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Functional disconnection between the visual cortex and the sensorimotor cortex suggests a potential mechanism for self-disorder in schizophrenia

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ABSTRACT

Self-disorder is a hallmark characteristic of schizophrenia. This deficit may stem from an inability to efficiently integrate multisensory bodily signals. Twenty-nine schizophrenia patients and thirty-one healthy controls underwent resting-state fMRI in this study. A data-driven method, functional connectivity density mapping (FCD), was used to investigate cortical functional connectivity changes in the patients. Areas with significantly different FCD were chosen to calculate functional connectivity maps. The schizophrenia patients exhibited increased local FCD in frontal areas while demonstrating decreased local FCD in the primary sensorimotor area and in the occipital lobe. The functional connectivity analysis illustrated decreased functional connectivity between visual areas and the primary sensorimotor area. These findings suggest disturbed integration in perception–motor processing, which may contribute to mapping the neural physiopathology associated with self-disorder in schizophrenia patients.
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1. Introduction

Schizophrenia patients have difficulty distinguishing between the self and other individuals and are uncertain whether their thoughts and actions are independent from external influences. These experiences may cause various passivity symptoms, such as auditory verbal hallucinations, thought insertion and replaced control of will. These passivity symptoms are often referred to as first-rank symptoms, which play a key role in the diagnosis of schizophrenia (Waters and Badcock, 2010). Recently, anomalies of self-experience have been considered a crucial factor for first-rank symptoms in schizophrenia patients (Waters and Badcock, 2010).

Neuroimaging has been broadly employed in the investigation of schizophrenia. It is widely accepted that the symptoms of schizophrenia may result from disconnectivity between brain regions (Fornito et al., 2012). Resting-state fMRI often acquires good compliance when studying patients. A voxel-wise, data-driven method based on a resting-state fMRI dataset, i.e., functional connectivity density mapping (FCD) (Tomasi and Volkow, 2010), might provide an unbiased approach to analyze whole-brain connectivity. This powerful method may be more sensitive in the detection of functional alterations of the distribution of brain hubs (Tomasi and Volkow, 2012; Luo et al., 2014). In the current study, we applied FCD analysis to investigate changes in cortical functional hubs in schizophrenia patients. We predicted that patients would exhibit altered local FCD, and these changes may contribute to mapping of the neural physiopathology of schizophrenia.

2. Methods

2.1. Participants

In this study, we recruited 29 schizophrenia patients who were diagnosed with schizophrenia using the structured clinical interview for DSM-IV Axis I disorders—clinical version (SCID-I-CV). All of the patients were recruited from inpatient and outpatient services at Chengdu Mental Health Center and underwent a semi-structured interview with the positive and negative symptom scale (PANSS). They were all treated with atypical antipsychotics. Healthy controls (31 subjects) were matched for age, gender and years of education to the extent

Abbreviations: BA, Brodmann area; EBA, Extrastriate body area; FCD, Functional connectivity density mapping; FWHM, Full-width at half-maximum; ROI, Region of interest; MOG, Middle occipital gyrus; PANSS, Positive and negative symptom scale; STG, Superior temporal gyrus.

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that was possible (see Table 1 for demographic parameters). The exclusion criteria for all of the participants included a neurological illness, traumatic brain injury or substance-related disorders. Written informed consent was obtained from all of the participants individually, and the experimental procedures were approved by the Ethics Committee of Chengdu Mental Health Center in accordance with the Declaration of Helsinki.

2.2. Data acquisition and image preprocessing

Using a 3 T MRI scanner (GE Discovery MR 750, USA) at the MRI Center of University of Electronic Science and Technology of China, functional images were obtained using a standard Echo Planar Imaging pulse sequence with the following parameters: TR/TE = 2000 ms/30 ms, flip angle = 90°, matrix size = 64 × 64, field of view = 24 × 24 and slice thickness = 4 mm (no gap). Two hundred and fifty-five volumes (35 slices per volume) of images were obtained.

We processed all images using the SPM 8 toolbox (http://www.fil.ion.ucl.ac.uk/spm8). The first 5 volumes were discarded for magnetization equilibrium prior to data preprocessing. Slice timing correction, head motion correction and spatial normalization ($3 \times 3 \times 3$ mm^3) were conducted. Subjects with a maximum displacement that exceeded 2 mm in any cardinal direction or with a maximum spin larger than 1 degree were excluded. In addition, we assessed head translation and rotation between the groups by averaging the frame-wise displacement from every time point for each subject as previously described (Power et al., 2012). After regressing out six head parameters obtained from the head motion correction, the functional images were temporally filtered (0.01–0.08 Hz) to remove the magnetic field drifts of the machine and physiological noise (Fox et al., 2005).

2.3. Local FCD analysis

We used local FCD to identify efficient hubs at voxel level in the whole brain. For a given voxel, the local FCD was equivalent to the number of voxels with significant connections in the local cluster around this voxel. Thus, there were two key criteria to define the number: (1) the threshold—the correlation coefficient between voxels had to be larger than a predefined threshold; and (2) the local cluster—all voxels in this cluster had to be included in a mass around the target voxel. In detail, for a given target voxel, our operations were as follows: first, Pearson correlations between the time courses of the target voxel and its adjacent voxels were calculated; the functional connections were subsequently identified according to criterion 1—the correlation coefficient had to be larger than the predefined threshold. The voxels with significant connections to the target voxel were added to the mass around the target voxel. Next, we calculated the relationships between the adjacent neighbors (new voxels) of the mass and the target voxel. If these neighbors had significant functional connections with the target voxel, they were likewise added to the mass. This procedure was repeated in an iterative manner until no new voxels could be added to the mass. In this way, the boundary of mass around the target voxel was established, and the local functional cluster was determined. The local FCD value of the target voxel was defined as the number of voxels in the cluster surrounding the target voxel.

This calculation was performed for all voxels to generate the local FCD map. Then, local FCD maps were normalized by dividing by the mean value of each individual map and were spatially smoothed with an isotropic Gaussian kernel (8 mm full-width at half-maximum, FWHM). The area with the highest local FCD was suggested to be the prominent local functional hub in the whole brain. More detailed information about the calculation of FCD can be found in our previous study (Luo et al., 2014).

The correlation threshold is a very important parameter in identifying FCD. To obtain reliable and robust results, we used multiple threshold levels (ranging from 0.45 to 0.85, in 0.05 steps) to determine the link; thus, there were nine local FCD maps for each participant in the current study.

Group-level comparisons of the FCD maps were assessed by one-sample *t*-test for each group. The two-sample *t*-test in SPM 8 was used to evaluate the between-groups FCD differences for each threshold, controlling for the effects of age and gender.

To identify robust between-groups differences, the regions exhibiting a significant difference ($p < 0.005$) in at least 5 comparisons (responding to the consecutive thresholds) were regarded as group differences. These areas were identified as the regions of interest (ROI) for the subsequent functional connectivity analyses.

2.4. Functional connectivity analyses

For the functional connectivity analysis, the preprocessed images were further processed using spatial smoothing (Gaussian kernel with an 8 mm FWHM) and nuisance signal regression (6 head motion parameters, white matter, cerebrospinal fluid and global signals). After filtering (0.01–0.08 Hz) (Fox et al., 2005), we calculated the Pearson's correlation coefficients between the average time course of the ROI and that of each voxel in the whole brain to define the functional connectivity map for each ROI. The resulting correlation coefficients were Fisher-*Z*-transformed. We used two-sample *t*-tests to assess the differences in the functional connectivity maps between the groups within the masks, which resulted from the union of the one-sample tests of the functional connectivity maps ($P < 0.05$, uncorrected) of the two groups, controlling for age and gender effects. Significance was set at $P < 0.05$ (FDR corrected and cluster size >621 mm^3).

2.5. Correlations between functional properties and clinical variables

To investigate the correlations between the altered brain functional connectivity and the clinical features (duration of disease and PANSS positive, negative, general psychopathology subscales and total scores) in the patient group, the average *z*-scores of the voxel, which illustrated a peak *T* value of different local FCD or different functional connections with the ROIs, and the adjacent 26 voxels were extracted. Then, we calculated the partial correlations between the averaged z-scores and the clinical features, controlling for both age and gender effects.

3. Results

One patient was excluded because of excessive motion. There were 28 schizophrenia patients and 31 healthy controls in the final analysis. For the remaining subjects, there were no significant differences in

Table 1
Demographic and clinical characteristics of the patients with schizophrenia and the healthy controls.

Characteristic	Schizophrenia	Control	*T* value/chi-square* (*P* value)
	M (SD)	M (SD)	
Age (years)	36.536(11.458)	35.194(12.684)	−0.425¶ (0.673)
Gender (% male)	64%	55%	0.544§ (0.597)
Education (years)	11.393(3.083)	12.807(3.772)	1.566¶ (0.123)
Handedness (% right)	93%	100%	
Duration of illness (years)	11.996 (8.937)		
PANSS-positive subscale	16.536 (5.770)		
PANSS-negative subscale	19.607 (4.131)		
PANSS-general psychopathology	27.714 (4.345)		
PANSS-total score	63.857 (9.529)		

*Two-tailed *t*-tests (¶) and chi-square tests (§) were conducted to assess group differences for continuous and discrete variables, respectively.
Abbreviations: M = mean value; SD = standard deviation; PANSS = positive and negative symptom scale.