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The diminished interhemispheric connectivity correlates with negative symptoms and cognitive impairment in first-episode schizophrenia

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ABSTRACT

Background: Previous studies imply that interhemispheric disconnectivity plays a more important role on information processing in schizophrenia. However, the role of the aberrant interhemispheric connection in the pathophysiology of this disorder remains unclear. Recently, resting-state functional Magnetic Resonance Imaging (fMRI) has reported to have potentials of mapping functional interactions between pairs of brain hemispheres.
Methods: Resting-state whole-brain functional connectivity analyses were performed on 41 schizophrenia patients and 33 healthy controls.
Results: The first-episode schizophrenia patients showed significant aberrant interhemispheric connection in the globus pallidus, medial frontal gyrus and inferior temporal gyrus. The correlation of Wechsler Adult Intelligence Scale scores with odds ratio of the aberrant interhemispheric connections revealed positive correlation in the pallidum (rho = 0.335, $p = .003$) and medial frontal gyrus (rho = 0.260, $p = .025$). The connection in the pallidum was also positively correlated with duration of illness (rho = −0.407, $p = .009$). Whereas, the aberrant interhemispheric connection in the inferior temporal gyrus was positively correlated with scores of Scale for the Assessment of Negative Symptoms (rho = 0.393, $p = .012$).
Conclusion: The present study provides fMRI evidence for the aberrant interhemispheric resting-state functional connectivity within resting-state networks in first-episode schizophrenia patients. These aberrant interhemispheric connections, in particular the pallidum, due to its anatomical and functional connectivities, may be the primary disturbance for cognitive impairment, negative symptoms and chronicity of schizophrenia.

1. Introduction

Schizophrenia is a serious mental disorder characterized by positive symptoms, negative symptoms, disorganization and cognitive deficits (Bleuler, 1911; Kraepelin, 1919). Prior research proposed this disorder to result from neuronal functional disconnectivity (Zhou et al., 2010; Venkataraman et al., 2012). The abnormality of white matter integrity in the corpus callosum in ultra-high risk group and in naïve first-episode schizophrenia patients (Cheung et al., 2008; Walterfang et al., 2008) suggests that interhemispheric disconnectivity plays an important role in schizophrenia. However, the relationship between the aberrant interhemispheric connections and its associated psychopathology in schizophrenia remains unclear.

Early postmortem studies reported increased corpus callosum thickness (Rosenthal and Bigelow, 1972) and this deficit has been associated with disruptions in interhemispheric information transferring (Beaumont and Dimond, 1973). In contrast, recent postmortem studies reported reduction in callosal thickness (Casanova et al., 1990), which is consistent with the majority of recent neuroimaging studies on schizophrenia which reported reduction in size, length or altered shape of the corpus callosum (Woodruff et al., 1997; Arnone et al., 2008), indicative of interhemispheric hypoconnectivity. Moreover, resting-state functional connectivity Magnetic Resonance Imaging (fMRI) in schizophrenia patients has reported bilateral aberrant functional connectivity in fronto-parietal, fronto-cingulate and frontal-thalamic (Liang et al., 2006; Zhou et al., 2007) and decreased functional connectivity between homotropic points to be associated with Positive and Negative Syndrome Scale (Hoptman et al., 2012). These studies consistently indicate that interhemispheric

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connectivity is more relevant in the pathophysiology of schizophrenia than unilateral connectivity. Thus, a better understanding of the aberrant interhemispheric functional connectivity may help in the development of new targeted pharmacological, surgical, and psychological therapies for patients with schizophrenia.

In the current study, as in our previous study (Tao et al., 2013); we used brain-wide functional connectivity analysis to assess the whole-brain interhemispheric functional disconnectivity during resting-state. This approach makes no prior assumptions regarding which connection will be affected. This approach thus has the potential to overcome the limitations of focusing only on a single connection or a circuit. In accordance with extensive available evidence from structural and functional MRI studies, we hypothesized that the diminished interhemispheric functional connectivity will be positively correlated with cognitive impairment and negative symptoms.

2. Methods and materials

2.1. Subjects

A total of 41 patients who were diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder within the past 18 months with no previous episodes of psychosis as per Diagnostic and Statistical Manual for Mental Disorders Fourth Edition (DSM-IV), were recruited from an inpatient unit at the Second Xiangya Hospital of Central South University, Changsha. A total of 33 healthy controls (HC) were recruited from the city of Changsha. Inclusion criteria for both patients and HC were similar, these include: (1) age between 18 and 45 years old; (2) Han Chinese; and (3) sufficient understanding and expressive capacity with $\geq$9 years of education. Exclusion criteria: (1) moderate to severe learning disability; (2) a history of current substance abuse or dependence; (3) a history of brain trauma or neurological disease; (4) left-handedness; and (5) previous electroconvulsive therapy and any other contraindications to MRI. HC who met the DSM-IV criteria for an Axis-I psychiatric disorder were excluded as well.

The Wechsler Adult Intelligence Scale (WAIS)-Chinese version was used to assess cognitive function (Gong, 1983). In subjects with schizophrenia, positive and negative symptoms within 1 month prior to the study were assessed using the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1990) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984, 1989), respectively. Dosage of antipsychotic medication equivalent to 100 mg/day of chlorpromazine was also calculated (Woods, 2003). Handedness was ascertained using the Annett Hand Preference Questionnaire (Annett, 1970).

To minimize the effects of chronicity of illness and neuroleptic medications on brain structure, this study preferentially recruited patients who were undergoing their first psychiatric hospitalization and just beginning treatment with antipsychotic medication for the first time. Of the 41 patients, 39 had $<$6 weeks of lifetime exposure to antipsychotics. The remaining two patients had been prescribed antipsychotics for 8 to 12 weeks. One patient was receiving typical antipsychotics (sulpiride), 37 patients were receiving atypical antipsychotics (clozapine, risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone), and three patients were receiving both typical and atypical antipsychotic therapies.

All participants received a description of the experimental procedures and gave written informed consent to participate in the study. The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central of Central South University, China.

2.2. Imaging acquisitions and data preprocessing

All functional imaging data were acquired using a 3.0-Tesla Philips Achieva whole-body MRI scanner (Philips, The Netherlands) at the Second Xiangya Hospital of Central South University in Changsha, Hunan Province, China. A total of 250 volumes of echo planar images were obtained axially (repetition time, 2000 ms; echo time, 30 ms; slices, 36; thickness, 4 mm; gap, 0 mm; field of view, 24×24 mm^2; resolution, 64×64; flip angle, 90°). T1-weighted images (TR/TE = 1924/20 ms, flip angle = 8°) and were acquired at the same location as the functional images in order to acquire anatomical information.

Before functional image preprocessing, the first 10 volumes were discarded to allow for scanner stabilization and the subjects' adaptation to the environment. Preprocessing of fMRI data was then conducted by SPM8 (University College London, UK; http://www.fil.ion.ucl.ac.uk/spm) and DPARSF (Data Processing Assistant for resting-state fMRI). The remaining functional scans were first corrected for within-scan acquisition time differences between slices, and then realigned to the middle volume to correct for inter-scan head motions. Subsequently, the functional scans were spatially normalized to a standard template (Montreal Neurological Institute) and resampled to $3 \times 3 \times 3$ mm^3. After normalization, the Blood Oxygenation Level Dependent (BOLD) signal of each voxel was first detrended to abandon linear trend and then passed through a band-pass filter (0.01–0.08 Hz) to reduce low-frequency drift and high-frequency physiological noise. Finally, nuisance covariates including head motion parameters, global mean signals, white matter signals and cerebrospinal fluid signals were regressed out from the Blood Oxygenation Level Dependent signals.

2.3. Construction of whole-brain function network

After data preprocessing, the time series were extracted in each pre-determined region of interest (ROI) by averaging the signals of all voxels within that region. Pearson's correlation coefficients between all pairs of ROIs were first calculated. Significant correlations were detected with a p-value < 0.01. A 90×90 correlation matrix was obtained for each subject. However, significant correlation between two ROIs may be spurious, that is, a by-product of the correlations of the two ROIs with a third region. To find out whether the correlation for the two ROIs is genuine, the third ROI should be kept constant. Statistically, this problem can be tackled by means of the partial correlation test. In such a test, the effects of the third ROI upon the relation between the other two ROIs are eliminated. By calculating partial correlation coefficients between all pairs of ROIs with all the remaining ROIs being controlling variables, a 90×90 connection matrix was obtained for each subject with a p-value < 0.01. The population level network can be obtained by summarizing all individual networks in patients with FES group and HC group, respectively, and thresholding them into binarized matrices with matched and reasonable sparsity values (defined as the total number of edges in a network divided by the maximum number of possible edges). In the analysis, the sparsities of the HC and patients with FES both were 4%.

2.4. Community mining algorithms

In this study, a community structure of the functional network of the brain corresponds to groups of brain regions that have similar functions and dense functional connectivity with each other. Our previously developed community-mining algorithm, described in Yang et al. (2010), tries to explore the notion of network modularity by means of understanding the dynamics of the network, which can naturally reflect the intrinsic properties of the network with modularity structure and exhibit local mixing behaviors. Based on large deviation theory by Yang et al. (2010), this algorithm sheds light on the fundamental significance of the network communities and the intrinsic relationships between the modularity and the characteristics of the network. The details have been described in our previous study (Tao et al., 2013).