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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.

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.,

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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 12–18 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 13–18 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 × 4 mm^3. For each participant, the fMRI scan lasted for 6 min, and 240 volumes were obtained.

2.2.1. 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).

2.2.2. 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