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Frequency-specific alteration of functional connectivity density in antipsychotic-naive adolescents with early-onset schizophrenia

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ABSTRACT

Early-onset schizophrenia (EOS) is a severe mental illness associated with dysconnectivity that widespread in the brain. However, the functional dysconnectivity in EOS are still mixed. Recently, studies have identified that functional connectivity (FC) arises from a band-limited slow rhythmic mechanism and suggested that the dysconnectivity at specific frequency bands may provide more robust biomarkers for schizophrenia. The frequency-specific changes of FC pattern in EOS remain unclear. To address this issue, resting-state functional magnetic resonance imaging data scans from 39 EOS patients (drug-naive) and 31 healthy controls (HCs) were used to assess the FC density (FCD) across slow-4 (0.027–0.073 Hz) and slow-5 (0.01–0.027 Hz). Results revealed that a remarkable difference between the FCD of the two bands existed mainly in the default mode network (DMN) and subcortical areas. Compared with the HCs, EOS patients showed significantly altered FCD involved in audiovisual information processing, sensorimotor system, and social cognition. Importantly, a significant frequency-by-group interaction was observed in the left precuneus with significantly lower FCD in the slow-4 frequency band, but no significant effect in the slow-5 frequency band. In addition, decreased FC was found between the precuneus and other DMN regions in the slow-4 band. Furthermore, the change in FCD in precuneus was inversely proportional to the clinical symptom in slow-4 band, indicating the key role of precuneus in schizophrenia progress. Our findings demonstrated that the dysconnectivity pattern in EOS could be frequency-dependent.

1. Introductions

Schizophrenia is a devastating disease characterized in part by altered connectivity in brain function (Epstein et al., 2014; Kyriakopoulos et al., 2012). A large but variable body of studies found functional connectivity (FC) deficits in adult-onset schizophrenia (Garrity, et al., 2007; Lynall et al., 2010). Adolescents with early-onset schizophrenia (EOS) provides a unique opportunity to explore the FC alterations as they are less affected by chronic antipsychotic medication and interaction with age-related neurodegenetation (Cannon et al., 2002; Douaud et al., 2007; Epstein et al., 2014). By using functional magnetic resonance imaging (fMRI) technique, many studies have focused in exploring the connectome abnormalities in EOS.

Some fMRI studies used the seed-based method to explore the abnormal connectome in EOS, as it is useful in studying functional connection patterns in selected brain regions or networks. For example, abnormal inter-region functional connectivity has been

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identified in EOS in the default mode network (DMN)(Garrity et al., 2007; Tang et al., 2013; Wang et al., 2015), cingulate-based networks (Kelly et al., 2009), and frontotemporal network (Yang, et al., 2014). However, accumulating evidence suggests that the dysconnectivity in EOS is distributed throughout the brain (Rapoport and Gogtay, 2008; Yang et al., 2014; Zhou et al., 2010). Therefore, using a global method to explore the connectome abnormalities in EOS may provide more details about the mechanism of this mental disorder. FC density (FCD) is a combination of voxel-wise functional connectivity and graph theory analyses (Zhuo et al., 2014) and is well suited for the systematic study of functional connectivity abnormalities in the brain (Chen et al., 2015; Dardo Tomasi, 2014; Dardo and Volkow, Nora D., 2010).

Recent fMRI studies have found specific relationships between FC and frequency in healthy controls (HCs) and schizophrenic patients. By analyzing the response to stimulated tasks in different frequency bands, Sun et al. found that the different regions of the visual cortex in healthy subjects have frequency selectivity (Sun et al., 2007). Thereafter, increasing evidence suggested that frequency-dependent effects exist in different brain regions, brain networks, and functional hubs (Gohel and Biswal, 2015; Thompson and Fransson, 2015). Meanwhile, numerous frequency-dependent changes were found in many psychiatric illnesses, such as amnestic mild cognitive impairment (Han et al., 2011), epilepsy (Song et al., 2016; Wang et al., 2014b), and Parkinson's disease (Hou et al., 2014). Therefore, in exploring the functional abnormalities at a general frequency band, the frequency effects may be overlooked. Several studies have explored the frequency effects in adult-onset schizophrenia. For example, Hoptman et al. found that the amplitude abnormalities of low-frequency oscillations in schizophrenia are frequency-dependent, and gray-matter-related activity mainly occurs in slow-4 and slow-5 bands (Hoptman et al., 2010). Moreover, Yu et al. found frequency-dependent changes in the amplitude of low-frequency fluctuations and regional homogeneity in schizophrenic patients (Yu et al., 2013, 2014). However, studies about frequency-specific changes of FC in EOS are lacking.

The current study aimed to assess whether the changes in functional connectivity of the whole brain in EOS are frequency specific. The FCD method was employed to investigate the functional connection pattern in EOS patients and HCs at two frequency bands (slow-4: 0.027–0.08 Hz and slow-5: 0.01–0.027 Hz). Two-way analysis of variance (ANOVA) was used for statistical analyses. Furthermore, the relationship between the altered FCD and clinical symptoms was investigated to test whether frequency-specific dysconnectivity contributes to the clinicopathology of EOS.

2. Materials and methods

2.1. Participants

A total of 39 EOS patients were recruited from the Second Affiliated Hospital of Xinxiang Medical University. All patients were independently diagnosed by research psychiatrists and satisfied the following criteria: (1) DSM-IV-TR criteria for schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision, American Psychiatric Association, 2000), (2) no co-morbid Axis I diagnosis, (3) duration of illness less than two years, and (4) antipsychotic naive. Patients were interviewed again after six months for a final schizophrenia diagnosis. The symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS). A total of 31 age-, gender-, education-, and IQ-matched healthy adolescents were included in this study. All HCs did not have any past or current neurological disorders, family history of hereditary neurological disorders, and history of head injury resulting in loss of consciousness and substance abuse.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University, and informed written consents were obtained from all subjects.

2.2. Data acquisition

All subjects were instructed to rest with their eyes closed, not to think of anything in particular, and not to fall asleep during the resting-state fMRI (rs-fMRI) scan (Marx et al., 2004; Pang et al., 2015; Wei et al., 2014). fMRI data were collected using the 3T MRI scanner (Siemens-Trio, Erlangen, Germany) in the Second Affiliated Hospital of Xinxiang Medical University. Scanning and clinical assessments were performed in one day. Functional images were collected transversely using an echo-planar imaging (EPI) sequence with the following settings: TR/TE = 2000/30 ms, flip angle = 90°, FOV = 220×220 mm^2, slices = 33, matrix = 64×64, interslice gap = 0.6 mm, and voxel size = $3.44 \times 3.44 \times 4$ mm^3. The scan lasted for 480 s for each subject, and 240 vol were acquired.

2.3. Image preprocessing

Data preprocessing was conducted using Statistical Parametric Mapping Software (SPM8, http://www.fil.ion.ucl.ac.uk/spm8). The first 10 vol of each participant were discarded because of the instability of the initial MRI signal and adaptation of the participants to the circumstance, leaving 230 volumes. The remaining rs-fMRI images were corrected for slice acquisition and head motion using a least squares approach with a six-parameter spatial transformation. Four patients and one healthy control with head motion scans exceeding 2 mm or 1° rotation were excluded. Subsequently, the corrected images were normalized according to the standard SPM8 Montreal Neurological Institute (MNI) template (Power et al., 2012) and resampled to $3 \times 3 \times 3\ mm^3$ voxel size. The resulting images were linearly detrended and filtered using a typical temporal bandpass, including slow-5 bandpass (0.01–0.027 Hz) and slow-4 bandpass (0.027–0.073 Hz) separately (Gohel and Biswal, 2014; Yu et al., 2014). Friston 24 motion parameters, cerebrospinal fluid, and white matter signals were included in the multiple regression model to reduce the effects of head motion and non-neuronal blood oxygenation level-dependent (BOLD) fluctuations (Friston et al., 1994; Tomasi and Volkow, 2012). Given that resting-state FCD is sensitive to minor head movements, we calculated the mean frame-wise displacement (FD) to further determine the comparability of head movement across groups. The largest mean FD of each subject was less than 0.3 mm and two-sample *t*-test showed that there was no significant difference in the mean FD between the two groups (HC: 0.09 ± 0.05; EOS: 0.10 ± 0.03; mean ± SD, $p = 0.33$). Subsequently, the "bad" time points as well as their 1-back and 2-forward time points were removed from the time series by employing a "scrubbing" method with a FD (Long et al., 2016; Power et al., 2012; Zeng et al., 2014) threshold of 0.5 mm. Participants retaining more than 80% of the original signals after scrubbing were included in the analyses. The number of time points remaining was nonsignificantly different between HC (227.8 ± 6.98) and EOS patients (225.1 ± 6.72) ($p = 0.09$).

2.4. Functional connectivity density analyses

The preprocessed image data underwent FCD mapping to compute the strength of global FCD (gFCD) defined by Tomasi and Volkow (Tomasi, Dardo and Volkow, Nora D, 2010). For a given voxel *i*, the gFCD was defined as the global functional connections n_i between *i* and all the other voxels in the brain. Two voxels were considered functionally connected if the correlation coefficient was

Table 1
Demographic and clinical characteristics in the study.

Demographics, Mean (SD)	EOS N = 35	Control N = 30	P value
Age (year)	15.5 (1.8)	15.3 (1.6)	0.57[a]
Gender (male/female)	20/15	13/17	0.27[b]
Education (years)	8.5 (1.48)	8.7 (1.42)	0.605[a]
Duration of psychosis (months)	16.0 (14.4)	–	–
Handedness (right/left)	35/0	30/0	–
PANSS Positive Sysptoms	20.42 (5.72)	–	–
PANSS Negative Sysptoms	20.91 (8.41)	–	–
PANSS General Sysptoms	33.28 (6.69)	–	–
PANSS Total Sysptoms	74.62 (10.61)	–	–

P^a-value was obtained by two-sample *t*-test.
P^b-value was obtained by χ^2 two-tailed test.

greater than a predefined threshold *T*, which was set using family-wise error (FWE) correction with $q < 0.05$ (Wei et al., 2014). The correlation coefficient threshold was used to reduce the chance of false-positive connections across all subjects. The calculation process was continued until all voxels in the brain were calculated.

Subsequently, the gFCD maps were spatially smoothed using a 6 mm Gaussian kernel in SPM8 to minimize the differences in the functional anatomy of the brain across subjects.

2.5. Statistical analyses

ANOVA was conducted in SPM8 with diagnosis (two levels: EOS and HC) as a group factor, frequency band (two levels: slow-4 and slow-5) as a within-subject factor, and age and sex as covariates of no interest. Age and gender were considered as covariates because the FCD distribution was reported to be affected by age and gender (Eranti et al., 2013). Gaussian random field correction theory was employed to correct multiple comparisons ($q < 0.05$, *voxel* $p < 0.001$, $F > 11.4$) for each main and interaction effect. Post-hoc two-sample *t* tests were employed on clusters that showed significant effect of group and band.

Brain areas that showed significant interaction effects were considered regions of interest (ROIs) for the following post-hoc analyses. ROIs were defined as a 6 mm spheres with the center at the peak position of statistical differences. Subsequently, seed-based method was used to explore the altered FC in specific frequency bands. Finally, a correlation analysis was performed between the mean FCD in the ROIs and the PANSS scores of the EOS patients.

3. Results

3.1. Demographic characteristics and clinical symptoms

No significant differences were found in gender, age, and years of education between the patients and HCs. For the patient group, the mean duration of illness was 16.0 months (SD = 14.4) (Table 1).

3.2. Main effect of frequency band factor

Brain regions showed a significant main effect of bands in the right lingual gyrus ($F_{(1,124)} = 34.94$), left posterior cingulate gyrus ($F_{(1,124)} = 75.18$), medial prefrontal cortex, orbital part ($F_{(1,124)} = 55.64$), right angular gyrus ($F_{(1,124)} = 87.10$), left inferior temporal gyrus ($F_{(1,124)} = 272.89$), right fusiform gyrus ($F_{(1,124)} = 214.83$), and right precentral gyrus ($F_{(1,124)} = 54.52$) (Fig. 1). Post-hoc analyses revealed that the FCD in slow-4 band was higher than that in slow-5 band mainly in the right lingual gyrus, left posterior cingulate gyrus, medial prefrontal cortex, orbital part, and right angular gyrus. Moreover, a significantly higher FCD was found in slow-5 band in the left inferior temporal, right fusiform, and right precentral gyrus than in the slow-4 band (Table 2).

3.3. Main effect of group factor

The significant main effect of the group was observed in the right inferior temporal gyrus ($F_{(1,124)} = 37.46$), left precuneus ($F_{(1,124)} = 33.02$), left superior temporal gyrus ($F_{(1,124)} = 22.98$), left inferior orbitofrontal cortex ($F_{(1,124)} = 21.90$), left cerebellum crus 1 ($F_{(1,124)} = 17.81$), left postcentral gyrus ($F_{(1,124)} = 18.06$), and right postcentral gyrus ($F_{(1,124)} = 16.46$) (Fig. 2). Post-hoc analyses revealed that EOS patients showed significantly lower FCD in the left precuneus, left superior temporal gyrus, and bilateral postcentral gyrus but higher FCD in the right inferior temporal gyrus, left inferior orbitofrontal cortex, and left cerebellum crus 1 compared with the HCs (Table 3).

3.4. Interaction effects between the frequency band and group

Remarkable frequency-by-group interaction effect was found in the left precuneus ($F_{(1,124)} = 16.95$) (Fig. 3 A). Post-hoc analyses revealed that FCD in the left precuneus were significantly lower in the slow-4 frequency band in EOS patients, but no significant effects were detected in slow-5 band (Fig. 3 B). Furthermore, EOS patients showed a lower FC between the precuneus and other brain

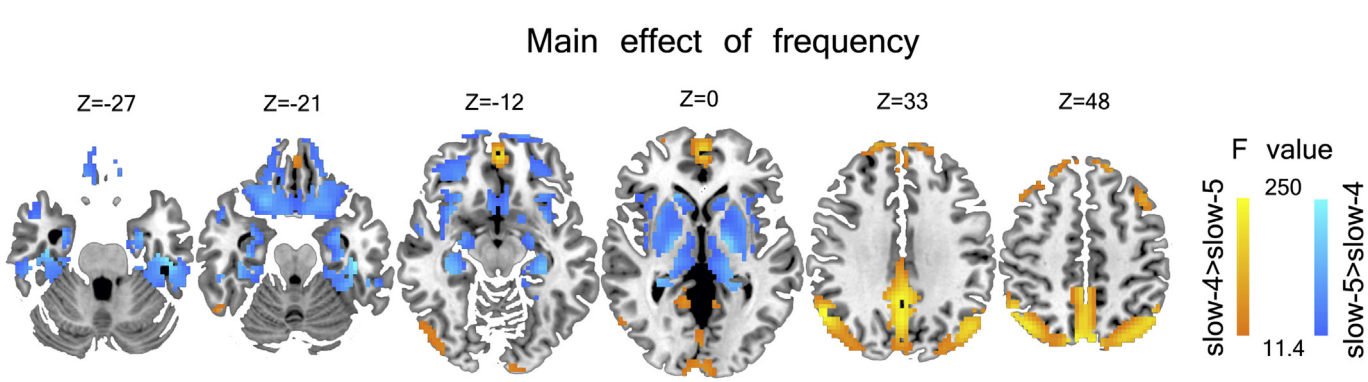

Fig. 1. Main effect of the frequency band factor. Warm color represents higher FCD and cool color represents lower FCD in the slow-4 band than slow-5 band. The results were obtained by two-way ANOVA. Statistical significance level is corrected for multiple comparisons using Gaussian random theory with ($q < 0.05$, *voxel* $p < 0.001$, $F > 11.4$). FCD, functional connectivity density; ANOVA, analysis of variance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Main effect of frequency band revealed by a two-way ANOVA.

Brain areas		L/R	Cluster size	F-value	Peak coordinate		
			voxels		X	Y	Z
slow-4>slow-5	Lingual gyrus	R	37	34.94	33	−84	−18
	Posterior cingulate gyrus	L	129	75.18	−3	−45	36
	Medial prefrontal cortex	L	62	55.64	−3	54	−9
	Angular gyrus	R	35	87.10	54	−60	33
slow-5>slow-4	Inferior temporal gyrus	R	385	272.89	−42	−24	−21
	Fusiform gyrus	R	384	214.83	39	−9	−33
	Precentral gyrus	R	116	54.52	21	−15	63

Statistical significance level is corrected for multiple comparisons using Gaussian random theory with ($q < 0.05$, *voxel* $p < 0.001$, $F > 11.4$). The peak coordinate is defined in MNI space. ANOVA, analysis of variance; L, left; R, right.

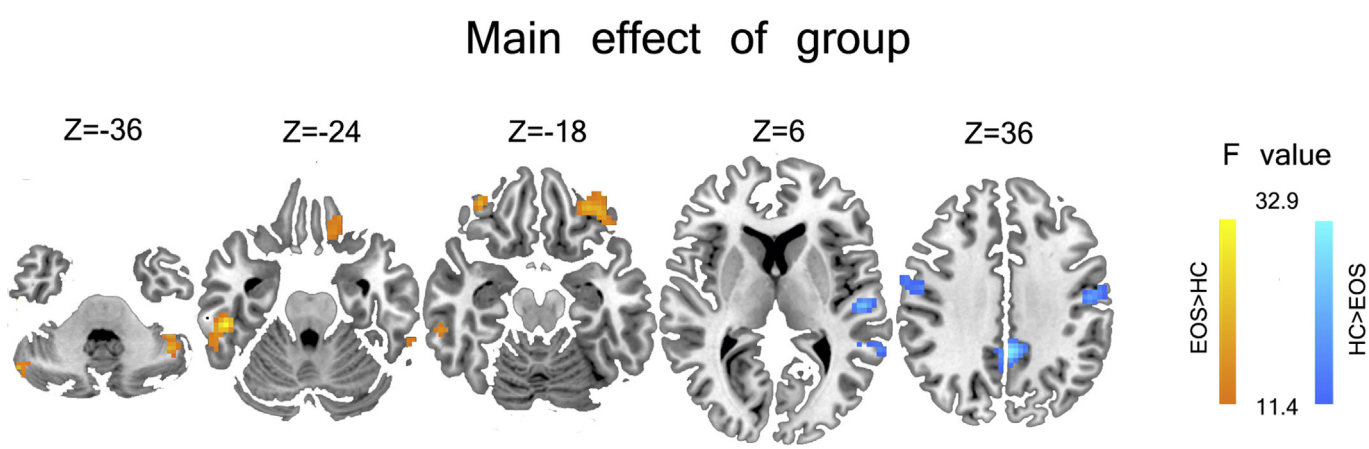

Fig. 2. Main effect of group factor. Warm color represents higher FCD and cool color represents lower FCD in the EOS group than HC group. The results were obtained by a two-way ANOVA. Statistical significance level is corrected for multiple comparisons using Gaussian random theory with ($q < 0.05$, *voxel* $p < 0.001$, $F > 11.4$). FCD, functional connectivity density; EOS, early-onset schizophrenia; HC, healthy control; ANOVA, analysis of variance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Main effect of the group revealed by two-way ANOVA.

Brain areas		L/R	Cluster size	F-value	Peak coordinate		
			voxels		X	Y	Z
EOS > HC	Inferior temporal gyrus	R	65	37.46	51	−30	−24
	Cerebellum crus1	L	31	17.81	−45	−51	−36
	Inferior frontal gyrus, orb part	L	35	21.90	−30	42	−18
HC > EOS	Superior temporal gyrus	L	33	22.98	−54	−18	6
	Postcentral gyrus	L	81	18.06	−51	−12	36
	Postcentral gyrus	R	25	16.46	51	−6	33
	Precuneus	L	116	33.02	−3	−45	39

Statistical significance level is corrected for multiple comparisons using Gaussian random theory with ($q < 0.05$, *voxel* $p < 0.001$, $F > 11.4$). The peak coordinate is defined in MNI space. EOS, early-onset schizophrenia; HC, healthy controls; ANOVA, analysis of variance; L, left; R, right.

areas, including the inferior temporal gyrus, middle temporal gyrus, median cingulate gyrus, superior frontal gyrus, and right precuneus, in the slow-4 band than the HCs ($p < 0.005$, uncorrected) (Fig. 3 C, Table 4).

3.5. Correlation with clinical symptoms

Shepherd's pi correlation was calculated between the FCD in the left precuneus and PANSS scores after removing potential outliers, which were identified by bootstrapping the Mahalanobis distance, D_S, of each observation from the bivariate mean and excluding all points whose average D_S is 6 or greater (Ding et al., 2014; Rousselet and Pernet, 2012; Schwarzkopf et al., 2012). In Fig. 4, the precuneus with reduced global FCD is significantly negatively correlated with the negative, general and total scores of PANSS ($p < 0.05$) in the slow-4 band in EOS patients. No significant correlation was found in the slow-5 band.

4. Discussion

In this study, we used the FCD method to investigate the changes in the FC pattern in EOS patients at two frequency bands (slow-4 and slow-5). Several brain regions exhibited significant differences in the FCD between the two bands and the two groups. Moreover, a significant frequency-by-group interaction effect was observed in the left precuneus. In addition, decreased FC between the left precuneus and other regions in the slow-4 band was found. Furthermore, in the slow-4 band, the FCD in the precuneus

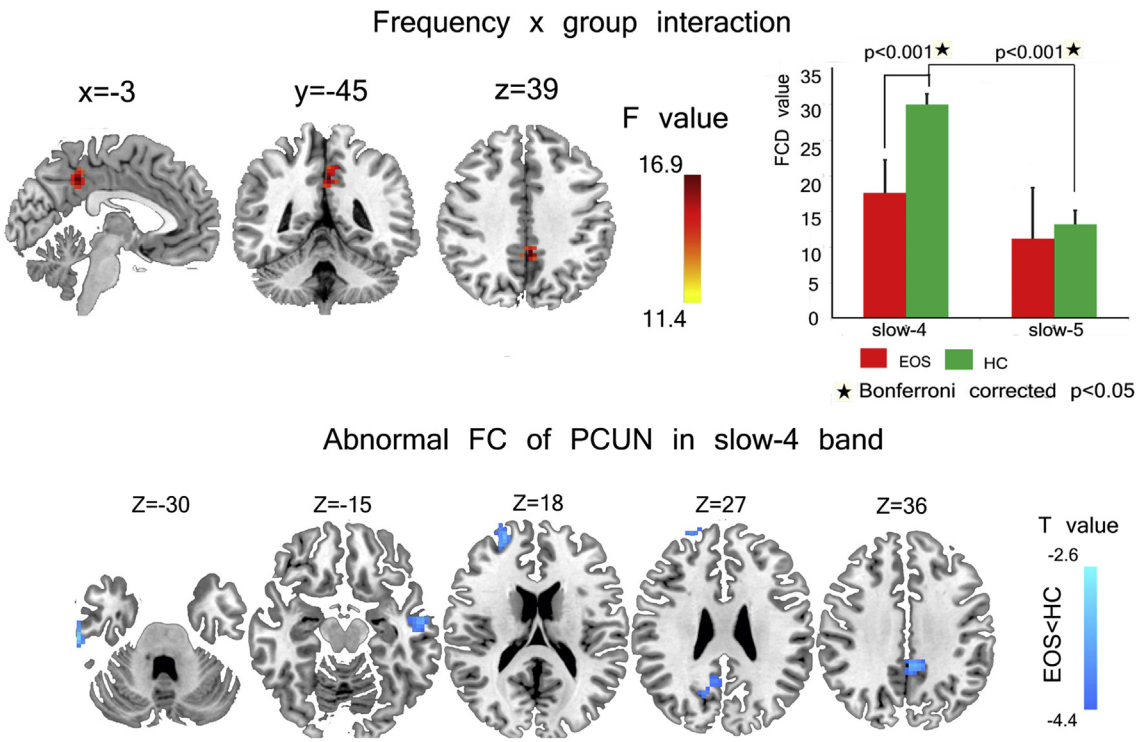

Fig. 3. The interaction between the frequency band and group on FCD (Fig. 3. A). The results were obtained by two-way ANOVA and post-hoc test. We found decreased FCD in the left precuneus in patients with EOS in the slow-4 band. No significant differences in FCD were observed between the groups in the slow-5 band (Fig. 3. B). Bonferroni corrected $p < 0.05$. By defining the left precuneus as seed region, Fig. 3. C represents the abnormal FC pattern of left precuneus in slow-4 band. The cool color represents lower FC in the patients with EOS in the slow-4 band. FCD, functional connectivity density; EOS, early-onset schizophrenia; HC, healthy control; ANOVA, analysis of variance; FC functional connectivity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Altered FC of the left precuneus in slow-4 band revealed by two-sample *t*-test ($p < 0.005$ *uncorrected*). FC, functional connectivity.

Brain areas		L/R	Cluster size	T-value	Peak coordinate		
			voxels		X	Y	Z
EOS < HC	Inferior temporal gyrus	R	20	−3.69	63	−17	−30
	Middle temporal gyrus	L	46	−3.45	−57	−9	−15
	Median Cingulate gyrus	L	62	−3.44	−9	−42	36
	Precuneus	R	25	−3.08	6	−54	27
	Superior frontal gyrus	R	36	−3.32	24	57	18

significantly correlated with the clinical symptoms. These results demonstrated that abnormal FC in the EOS patients was distributed throughout the brain and the changes are frequency dependent.

4.1. Difference in FCD between frequency bands

The slow-4 band showed higher FCD than the slow-5 band mainly in the DMN, including the medial prefrontal cortex, orbital part, and angular gyrus. The current results are consistent with those of the previous study, that is, the FC of DMN network arises from the low rhythmic mechanism in the slow-4 band (Gohel and Biswal, 2015; Han et al., 2011; Li et al., 2015). Furthermore, we found higher FCD in the temporal lobe, fusiform gyrus, and precentral gyrus in the slow-5 band, which implied that the FC in the slow-5 band was localized mainly within the primary sensory and motor cortices (Wu et al., 2016). As shown by the findings, FC is suggested to have different physiological functions at specific frequency bands.

4.2. Differences in FCD between groups

The difference between the two groups showed that EOS patients exhibited decreased FCD in the superior temporal gyrus (STG) and precuneus and increased FCD in the inferior temporal gyrus (IFG) relative to HC. Previous studies reported that STG is important in integrating audiovisual information and is widely connected to other regions of the brain (Straube et al., 2014). The precuneus is considered the center of a wide spectrum of highly integrated tasks (Cavanna, 2007; Utevsky et al., 2014). In addition, ITG is involved in visual processing (Dien et al., 2013; Su et al., 2015; Verhoef et al., 2015). These results were in line with those of previous studies, that is, schizophrenia is associated with the abnormality in the audiovisual integration system (Pearl et al., 2009; Stevenson et al., 2014; Szycik et al., 2009; Tseng et al., 2015).

Moreover, increased FCD in the cerebellum and bilateral postcentral gyrus was found in the EOS patients. Neuroimaging studies suggested that the cerebellum, which is involved in processing, especially in the sensorimotor control, is related to schizophrenia (Andreasen and Pierson, 2008; Barch, 2014; Picard et al., 2008;

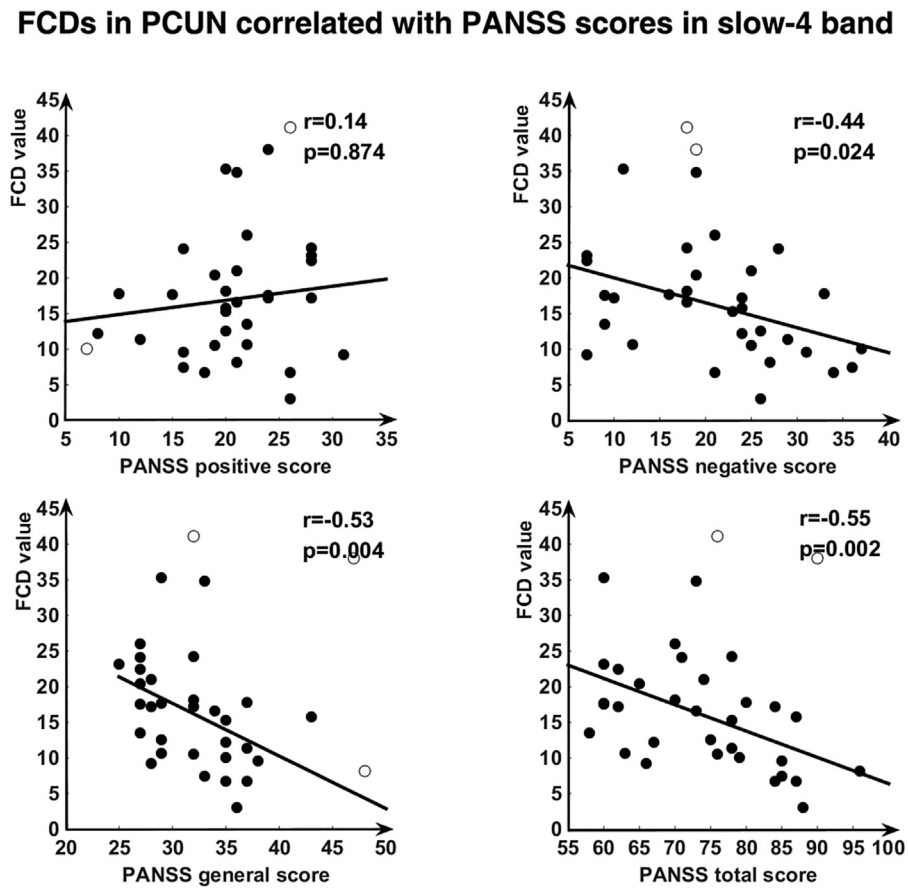

Fig. 4. Correlation between regions showing significant interaction and clinical scale of symptoms in patients with EOS ($p < 0.05$). Shepherd's pi correlations were calculated over the data after removing outliers. FCD, functional connectivity density; PCUN, precuneus.

Wang et al., 2014a). The postcentral gyrus, a pivotal region of the somatosensory system, plays a core role in primary motor processing (Prevosto et al., 2011; Tomasi and Volkow, 2012). The current findings reveal that EOS patients may have abnormal connections in somatosensory processing.

In addition, we found elevated FCD in the left orbitofrontal cortex. Similar spatial pattern of "hyperconnectivity" in the orbitofrontal areas in EOS were identified in other studies, suggesting the core role of the orbitofrontal cortex in social cognition (Bellani et al., 2010; Mingoia et al., 2012). Therefore, "hyperconnectivity" of the orbitofrontal cortex provides a possible explanation for the social cognition abnormalities in EOS.

4.3. Frequency-dependent changes in FCD in EOS

The FCD in the EOS patients was significantly lower in the left precuneus in the slow-4 band, but did not change significantly in the slow-5 band. Although the physiological mechanisms of slow-4 and slow-5 frequencies remain unclear, a recent study has suggested that the FC of some brain hubs have band-limited mechanisms (Li et al., 2015). Moreover, many neuroimaging studies found that the abnormalities in schizophrenia are frequency sensitive, and the results are more robust in the slow4-band (Hoptman et al., 2010; Yu et al., 2013). However, the abnormalities in the slow-4 band were still mixed in schizophrenic patients. For example, Yu and colleagues found that the activity of the precuneus in schizophrenia is greater in the slow-4 than in the slow-5 band (Yu et al., 2014). The difference in the method of measuring the activity may contribute to inconsistency of the findings between studies. In addition, decreased FC was found between the precuneus and other brain areas of DMN in the slow-4 band, including the right temporal gyrus, left middle temporal gyrus, left median cingulate gyrus, superior frontal gyrus, and right precuneus. These findings validated that the functional connection pattern of the precuneus is band-limited (Li et al., 2015). Accordingly, this study argues that the slow-4 band might have greater sensitivity in detecting the dysconnectivity in EOS patients than the slow-5 band. Therefore, frequency influence should be an additional concern in future studies of FC in EOS at resting-state.

4.4. Correlation analyses

In the slow-4 band, the changes of FCD correlated negatively with the negative, general, and total scores of PANSS in the left precuneus, and no correlation was found in the slow-5 band. The current findings suggested that the connectivity of the left precuneus decreased progressively in relation to the severity of the clinical symptoms in the slow-4 band. Our findings suggest that functional abnormalities in the precunues in the slow-4 band may be associated with abnormal mental activation in schizophrenia.

5. Limitation

The limitations of the current study should be considered. The size of our sample was relatively small. However, it is comparable with other recent studies that examined drug-naive EOS patients. A larger sample size is necessary to confirm the results of the current study.

6. Conclusion

In this study, we investigated the changes in FC within the brains of EOS patients at specific frequency bands. Many brain areas showed significant differences in specific frequency bands. Furthermore, in EOS patients brain areas with abnormal FC were widespread and mainly associated with audiovisual information processing, sensorimotor system, and social cognition. Moreover, the FC in the precuneus was significantly band-limited, and the changes in the slow-4 band were associated with the clinical symptoms, implying that the symptoms were related to abnormally functioning connections at specific frequency bands. Our observations may provide potential implications for exploring schizophrenia.

Contributors

Yan Zhang and Mi Yang designed the study and conceptualized the protocol for healthy subjects. Jingping Zhao and Huafu Chen adapted this protocol for schizophrenia patients and evaluated them. Junjie Zheng, Zhiliang Long and Shaoqiang Han managed the literature searches and analyses. Xiao Wang, Youxue Zhang, Yifeng Wang and Xunjun Duan undertook the statistical analyses, and Xiao Wang wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2017.07.014.

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