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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.

mean head motion between the groups (two-sample two-tailed *t*-test, $T = 0.949$, $P = 0.347$).

3.1. Local FCD map

We first illustrated the distribution of the local FCD for the nine thresholds in the two groups (one-sample *t*-test, $P < 0.05$, FDR corrected, cluster size > 621 mm^3) (Fig. 1). Regions located in the cerebellum, fusiform gyrus, occipital gyrus, lingual gyrus, calcarine, cuneus, precuneus and superior frontal gyrus had the densest local functional connectivity, which exhibited a pattern similar to that found in previous studies (Tomasi and Volkow, 2010). Then, we conducted two-sample *t*-tests to obtain group differences. As 0.6 is often chosen as the threshold to determine local FCD, we first displayed the group differences in local FCD with threshold = 0.6 ($P < 0.05$, FDR corrected, cluster size > 621 mm^3) in Fig. 2. Compared with the controls, the patients exhibited enhanced local FCD in the right superior frontal gyrus (BA 8) and the left supplementary motor area (BA 6) as well as decreased local FCD in the bilateral middle occipital gyrus (MOG) (BA 18/19), left paracentral lobule (BA 4/6) and left postcentral gyrus (BA 2).

In addition, in Fig. 3, we summarized all of the differences ($P < 0.005$, uncorrected) resulting from the nine thresholds. Stable between-groups differences for more than 5 comparisons (consecutive thresholds) were found in five regions (Table 2). These brain areas were chosen as the seeds in the subsequent functional connectivity calculations.

3.2. Functional connectivity analysis

For each ROI, a seed-based functional connectivity analysis was conducted. First, group-level functional connections were identified with one-sample *t*-tests, which can be found in the supplementary materials (Fig. S1). Then, based on the results of two-sample *t*-tests, three of the five ROIs exhibited remarkable differences between the two groups ($P < 0.05$, FDR corrected, cluster size > 621 mm^3) (Fig. 4). Compared with the healthy controls, the patients exhibited reduced functional connectivity between the bilateral MOG (BA 18/19) and the bilateral occipital lobe (BA 18/19), insula (BA 48), precentral gyrus (BA 6), postcentral gyrus (BA 3/4) and paracentral lobule (BA 4). Decreased functional connectivity between the paracentral lobule (BA 4/6) and the bilateral lingual gyrus (BA 18/19), superior occipital gyrus (BA 19), precentral gyrus (BA 6) and postcentral gyrus (BA 4) were also identified. In addition, the right MOG (BA 19) exhibited an increased functional connectivity with the right superior temporal gyrus (STG) (BA 48).

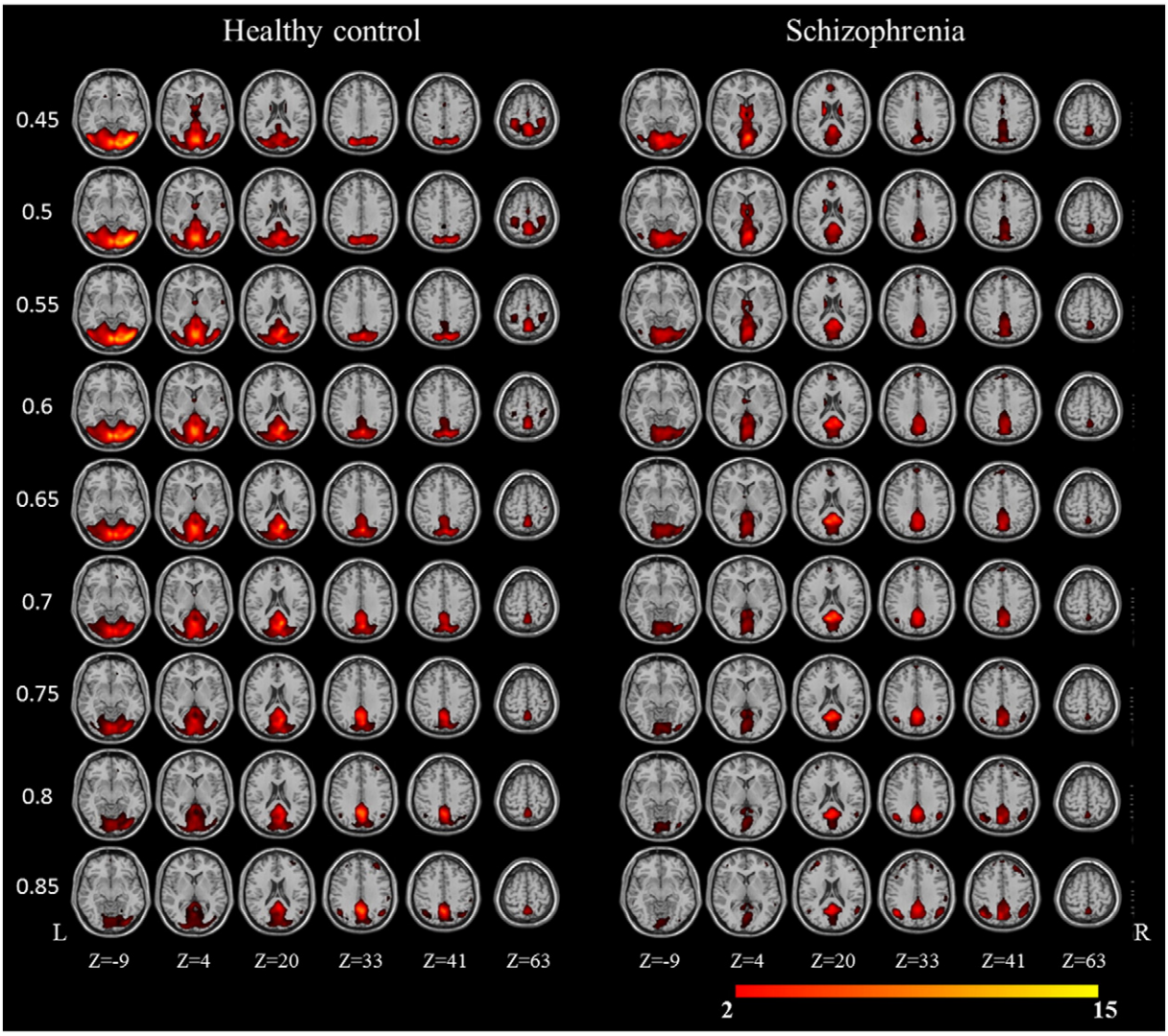

Fig. 1. The local FCD maps for the nine thresholds in the two groups (one-sample *t*-test, $P < 0.05$, FDR corrected, cluster threshold > 621 mm^3). L, left; R, right.

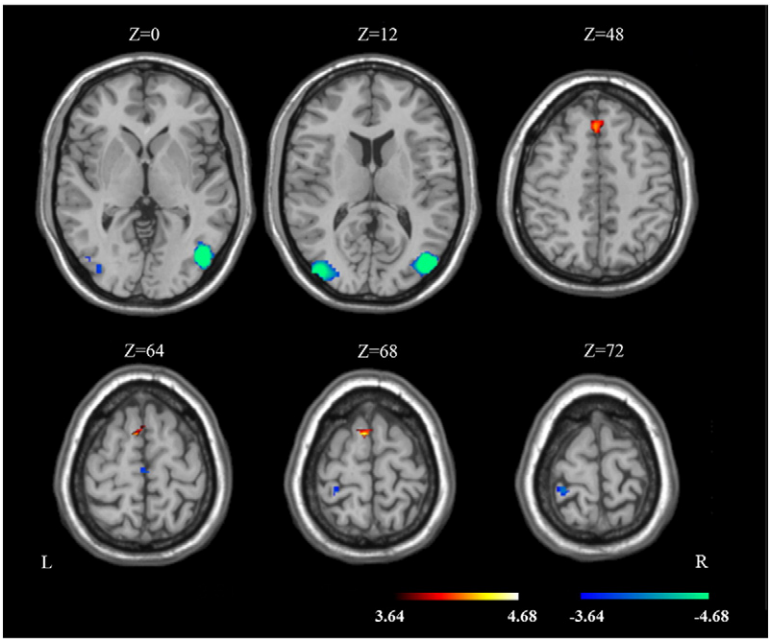

Fig. 2. The group differences in local FCD with the threshold = 0.6 (two-sample *t*-test, $P < 0.05$, FDR corrected, cluster threshold > 621 mm^3). L, left; R, right.

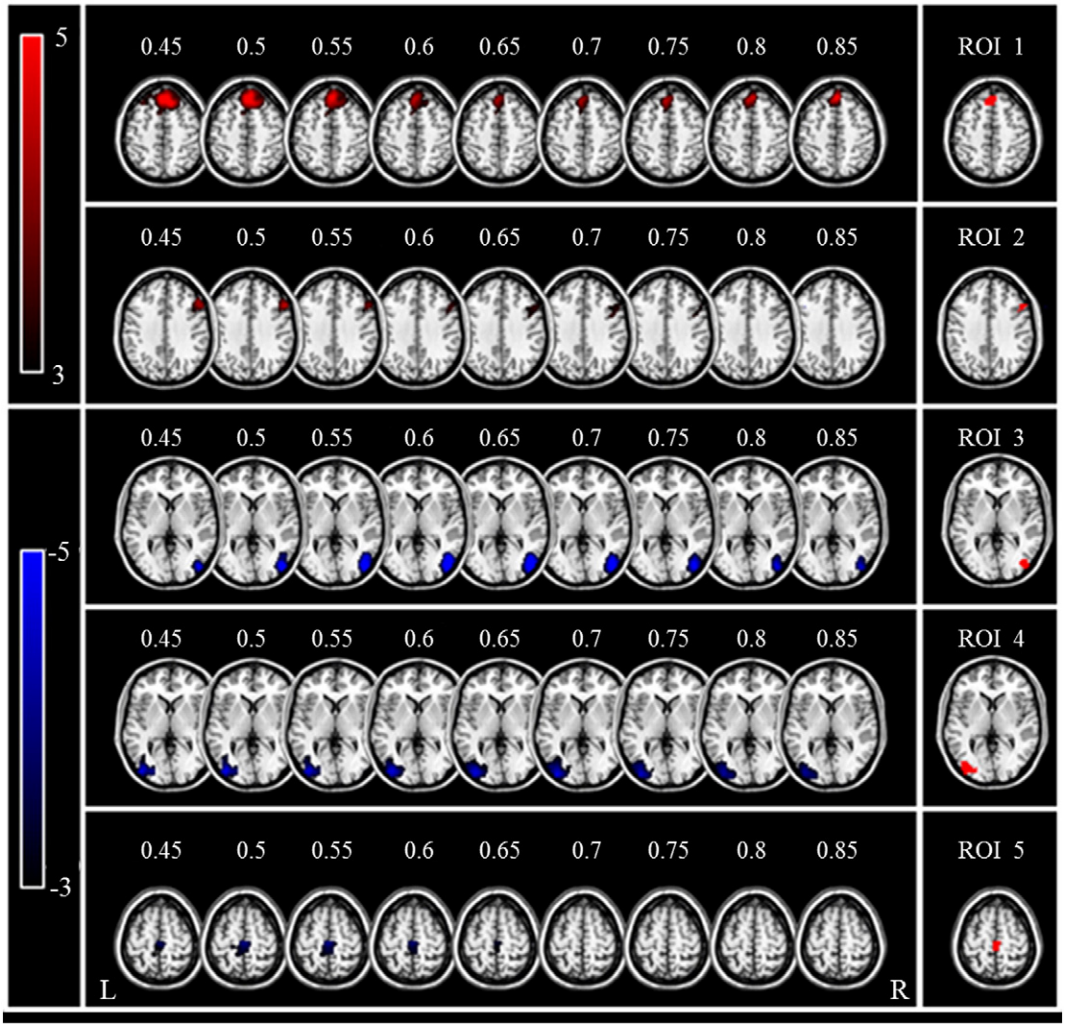

Fig. 3. The different FCD maps ($P < 0.005$, uncorrected) that resulted from nine comparisons (from threshold = 0.45 to 0.85, stepped by 0.05). The five ROIs shown in the right column were defined according to the different maps.

Table 2
Detailed information for the five ROIs ($P < 0.005$, uncorrected).

Name	Brain region	BA	Cluster size (voxels)*
ROI1	Right superior frontal gyrus	8	101
ROI2	Right inferior frontal gyrus	45	29
ROI3	Right middle occipital gyrus	19	43
ROI4	Left middle occipital gyrus	19/18	139
ROI5	Left paracentral lobule	4/6	29

Abbreviations: BA = Brodmann area; ROI = region of interest.
* The cluster size represents the number of voxels within the cluster.

3.3. Correlations between functional properties and clinical variables

A correlational analysis within the group of patients revealed a negative association between the duration of disease and the functional connections between the right MOG and the left MOG ($R = -0.609$, $P = 0.001$) and the right postcentral gyrus ($R = -0.469$, $P = 0.012$). In addition, the functional connectivity between the left MOG and the right MOG exhibited a negative correlation with disease duration ($R = -0.651$, $P = 0.000$). No significant correlations were identified for the remaining clinical parameters (Fig. 5).

4. Discussion

We demonstrated enhanced local FCD in the frontal lobe and decreased local FCD in the paracentral lobule, left postcentral gyrus and bilateral MOG in the schizophrenia patients. A functional connectivity analysis indicated that the connectivity between the visual and sensorimotor areas was significantly decreased in the schizophrenia patients, which suggests low-level perceptual processing deficits in patients with schizophrenia.

The patients exhibited reduced local functional connectivity in the supplementary motor area, the precentral gyrus and the postcentral gyrus. This finding was understandable because individuals with schizophrenia commonly exhibit a variety of symptoms, such as psychomotor and fine motor as well as touch, temperature, nociception, tension and vibration abnormalities (Huang et al., 2010).

The schizophrenia patients exhibited decreased local FCD in the MOG, which may serve as the potential functional basis for the deficits in early-stage visual processing, such as object recognition, perceptual closure and face processing (Butler et al., 2008). A negative association between disease duration and the functional connectivity between the left and right MOG was identified in the patients, which suggests this functional abnormality deteriorated with increasing duration of the disease. Importantly, in healthy subjects, the extrastriate body area (EBA), which is largely located in the MOG, selectively responds to the viewing of body parts and mental imagery of embodied self-location (Jeannerod, 2004). Quantitative lesion analysis has demonstrated that brain damage to the EBA is primarily associated with autoscopic phenomena (Heydrich and Blanke, 2013). Therefore, the relatively reduced local FCD in the MOG may impair the perception of body ownership in schizophrenia patients.

We identified a decreased functional connectivity pattern between visual areas and the primary sensorimotor area. Recent studies in healthy controls have emphasized the processing and integration of multisensory bodily signals as a fundamental mechanism that underlies a coherent self-experience (Botvinick and Cohen, 1998; Ehrsson, 2007). For example, in the "rubber-hand illusion" experiment, synchronous stroking of an observed fake hand and the individual's own unseen hand led to the fake hand being regarded as the individual's own hand (Botvinick and Cohen, 1998). In addition, Ehrsson (Ehrsson, 2007) demonstrated that a mismatch between visual perception and proprioceptive signals induces disturbances in self-experiences. In short, the sense of self relies on the spatial and temporal correlations of sensory

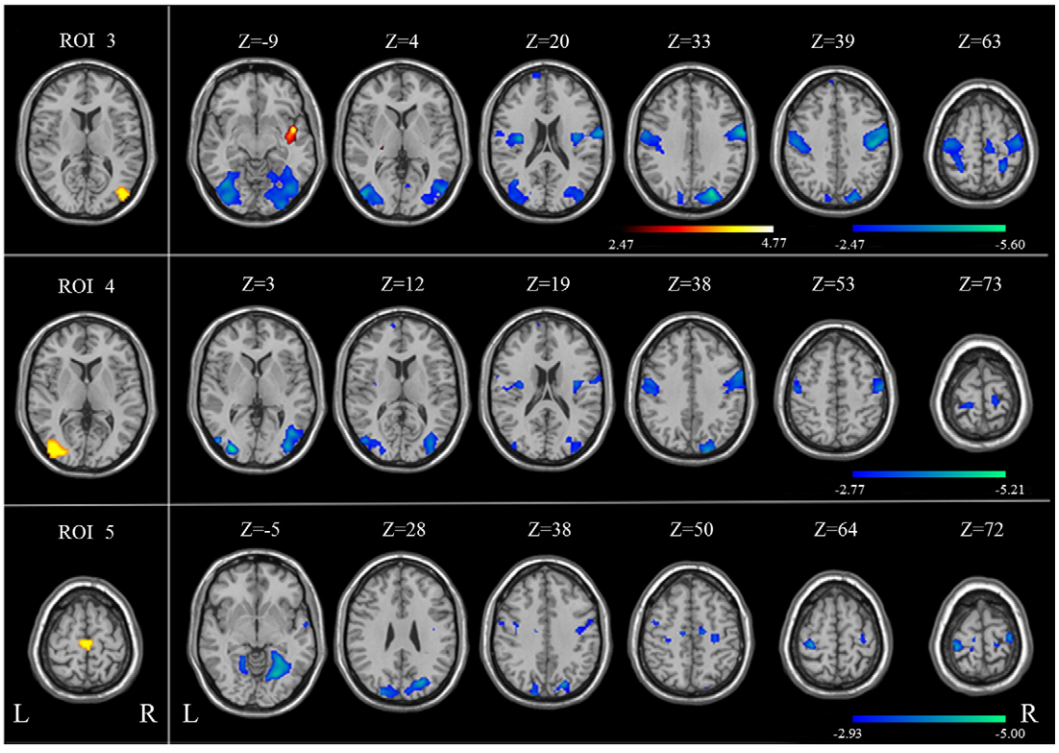

Fig. 4. The functional connectivity differences at the group level. (a) The right MOG exhibited decreased functional connectivity with the bilateral occipital area, insula, paracentral lobule and precentral and postcentral gyri as well as increased functional connectivity with the right superior temporal gyrus. (b) The left MOG exhibited decreased functional connectivity with the bilateral occipital area, insula, paracentral lobule and precentral and postcentral gyri. (c) The paracentral lobule exhibited decreased functional connectivity with the bilateral lingual gyrus, superior occipital gyrus and precentral and postcentral gyri ($P < 0.05$, FDR corrected, cluster size > 621 mm^3). L, left; R, right.

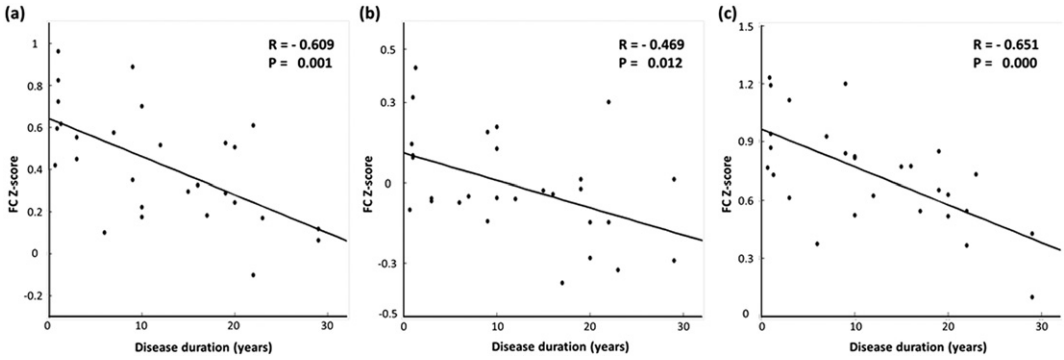

Fig. 5. Correlations between functional properties and clinical variables. (a) The functional connectivity between the right MOG and the left MOG was negatively associated with the duration of disease. (b) The functional connectivity between the right MOG and the right postcentral gyrus was negatively correlated with disease duration. (c) The functional connectivity between the left MOG and the right MOG was negatively correlated with disease duration.

signals, such as visual, tactile and proprioceptive signals, that arise from the body; a mismatch between these signals is sufficient to induce disturbances in self-experiences in patients with schizophrenia. Our results suggest that the decreased functional connectivity between the MOG and the primary somatosensory area in the schizophrenia patients might reflect impairments in the integration of various perceptual stimuli, which might help to explain the self-disorder in the schizophrenia patients. Moreover, weaker functional connectivity between the right MOG and the right postcentral gyrus was linked to longer disease duration. This finding may reflect injured brain function aggravated by a long duration of disease. In addition to responding to the viewing of body parts, the EBA is also activated by planning, executing and imagining movements of the limbs (Astafiev et al., 2004). A widely accepted explanatory model of the passivity symptoms in schizophrenia is the internal forward model system, which suggests that patients cannot predict the perceptual consequences of their intentional actions and that the salience of sensation is not diminished; thus, the actions are perceived to be externally generated (Frith, 2005). In action feedback tasks, schizophrenia patients with severe delusions of control made poor predictions of the sensory consequences of an action (Synofzik et al., 2010). Therefore, the diminished functional connectivity between the MOG and the primary sensorimotor area identified in the current study may impact self-processing in schizophrenia patients.

In our findings, the bilateral insula also demonstrated decreased functional connectivity with the MOG. The insula is considered the hub of the salience network (Palaniyappan and Liddle, 2012). The weakened functional connectivity between the MOG and the insula may reflect the aberrant mapping of saliency that originates from visual information.

The right STG demonstrated enhanced functional connectivity with the right MOG. The STG is the most consistently reported gray matter abnormality associated with the auditory verbal hallucinations of patients with schizophrenia (van Tol et al., 2014). Thus, this increased functional connectivity may be associated with the hallucination of patients.

Our study had several limitations. First, it included a relatively small sample, and the age range of the subjects was relatively wide. Second, this study lacked self-experience assessment tests. Additional assessments should be included in future studies. Finally, the nature of FCD data does not allow us to establish the directionality of the information stream.

In conclusion, we demonstrated that schizophrenia patients exhibited increased local FCD in frontal areas and decreased local FCD in the primary sensorimotor area and visual areas. Functional connectivity analysis demonstrated decreased functional connectivity between visual areas and the primary sensorimotor area in schizophrenia. These findings indicate disturbed integration in primary perception–motor processing, which could contribute to a range of schizophrenia. Our observations may have potential implications for the neural physiopathology of schizophrenia.

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Contributors

XC and MD designed the experiment and wrote the protocol; QX undertook the statistical analysis; YL, LD and WC collected the image data and clinical information; DY and CL reviewed this article critically and gave final approval of the version of the article to be published. All authors contributed to the manuscript and have approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.06.014.

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