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Abnormally increased and incoherent resting-state activity is shared between patients with schizophrenia and their unaffected siblings

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ABSTRACT

Background: Several resting-state neuroimaging studies in schizophrenia indicate an excessive brain activity while others report an incoherent brain activity at rest. No direct evidence for the simultaneous presence of both excessive and incoherent brain activity has been established to date. Moreover, it is unclear whether unaffected siblings of schizophrenia patients who share half of the affected patient's genotype also exhibit the excessive and incoherent brain activity that may render them vulnerable to the development of schizophrenia.
Methods: 27 pairs of schizophrenia patients and their unaffected siblings, as well as 27 healthy controls, were scanned using gradient-echo echo-planar imaging at rest. By using amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (Reho), we investigated the intensity and synchronization of local spontaneous neuronal activity in three groups.
Results: We observed that increased amplitude and reduced synchronization (coherence) of spontaneous neuronal activity were shared by patients and their unaffected siblings. The key brain regions with this abnormal neural pattern in both patients and siblings included the middle temporal, orbito-frontal, inferior occipital and fronto-insular gyrus.
Conclusions: This abnormal neural pattern of excessive and incoherent neuronal activity shared by schizophrenia patients and their healthy siblings may improve our understanding of neuropathology and genetic predisposition in schizophrenia.

1. Introduction

Psychotic symptoms, including false attribution of perceptual experience to external sources (hallucinations), grossly distorted thinking (delusions), and disorganized speech and behavior, are recognized as a defining feature of schizophrenia (DSM-5) (Association, 2013). It has been widely accepted that schizophrenic psychosis is closely related to disrupted self-generated mental activity at rest (Siegal and Varley, 2002). For instance, paranoid ideas regarding conspiracy may reflect an exaggerated sense of self-relevance. Thus, mental activity occurring during rest, in the absence of cognitive tasks, has been thought to be relevant to the clinical phenomenology of schizophrenia (Malaspina et al., 2004).

In the past, positron emission tomography (PET) and electroencephalography (EEG) have been the most commonly used techniques to investigate the spontaneous neuronal activity (Logothetis et al., 2001) at rest in schizophrenia. These studies have consistently demonstrated metabolic over-activity (Ebmeier et al., 1993; Kaplan et al., 1993; Parellada et al., 1994) and increased resting-state electric activity (Boutros et al., 2008; Knott et al., 2001; Lee et al., 2006) in schizophrenia. Importantly, this resting hyperactivity is associated with psychotic symptoms (Lee et al., 2006) such as reality distortion (Kaplan et al., 1993; Liddle et al., 1992). Recently, the amplitude of low-frequency fluctuations (ALFF) in the blood oxygen level-dependent (BOLD) signal measured by the fMRI has emerged as a consistent marker of spontaneous neuronal activity (Biswal et al., 1995; Logothetis et al., 2001; Raichle, 2006; Yu-Feng et al., 2007). Robust evidence has indicated the

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involvement of ALFF in various cognitive functions, including reading skills (Xu et al., 2015), conceptual processing (Wei et al., 2012), working memory (Zou et al., 2012), cognitive control and response inhibition (Mennes et al., 2010) and personality traits (Wei et al., 2012). Consistent with the findings using PET and EEG, resting-state fMRI studies applying ALFF have documented abnormally increased activity in various brain regions in schizophrenia (Hoptman et al., 2010; Huang et al., 2010; Yu et al., 2014). The combined evidence from PET, EEG and fMRI studies suggests that exaggerated brain activity at rest may be a potential neural substrate for schizophrenia.

Furthermore, numerous resting-state fMRI (Lawrie et al., 2002; Liu et al., 2006; Pettersson-Yeo et al., 2011; Yu et al., 2013) and EEG (Ford et al., 2002, 2008; Gross et al., 2007) studies have revealed schizophrenia as a functional "disconnectivity" disorder, concurring with Blueler's hypothesis of this disorder as mentally "splitting" (Bleuler, 1950). These abnormal functional connections have been documented to be associated with symptoms including hallucinations, delusions, distorted thinking and speech (Lawrie et al., 2002; MacDonald et al., 2005; Yoon et al., 2008). However, most previous studies have examined the synchrony of low-frequency fluctuations (LFFs) between remote brain regions (i.e., functional connectivity, FC). From this approach, no conclusion can be drawn on which region has the primary dysfunction. Recently, regional homogeneity (Reho) reflecting synchrony of LFFs (Zang et al., 2004) within circumscribed brain regions has been applied to evaluate regional brain function. Evidence of reduced Reho in recent resting-state fMRI studies (Liu et al., 2006; Yu et al., 2013) has indicated that the local synchrony of spontaneous neuronal activity is a key neuropathological feature of schizophrenia. Additionally, abnormal Reho has been found to be associated with impaired ability of specific information processing and integration in schizophrenia (Yu et al., 2013).

Collectively, the evidence on intensity and synchrony of spontaneous neuronal activity suggests that schizophrenia may be characterized by increased (Boutros et al., 2008; Yu et al., 2014) but incoherent neuronal activity (Liu et al., 2006; Yu et al., 2013) at rest. However, previous studies investigated regional brain function in terms of intensity and synchrony of the LFFs separately; thus, no evidence on both increased amplitude and reduced synchrony of spontaneous neuronal activity in the same dataset of schizophrenia patients has been documented. In this study, we combined the ALFF and Reho on resting-state fMRI data to investigate the intensity and synchrony of spontaneous neuronal activity and expected to observe excessive and incoherent neuronal activity at rest in schizophrenia.

Furthermore, a growing body of evidence indicates that schizophrenia is a neurodevelopmental disorder with high heritability (Keshavan et al., 2005; Raedler et al., 1998), suggesting that neural deficits related to psychosis may be present prior to the manifestation of behavioral/clinical symptoms in the unaffected siblings of patients (Keshavan et al., 2005; Raedler et al., 1998; Weinberger, 1987). Unaffected siblings of schizophrenia share half of their genotype with their ill relatives and are at an 8-fold higher risk for developing schizophrenia than the general population (Sadock and Sadock, 2011). Clinical evidence has consistently demonstrated that unaffected siblings of patients display mild psychotic and cognitive symptoms (Bediou et al., 2007; Chen et al., 2009; Delawalla et al., 2006). Genetic predisposition for schizophrenia may also affect normal brain functions in individuals at high-risk for schizophrenia (Whitfield-Gabrieli et al., 2009b). For example, elevated brain activity and reduced resting-state FC have been found in individuals at risk for schizophrenia (Guo et al., 2014; Howes et al., 2006) and individuals with prodromal symptoms of schizophrenia (Dandash et al., 2013; Howes et al., 2009). Notably, recent studies have showed increased intensity (Tang et al., 2015) and reduced synchrony (Liao et al., 2012) of spontaneous neuronal activity using ALFF and Reho, respectively, in unaffected families of schizophrenia patients. Based on these findings, we hypothesized that excessive and incoherent spontaneous neuronal activity seen in patients would be shared by their unaffected siblings.

2. Methods

2.1. Participants

The sample in this study includes 27 patients, 27 siblings and 27 healthy participants, with most of the participants coming from the dataset in our prior work (Liu et al., 2010). All participants were right-handed (Annett, 1970). 27 patients, independently diagnosed with schizophrenia (SCZ) based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Axis I Disorders, Patient Edition (SCID-I/P) (First et al., 1998), were recruited through the Department of Psychiatry, Second Xiangya Hospital of Central South University, Changsha, China. The patients had no history of neurological disorder, severe medical disorder, substance abuse, or electroconvulsive therapy. In addition, each patient had at least one unaffected sibling. In the patient sample, 15 patients were drug naïve, while the others were receiving antipsychotic medications at the time of image acquisition (risperidone [n = 6, 2–5 mg/day], clozapine [n = 1, 200 mg/day], quetiapine [n = 3, 400–600 mg/day], and sulpiride [n = 2, 100–300 mg/day]). The 27 patients with acute illness were all at the early-stage of schizophrenia (illness duration [Mean ± SD] = 18.32 ± 15.84), including 23 patients with illness duration less than 2 years, 3 patients less than 3 years, and 1 patient less than 5 years.

27 unaffected siblings (SIB) of the schizophrenic patients were recruited such that each patient had a sibling in the present study. The inclusion and exclusion criteria were the same as those for the patients except that the siblings did not meet the DSM-IV criteria for any Axis-I psychiatric disorders. 27 healthy controls (HCs) were recruited from the Changsha city area. The inclusion and exclusion criteria were the same as those for the siblings except that the controls had no first-degree relatives with a history of psychiatric disorders. All SIB and HCs were well matched with the SCZ in terms of age, gender and years of education. All participants provided their written informed consent to participate in this study. The study was approved by the ethics committee of the Second Xiangya Hospital, Central South University.

2.2. Image acquisition and preprocessing

Functional MRI images were collected on a 1.5-T GE Signa Twin speed scanner (General Electric Medical System, Milwaukee, Wisconsin) using a gradient-echo echo-planar imaging sequence. The details on the image acquisition protocol, and preprocessing steps for the fMRI data were presented in the Supplemental Materials Text (S.1) and also described elsewhere (Liu et al., 2010; Pu et al., 2012, 2014).

2.3. ALFF analysis

Voxel-wise ALFF maps were calculated for each subject and scan using REST software (http://www.restfmri.net). For a given voxel, the time series were first converted to the frequency domain using a Fast Fourier Transform. The square root of the power spectrum was computed and then averaged across a predefined frequency interval. This averaged square root was termed ALFF at the given voxel (Yu-Feng et al., 2007). The ALFF was the averaged square root of the power in the 0.01 to 0.08 Hz window. Following suggestions from Zang et al. (Yu-Feng et al., 2007), ALFF maps were normalized by the mean within-brain ALFF value for each subject to account for differences in scan intensity units, then smoothed with an 8-mm full width at half-maximum (FWHM) Gaussian kernel.

2.4. Reho analysis

Reho was performed on a voxel-by-voxel basis by calculating Kendall's coefficient of concordance of time series within a cluster of neighboring voxels (see Zang et al., 2004 for details). Here, cubic clusters of 27 voxels were used and the Reho value of every cubic cluster