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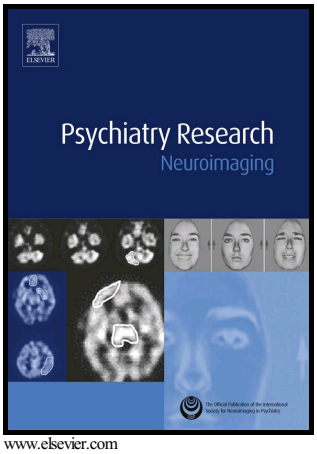

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Disrupted amplitude of low-frequency fluctuations in antipsychotic-naïve adolescents with early-onset schizophrenia

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Abstract

Evidence points to a crucial role for altered neural oscillations and synchrony in the pathophysiology of schizophrenia. Previous resting state functional magnetic resonance imaging (fMRI) studies found aberrant amplitudes of low-frequency oscillations in adult patients with schizophrenia. Whether the abnormality is also

present in adolescents with early-onset schizophrenia (EOS) is largely unknown. We recruited 39 adolescents with a first episode of EOS and 31 age- and education-matched healthy controls. Resting state fMRI was obtained using an echo-planar imaging sequence. Voxel-wise amplitude of low-frequency (0.01–0.08 Hz) fluctuations (ALFF) was compared between groups. We investigated seed-based functional connectivity between significantly disturbed ALFF regions and whole brain voxels in all participants. EOS participants exhibited significantly increased ALFF values in the orbitofrontal cortex (OFC) and decreased ALFF in the ventral precuneus compared with controls. Decreased ALFF values in the precuneus of EOS showed a significant negative correlation with negative symptom scores on the Positive and Negative Syndrome Scale. Disturbed functional connectivity mainly occurred between the orbitofrontal cortex and the temporal cortex in EOS. These findings demonstrate abnormal spontaneous neuronal activity and functional connectivity in the frontal and parietal cortex of EOS. Aberrant ALFF in the precuneus might be a biomarker of EOS.

Keywords: Early-onset schizophrenia, resting-state fMRI, Amplitude of low-frequency fluctuations, Positive and Negative Syndrome Scale, Functional connectivity

1. Introduction

Schizophrenia is a neurodevelopmental disorder in which psychotic symptoms, in most cases, emerge in late adolescence or early adulthood between the ages of 18 and 25 years (Feinberg, 1982-83; Lewis and Levitt, 2002a). Previous research speculates that the early onset of schizophrenia during adolescence or even before adolescence is associated with severe impairments and that schizophrenia might be a consequence of an exaggeration of typical synaptic pruning during adolescence (Feinberg, 1982-83; Paus et al., 2008). In recent years, a dysfunction in the synchronization of neural oscillations has been identified as a potential mechanism to explain cognitive dysfunctions and certain symptoms of schizophrenia (Uhlhaas and Singer, 2010). Aberrant neural oscillations during early critical periods may lead to imprecise temporal coordination of neural activity and result in pathological modifications of cortical circuits (Hebb, 2005; Uhlhaas and Singer, 2010). Thus, it is important to know if neural synchrony is involved in the aberrant development of cortical networks in schizophrenia and if the disrupted spontaneous neuronal activity is correlated with clinical symptoms in adolescent patients with early-onset schizophrenia (EOS).

Brain oscillatory modulations have been investigated with blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signals (Zuo et al., 2010). Functional MRI studies have revealed that spontaneous low-frequency (<0.1 Hz) oscillations (LFOs) reflect coherent networks in the somatosensory, visual,

and language-processing regions of the brain (Biswal et al., 1995; Hampson et al., 2002; van de Ven et al., 2004) and that gray matter exhibits a higher amplitude of LFOs than white matter (Biswal et al., 1995). In particular, the amplitude of LFOs measured as the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (Yang et al., 2007; Yu-Feng et al., 2007; Zou et al., 2008) has been applied as a measure of mental illness-related regional spontaneous neuronal disturbances in such conditions as attention-deficit hyperactivity disorder (Yu-Feng et al., 2007), mesial temporal lobe epilepsy (Zhang et al., 2010), major depressive disorder (Liu et al., 2013), amnestic mild cognitive impairment (Han et al., 2011), and schizophrenia (Hoptman et al., 2010). Hoptman et al. reported decreased ALFF values in the lingual gyrus, cuneus, and precuneus of adult patients with schizophrenia and increased values in the left parahippocampal gyrus in the same patients (Hoptman et al., 2010). Huang et al. found that ALFF values are significantly decreased in the medial prefrontal lobe (MPFC) and increased in the left and right putamen in treatment-naïve, first-episode schizophrenia patients; they opined that regional ALFF is altered in early stages of the disorder (Huang et al., 2010). Studying drug-naïve patients with first-episode psychosis is a useful approach to understanding the pathogenesis of psychosis because young patients are comparatively free of the confounding effects of environmental factors such as substance abuse, disease chronicity, education years, and treatment effects. Under the assumption that schizophrenia is a neurodevelopment disorder, researchers have hypothesized that local regional disturbed ALFF in the cerebral cortex might occur as a neurodevelopmental anomaly in adolescent patients

with schizophrenia (Feinberg, 1982-83; Lewis and Levitt, 2002b). Whether the regional brain functional abnormality in adolescent patients with early-onset schizophrenia is similar to that of adult patients remains unknown. Investigation of the alterations in ALFF in EOS may enrich our understanding of the pathophysiological development and the mechanisms underlying schizophrenia.

MRI studies have revealed brain functional abnormalities in patients with EOS. Previous fMRI studies have found aberrant brain networks and modularity, especially in the default mode network (DMN), in young schizophrenia patients (Alexander-Bloch et al., 2010; Tang et al., 2013). These findings suggest that both local regional abnormalities and aberrations in inter-regional connectivity might be present in EOS. Recent findings on the association between ALFF and functional connectivity in a resting state brain network have been presented (Di et al., 2013). A disrupted correlation between local functional abnormalities and aberrations in inter-regional connectivity in schizophrenia has been reported (Zalesky et al., 2012; Yu et al., 2013). Thus, we attempt to identify both ALFF abnormalities in local brain regions and seed-based functional connectivity across brain networks in EOS.

In this study, an exploratory voxel-wise analysis of ALFF (0.01-0.08 Hz) fluctuations was conducted in antipsychotic-naive patients with first-episode schizophrenia and in age-matched healthy controls. All of the participants were 12 to 18 years old. ALFF was measured with resting state fMRI to investigate possible early disruption of LFOs

and to explore any associations with clinical symptoms in patients with EOS. Additionally, a seed-based voxel-wise functional connectivity analysis was conducted between the disturbed ALFF regions and whole brain voxels to investigate inter-regional connectivity abnormalities in EOS.

2. Methods

2.1. Subjects

In this study, all participants were right-handed, of Han Chinese ethnicity, aged 13 to 18 years old. All of them had more than 6 years of formal education. Thirty-nine adolescent patients with first-episode schizophrenia were recruited from the consecutive admissions at the Second Affiliated Hospital of Xinxiang Medical University. They met the following additional inclusion 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 2 years; (4) antipsychotic-naive. Schizophrenia was independently diagnosed by two well-trained psychiatrists based on the Structured Clinical Interview for DSM-IV-TR, patient version (SCID-I/P). Patients were interviewed again 6 months later to confirm a final diagnosis of schizophrenia. Psychopathology was assessed in patients with the Positive and Negative Syndrome Scale (PANSS). A total of 31 age-, gender-, education- and IQ-matched healthy adolescents were recruited from the local community through advertisements. The healthy adolescents were screened with

structured interviews based on the Chinese version of the SCID to rule out individuals who had any history of psychiatric or medical conditions. All participants were excluded if they had (1) any past or current neurological disorders or family history of hereditary neurological disorders; (2) a history of head injury resulting in loss of consciousness; (3) alcohol or substance abuse; (4) claustrophobia; (5) incompatible implants (exclusion criterion for MRI). The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University. Clinical and demographic data are presented in Table 1.

2.2. Data acquisition

Imaging was performed on a 3.0 T Siemens Vision Scanner (Erlangen, Germany) equipped with high-speed gradients on the day that subjects were recruited. The following parameters were used for T1 anatomical imaging axially: repetition time/echo time (TR/TE) = 2530/2.43 ms, 256×256 matrix, 7° flip angle, voxel size =1×1×1 mm^3, 158 slices without inter-slice gap. At the same locations to anatomical slices, functional images were acquired by using an echo-planar imaging sequence with the following parameters: TR/TE=2000/30 ms, 33 slices, 64×64 matrix, 90° flip angle, field of view = 220×220 mm^2, inter-slice gap = 0.6 mm, voxel size = 3.44×3.44×4mm^3 . For each participant, the fMRI scan lasted for 6 min, and 240 volumes were obtained.

2.3.1. Data preprocessing

Functional image preprocessing was carried out using the DPARSF (http://www.restfmri.net) (Chao-Gan and Yu-Feng, 2010) and SPM8 (http://www..fil.ion.ucl.ac.uk/spm) toolkits. The first 10 functional volumes were discarded as signal equilibrium and subjects' adaptation to scanning noise. We corrected the remaining images for temporal differences and head motion. We also calculated individuals' mean frame-wise displacement (FD) by the translation and rotation parameters of head motion according to a previously described formula (Liu et al., 2008; Power et al., 2012) and evaluated group differences. We then warped the functional images into a standard stereotaxic space at a 3×3×3 mm^3 resolution, using the Montreal Neurological Institute (MNI) echo-planar imaging template, and then we spatially smoothed images with a 6-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. Finally, we removed linear trends from time courses and for temporal band-pass filtering (0.01–0.08 Hz).

2.3.2. ALFF analysis

We used ALFF to characterize amplitude measures at each voxel (Yu-Feng et al., 2007). The time series for each voxel was transformed to the frequency domain using a Fast Fourier Transform, and the power spectrum was then obtained. Since the power of a given frequency was proportional to the square of the amplitude of this frequency component, the square root was calculated at each frequency of the power spectrum and the averaged square root was obtained across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF value. The ALFF value of each voxel

was standardized by dividing the full-brain mean ALFF values. Then the whole brain voxel-wise ALFF was calculated in each participant in both the EOS and healthy control groups. Two-sample *t*-tests were used to compare the differences in ALFF between groups and the AlphaSim-corrected significance level of $p < 0.05$ was obtained for clusters with a minimum of 134 voxels and an individual voxel height threshold of $p < 0.01$(Meyer-Lindenberg, 2011). Corrections were confined within a whole brain mask and determined by Monte Carlo simulations. This process was performed by a plug-in implemented in REST software (http://www.restfmri.net) (Zang et al., 2012). We also investigated the relationship of abnormal LFOs in brain regions of patients with EOS and their clinical symptoms. We extracted the mean ALFF values in the disturbed regions of individuals with EOS and calculated the linear Pearson correlation coefficient between regional ALFF values and the PANSS scores of patients.

2.3.3. Functional connectivity analysis

Seed-based functional connectivity was then performed in our study. Regions showing significantly altered ALFFs were defined as seed regions of interest (ROIs) for subsequent functional connectivity analysis. The averaged time course was obtained from the ROI and correlational analysis was performed in a voxel-wise way to generate a functional connectivity map. In addition, six motion parameters, the cerebrospinal fluid, and the white matter signals were removed as nuisance variables to reduce the effects of head motion and non-neuronal BOLD fluctuations. Then,

two-sample *t*-tests were performed to assess between-group difference and the cluster correction. An AlphaSim-corrected significance level of $p < 0.05$ was obtained for clusters with an individual voxel height threshold of $p < 0.01$ and a cluster threshold of $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics of the participants

Four patients and one healthy control were eliminated from the study because of head movement. A total of 35 patients and 30 healthy controls completed the study. The patients with EOS and the controls did not significantly differ in age (t = 0.40, p = 0.68), gender ($\varkappa^2$ = 0.74, p = 0.39), or years of education (t = 0.51, p = 0.61) (Table 1). The individual FDs were not significantly different (t = 0.33, p = 0.73) between the EOS (mean±SD: 0.097±0.027) and healthy control (mean±SD: 0.094±0.047) groups.

3.2. ALFF group differences

Compared with the healthy controls, the adolescents with EOS showed a significantly increased ALFF in the bilateral orbitofrontal cortex ($p < 0.05$, AlphaSim-corrected) and a significantly decreased ALFF in the ventral precuneus ($p < 0.05$, AlphaSim-corrected) (Table 2 and Fig. 1).

3.3. Correlations between ALFF and clinical characteristics

The linear Pearson correlation between disturbed regional ALFF values and PANSS scores in patients with EOS was calculated. ALFF in the precuneus had a significant negative correlation with PANSS negative symptom scores (r = -0.44, p = 0.0067) (Fig. 1) and tended to correlate with PANSS general psychopathology scores (r =

-0.39, $p = 0.022$) and PANSS total scores ($r = -0.38$, $p = 0.023$) in patients with EOS (Fig. 1). No significant correlation was found between disturbed ALFF in the orbitofrontal cortex (OFC) and clinical symptoms, as indicated by PANSS scores, in patients with EOS.

3.4. Seed-based functional connectivity abnormality in EOS

Ventral precuneus seed-based functional connectivity was reduced relative to control values in the dorsal precuneus and the mid-cingulate cortex (MCC) in EOS patients ($p < 0.05$, AlphaSim-corrected) (Table 3). Left OFC functional connectivity was reduced in the bilateral superior temporal gyrus, bilateral postcentral gyrus, left middle temporal gyrus, and right temporal pole ($p < 0.05$, AlphaSim-corrected) (Table 3). Right OFC functional connectivity was also reduced in the bilateral superior temporal gyrus, bilateral temporal pole, and bilateral insula in EOS patients ($p < 0.05$, AlphaSim-corrected) (Table 3 and Fig. 2).

4. Discussion

We investigated ALFF with data obtained from BOLD-fMRI and noted a functional brain abnormality in adolescents with EOS. Aberrant ALFF was initially observed in treatment-naive adolescent patients with first-episode schizophrenia. Additionally, we found that decreased ALFF is significantly correlated to the clinical symptoms of EOS patients and could serve as a potential biomarker of EOS.

Recent evidence from electrophysiological, physiological, and anatomical studies suggests that abnormalities in the synchronized oscillatory activity of neurons may have a critical role in the neurodevelopment of schizophrenia (Uhlhaas and Singer, 2010). Resting state fMRI studies indicate that the ALFF of BOLD signals may represent a potentially meaningful and stable property of the brain (Zuo et al., 2010). ALFF was measured to identify abnormalities in baseline brain activity in a number of different mental disorders in recent years (Yu-Feng et al., 2007; Hoptman et al., 2010; Zhang et al., 2010; Di Martino et al., 2014). Previous findings on ALFF abnormalities in patients with schizophrenia suggested spontaneous brain functional deficits in frontal and occipital regions (Hoptman et al., 2010; Huang et al., 2010). The inconsistent locations of disturbed ALFF in previous studies on schizophrenia could be due to differences in the studied populations, such as differences in symptom severity and illness duration. In the current study, we attempted to identify ALFF

abnormalities in treatment-naïve adolescent patients with EOS. Our findings illustrate that low-frequency oscillation abnormalities might be present in the prefrontal and pariatal cortex in EOS patients. The study of patients with untreated first-episode schizophrenia is especially useful in understanding disorder-related clinical and neurophysiological brain functional changes (Lui et al., 2009). Several studies have reported abnormalities in the amplitude and phase of gamma-band oscillations, which might suggest that dysfunctions in neural oscillations and synchronization are present at the early phase of illness (Symond et al., 2005; Spencer et al., 2008; Uhlhaas and Singer, 2010). Our findings reveal that low-frequency (<0.1 Hz) oscillation abnormalities occur in adolescent patients with early-stage schizophrenia. Moreover, abnormal neural oscillations and synchrony, related to late maturation and the restructuring of brain functional networks, are important to the emergence of psychosis (Uhlhaas et al., 2009). The findings of ALFF abnormalities in EOS in our study might be linked to the neurodevelopmental pathogenesis of schizophrenia.

In the present study, a significant decrease in ALFF was observed in the ventral precuneus (PCu) of patients with EOS. This finding is in line with that of Hoptman et al. (Hoptman et al., 2010) and a recent multi-site resting state fMRI study on ALFF in schizophrenia (Turner et al., 2013). Moreover, this finding on decreased ALFF in the PCu of treatment-naïve patients with schizophrenia reinforces previous findings by eliminating the effect of medication on findings; the reduced ALFF in the PCu might be a feature of the continuous course of schizophrenia. The PCu, which is a part of the

structural core of the human cortex (Hagmann et al., 2008) and forms part of the so-called “rich club” organization in the brain network (i.e., "a tendency for high-degree nodes to be more densely connected among themselves than nodes of a lower degree"; van den Heuvel and Sporns, 2011), also plays a central role in the default mode network (Utevsky et al., 2014). Precuneus-involved rich club connectivity was found to decrease in both psychotic patients and their siblings, suggesting that the structural connections of the PCu are more likely affected by genetic factors of schizophrenia (Collin et al., 2014). The functional aspect of the PCu was found to be involved in visuo-spatial imagery, episodic memory retrieval, and self-processing operations (Cavanna and Trimble, 2006a; Cavanna and Trimble, 2006b). An fMRI study has also found decreased neural activities in the posterior cingulate cortex and the PCu in schizophrenia patients during self- and other-refection processing operations (van der Meer et al., 2013). Thus, our finding suggests that aberrancies in intrinsic brain function might be a potential disease-related mechanism of schizophrenia and may affect facets of patients’ cognitive functions.

Decreased ALFF values in the PCu of EOS patients had a significant negative correlation with scores on the Positive and Negative Syndrome Scale (PANSS). In this study, we performed 12 linear Pearson correlation tests between ALFF values of three ROIs and four lists of PANSS scores in the EOS patients. The significant correlations between PANSS on clinical symptoms did not survive the Bonferroni correction for multiple comparisons ($p < 0.05$). A potential factor was the small sample size, a

drawback of our study. Although not significant after Bonferroni correction, the correlation between decreased ALFF values and PANSS scores is suggestive and should be tested further in larger numbers of patients. The strongest correlation was with negative symptoms. The negative schizophrenic syndrome includes affective flattening, alogia, avolition, anhedonia, and attentional impairment (Kay et al., 1987). Abnormal decision making and emotional processing were recently found to be associated with negative symptoms of schizophrenia (Gold et al., 2013; Oorschot et al., 2013), and a cerebral blood flow abnormality in the cingulate cortex was reported to be associated with PANSS negative scores in first-episode schizophrenia (Ashton et al., 2000). The functional connectivity between the posterior cingulate and the frontal and temporal gyri was correlated with PANSS negative scores in schizophrenia; this finding suggests that abnormal default mode network activity is involved in the psychotic symptoms of patients with schizophrenia (Bluhm et al., 2007). Our finding that ALFF abnormalities in the PCu of EOS patients are correlated with PANSS negative symptoms provides evidence that the functional abnormality of the default mode network is associated with the pathophysiology of schizophrenia. This functional deficit in the PCu might be a potential biomarker of patients with schizophrenia during adolescence.

We also observed functional hyperactivity in the bilateral OFC in EOS patients compared with healthy controls. The OFC is involved in sensory integration, representation of the affective value of the reinforcer, and decision making and

expectation (Kringelbach, 2005). Regional cerebral blood flow in the OFC was reduced in patients with schizophrenia, especially in deficit syndrome groups. This result suggests that the OFC plays an important role in the development of severe negative symptoms in patients with schizophrenia (Kanahara et al., 2013). Previous fMRI research found decreased ALFF values in the orbital/medial frontal lobe in adult patients with first-episode schizophrenia (Huang et al., 2010). In the current study, increased ALFF in the frontal lobe of EOS patients was located in the lateral OFC. This finding does not contradict those of previous research. Actually, the medial and lateral orbitofrontal cortices perform different brain functions in sensory integration. The former is related to the monitoring, learning, and memory of the reward value of reinforcers; the latter is related to behavioral influences (Kringelbach and Rolls, 2004). Adolescents are more prone to exhibit risk-taking behaviors than adults (Steinberg, 2004). Researchers speculate that adolescent patients with schizophrenia might present higher rates of substance use compared with the general population because of decision-making impairment (Kester et al., 2006). Thus, the abnormal ALFF in OFC might potentially be a characteristic brain functional deficit in adolescent patients with schizophrenia. Whether the increased ALFF in the lateral OFC of EOS patients is related to hypersensitivity to reward in adolescent patients with schizophrenia should be investigated in future studies.

In the current study, reduced functional connectivity of the OFC was observed in the temporal lobe and insula of EOS patients. Recent research has demonstrated that

impaired insight is related to brain activation during self-reflection in the insula, inferior frontal gyrus (IFG), and temporo-parietal junction, angular gyrus, inferior parietal lobule (IPL) regions in schizophrenia (van der Meer et al., 2013). Previous research on the brain network has also revealed that frontal and temporal cortex structural connectivity is altered in schizophrenia (van den Heuvel et al., 2010). Frontotemporal functional connectivity involving auditory and cognitive tasks is likewise disrupted in schizophrenia (Lawrie et al., 2002; Ragland et al., 2004). The structural connection of the frontotemporal connection is possibly weakened because of the focal reductions in myelin in schizophrenia (Mandl et al., 2010). The abnormalities in the OFC functional connections in the superior temporal gyrus, temporal pole, and middle temporal gyrus in EOS patients observed in the current study suggest that the frontotemporal connection is disrupted in the early stage of schizophrenia.

The present study has several limitations. The first one is the low statistical power of identifying brain functional disturbed regions in a case-control study. Owing to the scarcity of EOS patients and small sample sizes of adolescent participants, we could not achieve the most powerful results. We applied cluster correction on the voxel-wise statistical results to obtain clustered brain functional abnormal regions in EOS, and the post hoc correlation analysis of clinical symptoms with ALFF was performed as an exploratory test of potential positive results. The second limitation is that we did not record physiological signals, such as cardiac pulsation. Indeed, the effect of

regression is strong on ALFF for individuals, but previous research has shown that it has no notable effect on comparisons between patients with schizophrenia and controls (Turner et al., 2013). Third, a longitudinal study is necessary to establish whether altered neural activities in patients relate to a common neurobiological process in schizophrenia or whether they are independent of the disease. Moreover, the genetic risk of disrupted neural oscillations and synchrony in the PCu should be identified to learn more about the neurodevelopment of adolescent psychotic patients and the etiology of schizophrenia.

In summary, this study investigated aberrant ALFF (0.01–0.08 Hz) fluctuations in first-episode adolescents with EOS. We found increased ALFF in the OFC and decreased ALFF in the PCu in patients with EOS; the decreased ALFF in the PCu was found to be correlated to the clinical negative symptoms of patients.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Junjie Zheng, Yan Zhang, Huafu Chen and Jingping Zhao designed the study. Yan Zhang acquired the data, which Junjie Zheng, Yan Zhang and Xiaofeng Guo analyzed. Junjie Zheng and Yan Zhang wrote the article, which all authors reviewed and approved for submission.

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Table 1. Demographic and clinical characteristics for EOS and HC groups

	EOS (n = 35)	HC (n = 30)	Statistic	P
	Mean±SD	Mean±SD		
Age, years	15.50±1.76	15.43±1.54	t = 0.40	0.68[a]
Gender, male:female	20:15	13:17	χ^2 = 0.74	0.39[b]
Education, years	8.7±1.24	8.5±1.48	t = 0.52	0.61[a]
Duration of illness, months	6.6±6.7			
Handness, right/left	35/0	30/0		
PANSS positive score	20.42±5.72			
PANSS negative score	20.91±8.41			
PANSS general score	33.28±6.69			
PANSS total score	74.62±10.61			

EOS: early-onset schizophrenia; HC: healthy controls; PANSS: Positive and Negative Syndrome Scale

[a]The *P* values were obtained by two-sample *t*-test.

[b]The *P* value for gender distribution in the three groups was obtained by chi-squared test.

Table 2. Regions showing abnormal amplitude of low-frequency fluctuation in EOS

Regions	BA	MNI coordinate			Voxels	*t*-values
		x	*y*	*z*		
EOS>HC						
Orbitofrontal cortex L	11	-42	45	-3	173	3.86
Orbitofrontal cortex R	11	36	42	-18	189	4.36
EOS<HC						
Precuneus	31	-3	-45	39	476	-4.73

Note: EOS>HC: Increased in schizophrenia; EOS<HC: decreased In schizophrenia; L: left, R: right; EOS: early-onset schizophrenia; HC: healthy controls; BA: Brodmann area; MNI: Montreal Neurological Institute.

Table 3. Seed-based functional connectivity abnormalities in EOS.

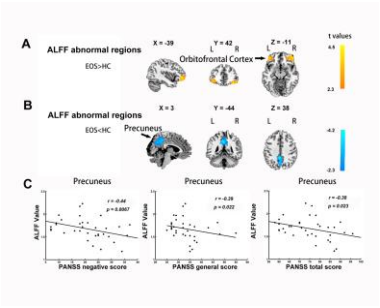
Seed ROI	Connected regions	BA	MNI coordinate			Voxels	*t*-values
			x	*y*	*z*		
	EOS<HC						
Precuneus	Precuneus	7	-6	-45	42	201	-3.95
	Middle cingulate cortex L	23	-6	-42	36	65	-3.78
Orbitofrontal cortex L	Superior temporal gyrus R	48	66	-3	6	316	-3.73
	Temporal pole R	38	51	9	-18	72	-3.29
	Postcentral gyrus R	41	66	0	30	73	-3.48
	Middle temporal gyrus L	21	-54	-45	9	304	-3.83
	Superior temporal gyrus L	22	-54	-45	15	155	-3.22
Orbitofrontal cortex R	Temporal pole R	38	51	9	-15	135	-3.68
	Insula R	48	45	0	-6	126	-3.59
	Superior temporal gyrus R	30	48	-3	-6	154	-3.58
	Superior temporal gyrus L	47	-45	3	-6	169	-3.52
	Insula L	48	-42	6	-3	204	-3.65
	Temporal pole L	38	-57	9	-6	50	-3.49

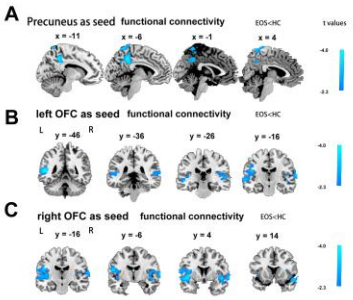
Note: EOS<HC: Decreased in schizophrenia; L: left, R: right; EOS: early-onset schizophrenia; HC: healthy controls; BA: Brodmann area; MNI: Montreal Neurological Institute.

Figures

Fig. 1. Brain regions showing ALFF differences between patients with EOS and controls; A: increased ALFF values regions in EOS; B: decreased ALFF values regions in EOS, C: ALFF values of precuneus negatively correlated with patients PANSS scores; color bars indicate the *t* value from group comparison, blue = higher in controls, yellow: higher in EOS.

Fig. 2. Seed-based functional connectivity abnormality in EOS; A: Precuneus as seed decreased functional connectivity regions in EOS; B: left OFC as seed decreased functional connectivity regions in EOS; C: right OFC as seed decreased functional connectivity regions in EOS; Color bars indicate the *t* value from group comparison, blue: lower in EOS. OFC: Orbitofrontal cortex.





Highlights

- We obtained resting-state fMRI images of adolescent patients with early onset schizophrenia (EOS) and healthy controls to compare the amplitude of low-frequency fluctuations (ALFF) between groups.
- We found increased ALFF in orbitofrontal cortex and decreased ALFF in precuneus of EOS.
- We also found decreased ALFF value of precuneus in EOS was significantly negative correlated with Positive and Negative Symptom Scale (PANSS) scores of patients.
- The reduced functional connectivity in disturbed ALFF regions was also found in patients with EOS.