220 × 220 $mm^2$, interslice gap = 0.6 mm, and voxel size = 3.44×3.44 × 4 $mm^3$. For each participant, 240 volumes were obtained.

### 2.3. Data preprocessing

Functional data preprocessing was carried out using the Data Processing Assistant for resting-state fMRI (DPARSF_A) package (http://www.restfmri.net). The first ten volumes of functional images were discarded because of the instability of the initial MRI signal and adaptation of participants to the circumstance. Images were then corrected for slice-timing and realigned to the first image. Subjects were excluded from further analysis if translational and rotational displacement exceeded 1.5 mm or 1.5°. One subject was excluded based on the criterion. Controls and patients showed no significant difference in frame-wise displacement (FD) ($p = 0.99$). Processed images were normalized to the standard EPI template (resampled into 3 × 3 × 3 $mm^3$) and smoothed using an 8 × 8 × 8 $mm^3$ full width at half maximum (FWHM) Gaussian kernel. After normalization, the BOLD signal of each voxel was detrended to abandon the linear trend and filtered within the range of 0.01–0.08 Hz to reduce low-frequency drift and high-frequency physiological noise. Finally, nuisance covariates, including Friston 24 motion parameters (Satterthwaite et al., 2012), the "bad" time point with a frame-wise displacement (FD) threshold of 0.5 (Power et al., 2012), global mean signals, white matter signals and cerebrospinal fluid signals were regressed out. We did not discard the scans which with large head movements because EMD was designed for continuous data. Corruption of continuity of data would lead to biased result (Flandrin et al., 2004).

### 2.4. EMD

EMD is based on the assumption that the signal consists of different simple intrinsic modes of oscillations. In the decomposition result, the complicated signal, which shows numerous different coexisting modes of oscillations, will be decomposed into simple intrinsic mode functions (IMFs) (Flandrin et al., 2004).

Signals extracted from each voxel in the Anatomical Automatic Labeling (AAL) (Tao et al., 2013) gray template were decomposed into numerous IMFs (Fig. 1). The power spectrum of each averaged IMF was calculated using Welch's method. An IMF would be selected if the peak of power spectrum were between 0.01 and 0.08 Hz (signals may present noises despite being band-pass filtered). The main power of the third IMF was around 0.017 Hz, while that of the forth was considerably lower than 0.01 Hz. Thus, we obtained three IMFs. The peak power values of the first, second, and third IMFs were approximately 0.06 Hz, 0.035 Hz, and 0.017 Hz (Table 2), respectively Each IMF was treated as a frequency band. Subsequent calculations were then conducted within each band.

### 2.5. Functional connectivity analysis

In each frequency band, the averaged signals of 90 brain regions of the AAL (excluding brain areas in the cerebellum) template were calculated. We then computed the Pearson's correlation between each pair of signals. Thus, a $90 \times 90$ connectivity matrix for each subject was obtained. Finally, the correlation coefficients were translated into Fisher z-scores that were used for further analysis. Thus, for each subject $(90 \times 90 - 90) \div 2 = 4005$ connections were obtained.

At two-sample *t*-test was carried out on each connection to test the hypothesis sating that no difference exists between the schizophrenia group and controls. The false discovery rate (FDR) was used for control multiple comparison correction with a $p < 0.05$ to find significantly altered connections in each frequency band.

**Table 2**
Frequency in which the main power of the first three IMFs belongs.

| IMFs | Peak of power spectrum (Hz) |
|---|---|
| 1 | 0.060 |
| 2 | 0.035 |
| 3 | 0.017 |

### 2.6. Relationship between altered connections

To evaluate the relationship between the altered connections paired correlation was altered connections were calculated in both groups. As we had 12 significantly altered connections, therefore a $12 \times 12$ correlation matrix would be obtained. Next, the false discovery rate (FDR) was used for control multiple comparison correction with a $p < 0.05$ to find significant correlations in $(12 \times 12 - 12) \div 2 = 66$ connections.

### 2.7. Association with symptom severity

To investigate the relation between these altered connections and symptom severity, we explored the relationship between altered connections between patient's total positive score, total negative score using Linear Support Vector Regression (SVR) in LIBSVM with these connections (Chang and Lin, 2011). The proportion of variance ($R^2$) was estimated using a leave-one-out cross validation (LOOCV). Then, the statistical significance was assessed using nonparametric analysis (Supekar et al., 2013).

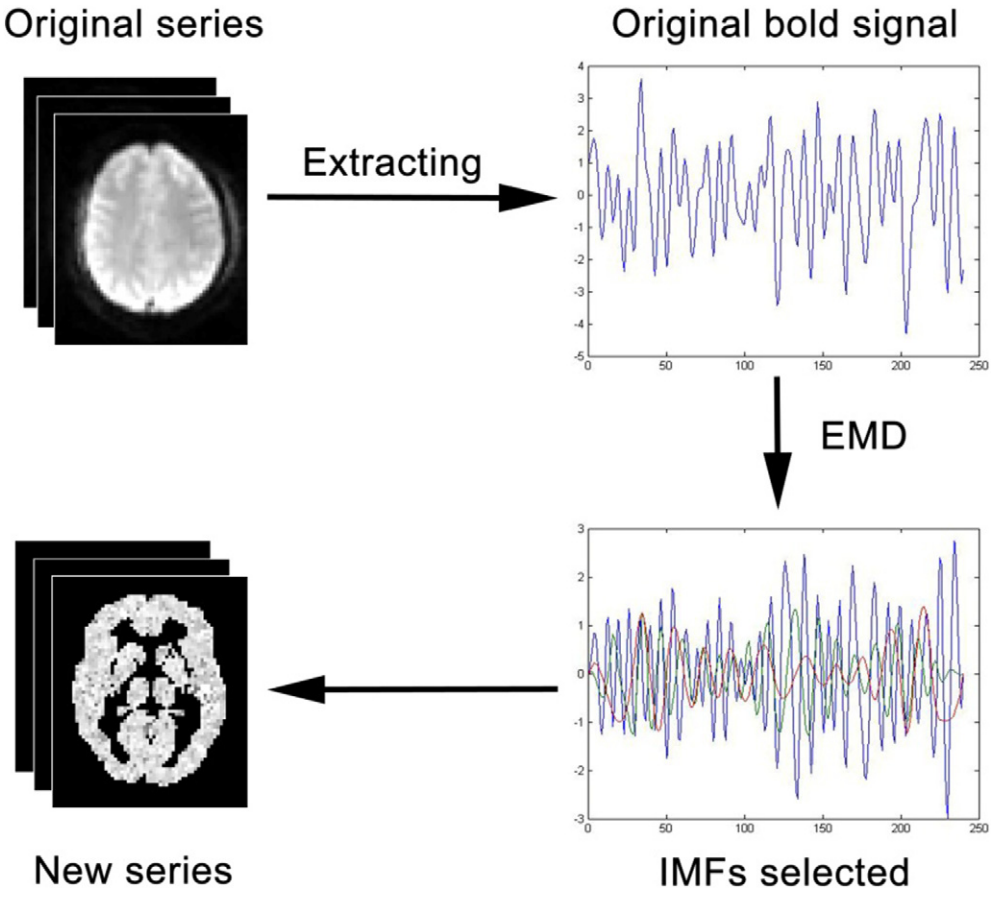


**Fig. 1.** IMFs selected. 1.) Original signals were extracted from images that underwent previous preprocessing; 2.) original signals of each voxel were decomposed into IMFs using EMD; 3.) IMFs were treated as different frequency bands. An IMF would be selected if the peak of power spectrum was between 0.01 and 0.08 Hz.

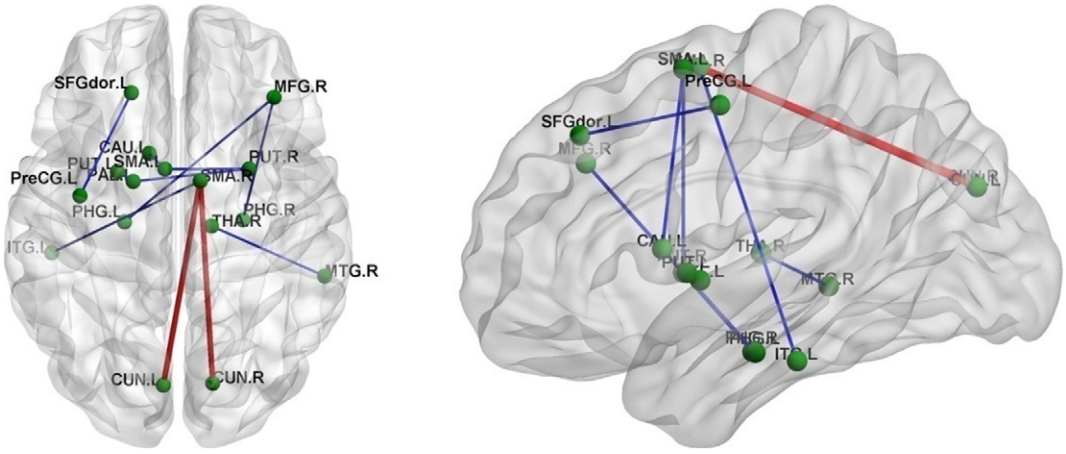


**Fig. 2.** Altered connectivity of patients in the first frequency band. Blue lines mean edges decreased in patients, and red lines mean edges increased in patients compared with controls.

## 3. Results

### 3.1. Altered connections in schizophrenia are frequency specific

Significantly altered connections only survived for the highest frequency band. Within the first frequency band, Connections within the basal ganglia, and between the basal ganglia and SMA, were reduced in patients with schizophrenia. Connections between the right SMA and bilateral cuneus were increased in schizophrenia (Fig. 2; Table 3).

### 3.2. Relationship between altered connections

The altered connections in patients with schizophrenia, but not controls, were significantly correlated (Table 4). For example, a connection linking the left dorsal superior frontal gyrus and the left precentral gyrus was significantly correlated with a connection linking the left pallidum and left putamen; However, this relationship was not observed in controls.

### 3.3. Altered connections in schizophrenia predicts symptom severity

To investigate the extent to which significantly altered connections are associated with the severity of symptoms in schizophrenia, we examined the relationship between altered connections and the PANSS scores of patients with schizophrenia using SVR and nonparametric hypothesis testing. We found that these altered connections predicted the total positive score ($R^2 = 0.55$, $p < 0.05$, Bonferroni 0.05 corrected), total negative score ($R^2 = 0.70$, $P < 0.05$, Bonferroni 0.05 corrected).

## 4. Discussion

In present study, significantly altered functional connectivity in schizophrenia occurred only in the first frequency band (with a peak spectrum power of 0.06 Hz) using EMD in first-episode drug-naive patients with schizophrenia. In this frequency band, corticostriatal-thalamo-cortical circuits were altered in patients with schizophrenia. In addition, striatal dysfunction had a close relationship with prefrontal dysfunction. Moreover, these altered functional connections in the first frequency band (0.06 Hz) were significantly correlated with symptom severity. These findings suggest that frequency-selective altered corticostriatal-thalamo-cortical circuits underlie the physiopathological mechanism of schizophrenia.

The altered resting-state functional connectivity of corticostriatal-thalamo-cortical circuits in schizophrenia were frequency-selective. In our study, corticostriatal-thalamo-cortical circuits were found only in a comparatively higher frequency band. Consistent with previous studies (Lynall et al., 2010; Zuo et al., 2010b), schizophrenia-related altered functional connectivity was 0.06 Hz. EEG studies show that the physiopathological mechanism of schizophrenia is associated with specific frequency band, the gamma-frequency (Lewis et al., 2005; Moran and Hong, 2011; Sohal et al., 2009; Yizhar et al., 2011). In addition, fMRI studies report frequency related phenomena (Garrity et al., 2007; Lynall et al., 2010; Yu et al., 2014). Moreover, schizophrenia psychopathology has been associated with the frequency-selective aberrant intrinsic organization of functional brain networks (Rotarska-Jagiela et al., 2010). These results suggest that a specific frequency band is related to the physiopathological mechanism of schizophrenia. Corticostriatal-thalamo-cortical circuits were altered only in a comparatively higher frequency band, suggesting that this frequency band is cortical to

**Table 3**
shows altered edges in patients. The symbol "↓" indicates that the mean strength of connectivity in patients is smaller than that in controls, and "↑" indicates that the mean strength of connectivity in patients is larger than that in controls. P-corrected means *p*-value after corrected by FDR 0.05.

| Region | Region | Abnormal | P ($10^{-5}$) | T | P-corrected |
|---|---|---|---|---|---|
| Superior frontal gyrus_L(dorsal) | Precentral gyrus_L | ↓ | 3.62 | −4.40 | 0.02 |
| Parahippocampal gyrus_L | Middle frontal gyrus_R | ↓ | 3.11 | −4.44 | 0.01 |
| Parahippocampal gyrus_R | Middle frontal gyrus_R | ↓ | 6.54 | −4.24 | 0.02 |
| Caudate_L | Supplementary motor area_L | ↓ | 5.21 | −4.92 | 0.01 |
| Putamen_L | Supplementary motor area_L | ↓ | 5.31 | −4.30 | 0.02 |
| Putamen_R | Supplementary motor area_L | ↓ | 4.05 | −4.37 | 0.02 |
| Cuneus_L | Supplementary motor area_R | ↑ | 5.37 | 4.30 | 0.02 |
| Cuneus_R | Supplementary motor area_R | ↑ | 2.29 | 4.53 | 0.02 |
| Pallidum_L | Putamen_L | ↓ | 1.21 | −4.70 | 0.01 |
| Pallidum_L | Putamen_R | ↓ | 0.031 | −5.63 | 0.001 |
| Middle temporal gyrus_R | Thalamus_R | ↓ | 4.47 | −4.96 | 0.007 |
| Inferior temporal gyrus_L | Supplementary motor area_R | ↓ | 4.98 | −4.32 | 0.02 |

**Table 4**
Altered connections presented correlations. "*" means these correlations existed in patients only. r means the correlation coefficient. All *P* values were significant after corrected by FDR 0.05.

| Connection | Connection | r |
|---|---|---|
| R-SMA and L-Cuneus | R-SMA and R-Cuneus | 0.79 |
| L-Pallidum and L-Putamen | L-Pallidum and R-Putamen | 0.81 |
| R-MFG and L-PHG | R-MFG and R-PHG | 0.44* |
| L-SMA and L-Caudate | L-SMA and R-Putamen | 0.52* |
| L-Precentral gyrus and L-DSFG | L-Pallidum and L-Putamen | 0.57* |
| L-Precentral gyrus and L-DSFG | L-Pallidum and R-Putamen | 0.48* |

DSFG means dorsal superior frontal gyrus, MFG means middle frontal gyrus, PHG means parahippocampal gyrus.

schizophrenia. However, another possibility is that this frequency band (0.06 Hz) is the most reliably frequency band (Glerean et al., 2012) that is immune to "low-frequency drift" and the influence of respiratory and cardiac fluctuations, therefore this frequency band was significantly altered. More research is need to determine whether this altered frequency band is more important than others. Nonetheless, our present results demonstrate that altered functional connections in schizophrenia are frequency-selective.

The altered corticostriatal-thalamo-cortical circuits were associated with symptom severity in patients with schizophrenia. In the DA hypothesis, abnormal mesostriatal DA release generates an over-attribution of meaning and motivational value to irrelevant environmental events. This persistent aberrant salience eventually results in schizophrenia symptoms (Howes and Nour, 2016; Kapur, 2003). Many studies have found evidence in fMRI task, like Anne Pankow et al. found that higher aberration salience attribution in patients with schizophrenia is related to reduced prefrontal cortex activation during self-referential judgments (Pankow et al., 2015). Similarly, middle frontal gyrus-related functional connectivity was decreased, consistent in our results. Corticostriatal abnormalities have an important role in the pathophysiology of schizophrenia. In addition, increased functional connectivity of the striatum with prefrontal and limbic regions is thought to be a biomarker for the improvement in symptoms associated with antipsychotic treatment (Sarpal et al., 2015). We show that the dysfunction of the prefrontal cortex correlated with the dysfunction of other regions such as the putamen and parahippocampal gyrus; this correlation was only observed in patients with schizophrenia. Our results suggested that corticostriatal regions cooperatively act in the emergence of the psychopathological symptoms of schizophrenia.

## 5. Limitations

The original BOLD signal was band-pass (0.01–0.08 Hz) filtered, removing any respiratory- and cardiac-related oxygenation fluctuations (Lowe et al., 1998), and reducing low-frequency drift and high-frequency physiological noises (Tao et al., 2013). Cardiac and respiratory sources are considered to contribute to oscillations in the frequency interval (0.06–0.125 Hz) (Lynall et al., 2010). However, studies have found that neuronal fluctuations at high and low frequencies are closely associated, with lower-frequency fluctuations corresponding to the power modulations of higher-frequency bands (Bruns et al., 2000; Buzsaki and Draguhn, 2004). Future studies should investigate this association in patients with schizophrenia.

## 6. Conclusion

In the present study, we used the EMD method to identify frequency-selective altered corticostriatal-thalamo-cortical circuits in first-episode drug-naive patients with schizophrenia. The patients with schizophrenia showed significantly altered functional connectivity only at a higher frequency band (~0.06 Hz). For this frequency, the dysfunction of frontal regions correlated with the dysfunction of striatal and limbic regions. This dysfunctional functional connectivity was associated with the severity of schizophrenia symptoms. These corticostriatal regions with frequency-selective dysfunction cooperate in the emergence of the psychopathological symptoms in schizophrenia.

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