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Functional abnormalities of the right posterior insula are related to the altered self-experience in schizophrenia ☆

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ABSTRACT

The insula is involved in detecting the salience of internal and external stimuli, and it plays a critical role in psychosis. Previous studies have demonstrated the structural and functional alterations of the insula in schizophrenia. To acquire a full picture of the functional alterations of the insula in schizophrenia, the resting-state fMRI data of 46 patients with schizophrenia and 46 healthy control subjects were collected. We used clustering analysis to divide the insula into three subregions: the dorsal anterior insula (dAI), ventral anterior insula (vAI) and posterior insula (PI). Then, whole-brain functional connectivity analysis was conducted based on these subregions. The results showed that the right dAI and PI in patients exhibited altered functional connections with the primary sensorimotor area. In addition, the right PI of the patients exhibited increased functional correlations with the thalamus. More importantly, the altered functional properties of the right PI were significantly correlated with the severity of the delusion and poor insight in schizophrenia. The results suggested that the right PI might play an important role in self-experience processing in schizophrenia. Accordingly, the right PI should be considered very important in the pathological mechanism of schizophrenia.

1. Introduction

We live in a world that is full of information. Due to the limited processing power of the brain, humans must determine which stimuli are salient and should capture their attention for further processing. The brain determines salience based on an individual's previous experiences, goals and current psychological state (Uddin, 2015). Meta-analyses of task-based functional MRI studies suggest that the insula is a key node of salience detection (Chang et al., 2013; Singer et al., 2009). The insula can be divided into three subregions (Deen et al., 2011): the dorsal anterior insula (dAI),[1] the ventral anterior insula (vAI) and the posterior insula (PI) (Deen et al., 2011). In detail, the dAI and anterior cingulate cortex are thought to be the core brain regions of the salience network. The dAI is activated in almost all tasks that involve goal-directed cognition and executive control (Cao et al., 2016; Chang et al., 2013; Luo et al., 2014b). The vAI, which is always coactivated with limbic cortices, is involved in emotion and chemosensory information processing (Chang et al., 2013; Pritchard et al., 1999). The PI acts as a multimodal convergence zone for exteroceptive and interoceptive information. It is always coactivated with the somatosensory cortex (Craig, 2002).

The ascending interoceptive and exteroceptive inputs were received by the insular cortex (Craig, 2002; Critchley and Harrison, 2013; Luo et al., 2014a). In the insula, this information communicates to form the current state of the body (Seeley et al., 2012) according to how the individual evaluates the significance of excessive inner and outer stimuli. One important hypothesis about schizophrenia considers that the different symptoms of this disease, such as delusion and hallucination, are caused by the aberrant assignment of salience to one's own experience (Kapur, 2003). This hypothesis involves the dysfunction of the insula. Recent evidence has suggested that dysregulation of the function of the insula could appear in many psychiatric disorders, especially schizophrenia (Palaniyappan and Liddle, 2012). Structural MRI studies have identified that the insula shows the most consistent

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[1] dAI: dorsal anterior insula.
vAI: ventral anterior insula.
PI: posterior insula.
ROI: region of interesting.
PANSS: Positive and Negative Symptom Scale.

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grey matter reduction and shape deformation in schizophrenia (Fusar-Poli et al., 2012; Jang et al., 2006; Pu et al., 2012). Reduced functional activation of the insular cortex during various tasks, such as an aversive electrical stimulus, reward learning tasks and facial expressions (Gradin et al., 2013; Lindner et al., 2014; Linnman et al., 2013), are found in schizophrenia patients. Further, in resting state fMRI, schizophrenia patients always exhibit an aberrant dependence of both the default mode network and central executive network interactions on anterior insula activity (Manoliu et al., 2014; Moran et al., 2013).

Although researchers have discovered an abnormality of the insula in schizophrenia (Ebisch et al., 2014; Manoliu et al., 2014), studies focused on mapping the functional alteration pattern of the insula in schizophrenia are relatively few. Considering the important role of the insula in schizophrenia, the present study focused on the functional connectivity pattern of the insula in patients with schizophrenia compared to healthy controls. The results of the current study may provide us with more information about the insula's abnormality in schizophrenia and help us understand the altered insula modulation of large-scale brain networks in schizophrenia.

In the current study, we first divided the insula into three subregions using a clustering analysis based on whole-brain functional connectivity maps in resting-state data. This conduction was used to obtain seeds instead of using the ready-made templates that are based on healthy participants. Then, each subregion was treated as a seed region in the subsequent whole-brain functional connectivity analysis to acquire the connectivity patterns. The connectivity patterns of the schizophrenia patients were compared with those of healthy controls. We hypothesized that schizophrenia would show altered functional connectivity patterns in the insula and that these alterations would be related to the pathological syndromes of the patients.

2. Procedures

2.1. Participants

Subjects ranging from 25 to 55 years of age were included in this study. Resting-state fMRI data of forty-six schizophrenia patients in a stable phase of illness and forty-six healthy controls were collected. The two groups were matched for age, sex, handedness and years of education (see Table 1 for demographic parameters). The experimental procedures were approved by the Ethics Committee of the Chengdu Mental Health Center in accordance with the Helsinki Declaration and were registered in the center of Chinese Clinical Trial Registry (No. ChiCTR-RCS-14004878). Written informed consent was obtained from all participants individually.

Schizophrenia patients were recruited from the Chengdu Mental Health Center. They were diagnosed using the structured clinical interview for DSM-IV Axis I disorders - clinical version (SCID-I-CV), and all were treated with atypical antipsychotics. The severity of clinical symptoms was measured using the Positive and Negative Symptom Scale (PANSS).

The exclusion criteria for all participants included a history of neurological illness, traumatic brain injury, substance-related disorders and standard contraindications for fMRI. For the control group, subjects with a personal history of psychosis or a history of psychosis in first-degree relatives were excluded. The DSM-IV (SCID-I-CV) was used to assess the presence of psychiatric diagnoses.

2.2. Data acquisition and image pre-processing

Resting-state fMRI data acquisition was performed on a 3-Tesla MRI scanner (GE DISCOVERY MR 750, USA) at the Center for Information in Medicine of University of Electronic Science and Technology of China. The subjects were requested to close their eyes without falling asleep and to let their thoughts come and go. Functional scans (8.5-min runs) involved a standard Echo Planar Imaging pulse sequence, TR=2000 ms, TE=30 ms, flip angle=90°, field of view=24 cm × 24 cm, matrix size=64 × 64, in-plane voxel size=3.75 mm × 3.75 mm × 4 mm. The functional volume consisted of 35 slices. A total of 255 volumes were collected for each subject.

All images were processed using the SPM8 (Statistical Parametric Mapping 8) toolbox (http://www.fil.ion.ucl.ac.uk/spm8). The first five volumes were discarded for the magnetization equilibrium. Then, pre-processing methods, including slice timing correction, head motion correction, spatial normalization (3 mm × 3 mm × 3 mm) to the EPI template, and band-pass filtering (0.01–0.08 Hz), were conducted (Luo et al., 2015). No smoothing was conducted to avoid possible blurring between insula subregions. Subjects with a maximum displacement in any cardinal direction that exceeded 1.5 mm or a maximum spin larger than 1.5° were excluded from analyses. The head translation and rotation between the groups was assessed by averaging the framewise displacement (Power et al., 2012).

2.3. Cluster analysis

The insula was defined according to the AAL standard brain. The cluster analysis was performed according to our previous study (Cao et al., 2014). First, each voxel in the insula was used as a

Table 1
Demographic and clinical characteristics of the participants.

Characteristic	Schizophrenia (Mean ± SD) (n=46)	Healthy control (Mean ± SD) (n=46)	T value/chi-square*	P value (two-tailed)
Age (years)	41.54 ± 8.86	39.05 ± 6.99	1.47[a]	0.15
Gender (% male)	69.57%	52.38%	2.74[b]	0.10
Education (years)	11.65 ± 2.72	10.79 ± 3.00	1.42[a]	0.16
Handedness (% right)	95.65%	100%	2.04[b]	0.15
Disease duration (years)	16.27 ± 9.19			
Medication dosage in CPZ equivalents (mg)	337.95 ± 162.63			
PANSS-positive score	12.52 ± 5.39			
PANSS-negative score	20.61 ± 6.41			
PANSS-general score	27.63 ± 5.28			
PANSS-total score	60.76 ± 12.18			

Abbreviations: M=Mean value; SD=Standard deviation; CPZ=chlorpromazine.

* Two-tailed *t*-tests.

[a] Chi-square tests.

[b] Were conducted to assess group differences for continuous and discrete variables, respectively.

seed to calculate the whole-brain functional connectivity map. The head motion parameters, global mean signal, white matter, cerebrospinal fluid and linear drift signal were regressed to remove confounders that contributed to non-neural noise. Fisher z-transformed correlation coefficients were then averaged across subjects to create the cross-subject connectivity maps for a given seed region. Then, k-means clustering, which used the squared Euclidean distance as the distance measure, was utilized in these averaged maps. This analysis was conducted for the left and right insula separately. The above conduction was repeated 100 times to minimize random variance and achieve stability.

Because previous research has identified three insula subregions (Chang et al., 2013; Deen et al., 2011; Uddin, 2015), we defined k=3 to parcellate the insula into three distinct functional regions: dAI, vAI and PI.

2.4. Functional connectivity analysis

Functional connectivity analysis was conducted using the insula clusters as seeds. To avoid any possible errors caused by clustering differences, the seeds were defined as the intersections of each of the insula subregions across subjects. In other words, the seed would include only the common regions of clusters with the same functional connectivity map across subjects. The previously pre-processed images were further spatially smoothed (Gaussian kernel with an 8-mm FWHM). Then, nuisance signal regressions (head motion parameters, global mean signal, white matter, cerebrospinal fluid and linear drift signal) were performed. After filtering (0.01–0.08 Hz), Pearson's correlations between the time course of the seeds and that of each of the remaining voxels in the brain were calculated. Fisher transformations were performed for the correlation coefficients to obtain Z scores (Luo et al., 2011). Then, group differences between patients and healthy subjects were assessed by the two-sample *t*-test (FDR corrected, $p < 0.05$, cluster size > 621 mm^3).

2.5. Correlations between functional properties and clinical variables

Within the group of schizophrenia patients, the average Z score of the 27 voxels in a cube with the center at the peak values of the difference in functional connections was extracted. Then, partial correlations were computed between the measures of disease severity (PANSS positive, negative, general psychopathology subscales, the total scores and the score of PANSS P1, P3, G12 item which represent the delusion, hallucination and poor insight) and the Z value indexes of functional connectivity. Then, age, gender, education level and medication dosage were included as covariates. Because the scores of P1, P3 and G12 items were on an ordinal scale, we performed Spearman correlation analysis to reveal the relationship between the functional properties and clinical variables.

3. Results

Three healthy controls were excluded due to excessive motion. There were 46 schizophrenia patients and 43 healthy controls in the final analysis. For the remaining subjects, the mean head

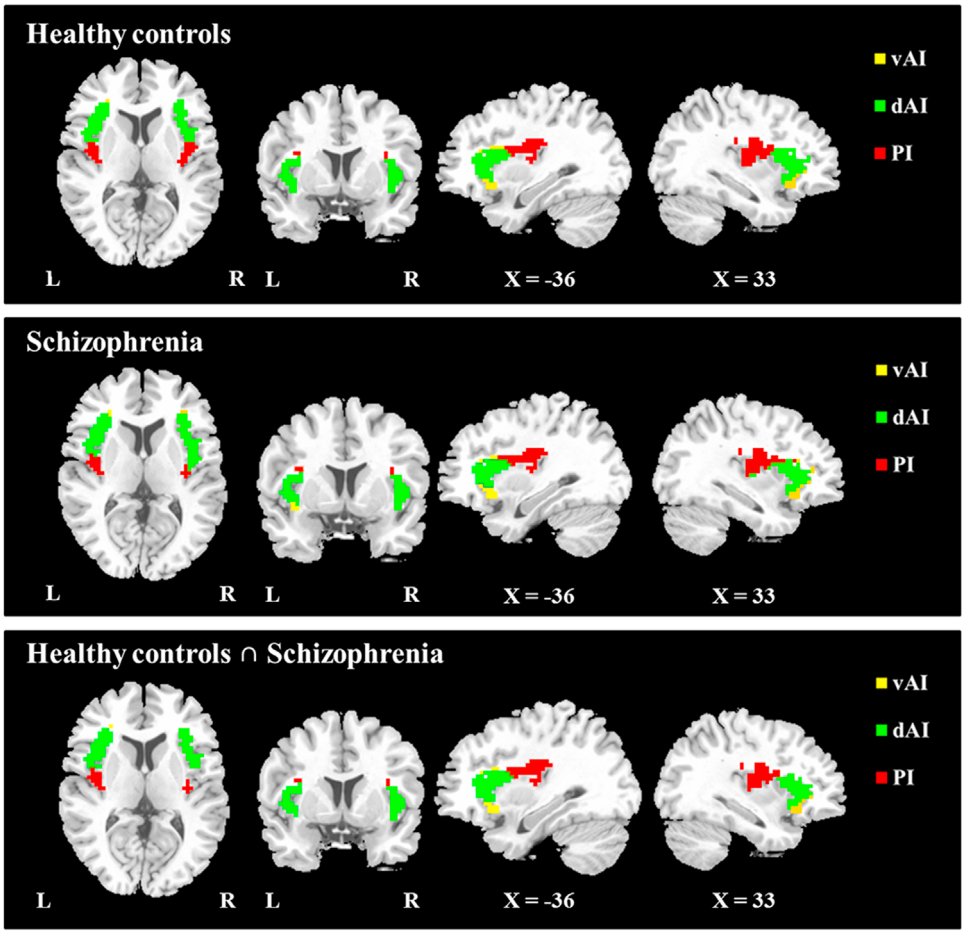

Fig. 1. Three subregions of the bilateral insula identified by cluster analysis. The first row represents the cluster analysis results of the control group. The second row represents the results of the schizophrenia patient group, and the last row represents the intersection results of the two groups.

Table 2
Mean coordinates of insula subregions (MNI).

Region	Healthy control (cluster size)[a]	Schizophrenia (cluster size)[a]	The intersection of two groups (cluster size)[a]
Left dAI	−37, 12, 2 (339)	−37, 13, 3 (292)	−37, 13, 3 (292)
Right dAI	39, 12, 1 (307)	40, 8, 1 (343)	40, 11, 0 (307)
Left vAI	−30, 18, −7 (70)	−32, 18, −7 (93)	−30, 19, −8 (70)
Right vAI	33, 20, −12 (70)	34, 20, −9 (85)	33, 20, −12 (70)
Left PI	−37, −12, 12 (157)	−37, −11, 9 (181)	−37, −13, 12 (157)
Right PI	37, −11, 11 (162)	35, −12, 15 (111)	36, −13, 15 (111)

[a] The cluster size represents the number of voxels within the cluster.

motion was matched for the two groups (two-sample *t*-test, t=0.0522, p=0.9585).

3.1. Cluster analysis

Cluster analysis revealed three subregions for the left and right insula, including dAI, vAI and PI (Fig. 1). This classification of the insula was consistent with previous research (Deen et al., 2011). The allocation of the three clusters was comparable for the two groups. The center coordinates for each cluster combining two groups are presented in Table 2. These subregions were used in the following functional connectivity analysis as region of interest (ROI). Overall, 86.7% of the insula voxels were assigned to the same subregion for both groups.

3.2. Functional connectivity analyses

For each ROI, a seed-based whole-brain functional connectivity analysis was conducted. One-sample *t*-tests were performed for the group level functional connections (Fig. S2). Functional connectivity patterns were similar for ROIs in the left and right hemispheres. The dAI exhibited significant correlations with the insula and adjacent frontal and temporal regions and with the dorsal anterior cingulate cortex and the adjacent supplementary motor area. The PI seeded functional connectivity analysis revealed significant correlations with the insula and the adjacent frontal, temporal and parietal cortices, especially the pre- and postcentral gyrus. The vAI is functionally associated with the insula and adjacent frontal and temporal cortices as well as the anterior cingulate cortex and amygdala. Two-sample *t*-tests revealed that two of the six seeds (right dAI, right PI) exhibited significant differences between groups (FDR corrected, $p < 0.05$, cluster size $> 621\ mm^3$) (Fig. 2) (Table 3). For the right dAI, compared with controls, the patients revealed decreased correlations with the bilateral anterior insula and the adjacent inferior frontal gyrus, caudate nucleus and putamen, and bilateral inferior parietal lobe. In addition, patients exhibited increased functional connections with the bilateral postcentral gyrus. For the right PI seeded connectivity analysis, the schizophrenia patients exhibited a decreased connection with the bilateral occipital area, posterior insula, and precentral and postcentral gyrus compared with controls, whereas the functional connection between the right PI and bilateral thalamus was increased in patients compared with controls. According to Fig. S2, the decreased functional connectivity in patients was due to the less positive connectivity in patients, such as the functional connectivity between the bilateral insula and between the insula and the occipital cortex. In addition, the increased functional connectivity in patients was more likely due to the more positive connectivity in patients, such as the functional connectivity between the insula and the bilateral thalamus.

3.3. Correlations between functional properties and clinical variables

The correlational analysis was performed within the patient group to demonstrate the association between the strength of functional connectivity and the clinical variables. Controlling for the effects of age, gender, education level and medication dosage, there was a negative association between the P1 score (delusion) in PANSS and the strength of the functional connectivity between the right PI and the thalamus ($p < 0.01$). In addition, the strength of the functional connectivity between the right PI and the pre- and postcentral gyrus exhibited a significantly negative correlation

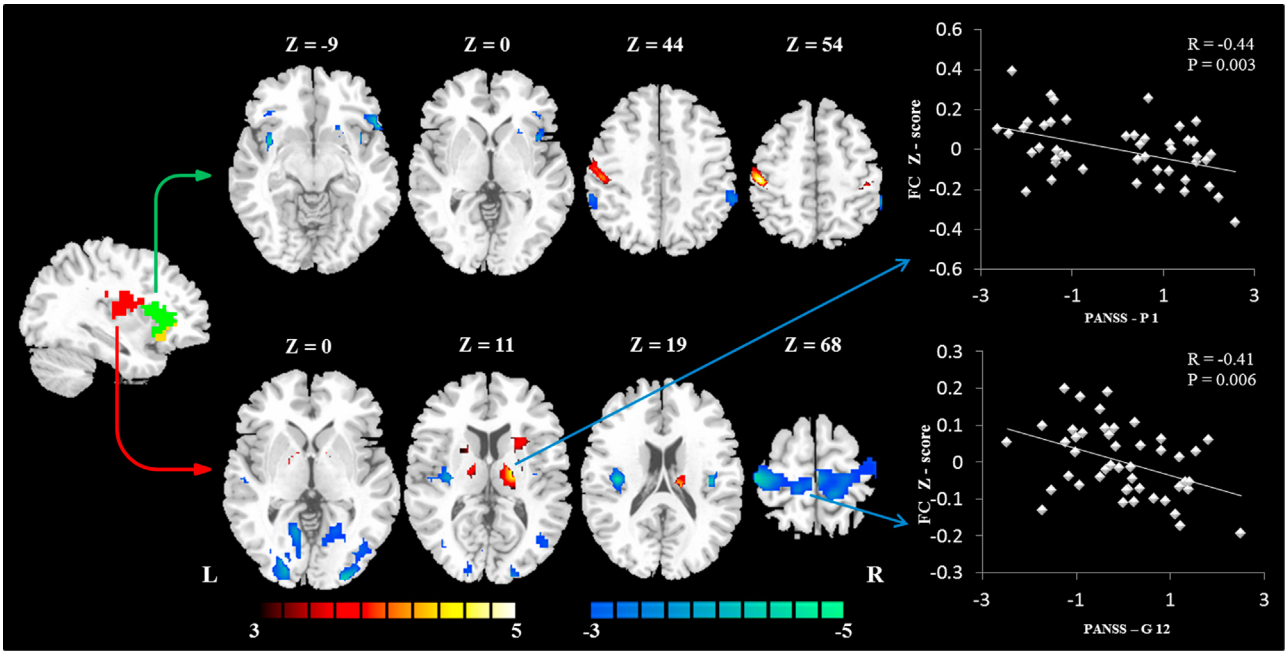

Fig. 2. Group differences in the functional connectivity analysis (FDR corrected, $p < 0.05$, cluster size $> 621\ mm^3$). The upper row represents the group differences of the functional connectivity between the right dAI and the whole brain, and the lower row represents the group differences of the functional connectivity between the right PI and the whole brain. Color scale represents T values from ±3 to ±5.

Table 3
Brain regions with significant group differences in funtional connectivity analysis (FDR corrected, $p < 0.05$, cluster size > 621 mm^3).

ROI	Regions	BA	Center (MNI)	Peak T value
Right dAI	Postcentral_L	2/3	−48, −24, 57	5.40
	Postcentral_R	3/4/6	60, −9, 33	4.21
	Parietal_Inf_L	40	−57, −42, 39	−3.72
	Frontal_Inf_Orb_L	47	−33, 33, −6	−4.01
	Insula_L	48	−36, 6, −12	−4.75
	Parietal_Inf_R	40	60, −45, 48	−4.92
	Frontal_Inf_Orb_R	38	57, 18, −9	−5.07
Right PI	Thalamus_R		18, −12, 6	4.85
	Thalamus_L		−9, 3, −3	4.39
	Occipital_Mid_L	17/18	−24, −93, −9	−4.68
	Occipital_Mid_R	18	30, −99, −6	−4.73
	Insula_R	13	39, −21, 18	−4.76
	Insula_L	13/41	−39, −18, 18	−4.79
	Precentral_R/ Postcentral_R	3/4/6	15, −33, 75	−4.83
	Precentral_L/ Postcentral_L	3/4/6	−15, −30, 78	−6.06

Abbreviations: BA=Brodmann area.

with the G12 score (poor insight) ($p < 0.01$) (Fig. 2).

4. Discussion

Because the insula is supposed to play a cardinal role in psychosis (Palaniyappan and Liddle, 2012), the current study aimed to depict the functional properties of the insula in schizophrenia. Consistent with previous studies, the insula was parcellated into three subregions: the dAI, vAI and PI. The functional connectivity analysis seeded at these subregions showed a decreased functional connection between the bilateral insula in schizophrenia patients compared to controls. The functional connection between the right dAI and the primary sensorimotor system exhibited the opposite pattern as that of the connection between the right PI and the primary sensorimotor system in patients. In addition, the right PI of the patients showed increased functional connection with the bilateral thalamus. These brain functional alterations were related to the severity of the symptoms of schizophrenia.

The present study used a data-driven approach to parcellate the insula and identified three subregions: vAI, dAI and PI. The spatial allocation of these regions extended from the ventral anterior, dorsal anterior to posterior insula, which corresponded to the known cytoarchitectonic patterns (Augustine, 1996) and functional profiles (Kurth et al., 2010) in the insula. The decreased functional connection between the bilateral insula of patients in the current study was consistent with the structural abnormality of the insula in schizophrenia patients identified in previous studies (Shepherd et al., 2012; Virupaksha et al., 2012). Schizophrenia is associated with difficulties to discriminate self-generated sensory stimuli from externally generated stimuli, resulting in a broad range of symptoms (Waters and Badcock, 2010). These deficits may be caused by damage to the function of the insula. The decreased functional coordination between the bilateral insula may suggest a reduced capacity for integrating diverse stimuli and generating appropriate emotional responses in schizophrenia patients.

The PI is a core brain region for processing interoception (Craig, 2002; Heydrich and Blanke, 2013). This information projects first to the spinal cord and brainstem and then to the PI via the posterolateral thalamus, and it terminates in the anterior insular cortex (Craig, 2002). By perceiving the changes in the body's physiological state, the insula forms the interoceptive information (Devue et al., 2007). Disrupted interoception processing may disturb the boundaries of the self and cause self-disorders. In addition, the thalamus acts as an important alert system in the human brain (Matsumoto et al., 2001) and promotes attentional and behavioral shifts to the changing external cues (Smith et al., 2011). The increased functional coordination between the PI and the thalamus in patients might increase the tendency to misattribute self-generated activity to outside sources. This misattribution underlies several symptoms in schizophrenia, especially the positive symptoms (Vukadinovic and Rosenzweig, 2012). The significant negative correlation between the degree of delusion and the functional connection between the right PI and the thalamus identified in our study may be related to this dysfunction.

In contrast, the PI is supposed to anatomically and functionally connect with the primary and secondary somatosensory and motor cortices (Uddin, 2015) and plays a role in multimodal sensory processing (somatosensory, motor and visual) (Lovero et al., 2009). It has been suggested that self-disorder, which is a hallmark characteristic of schizophrenia, may stem from an inability to efficiently integrate multisensory bodily signals (Chen et al., 2015; Duan et al., 2015). Previous studies found that the loss of body ownership may be due to the disintegration of sensorimotor and visual cues caused by damage to the PI (Baier and Karnath, 2008; Heydrich and Blanke, 2013). The decreased functional connection between the PI and the sensorimotor area (pre- and postcentral gyrus and the occipital area) identified in the current study might suggest the abnormal integration of the somatosensory and the visual signals, which may give rise to the breakdown of self-other discrimination (Ebisch et al., 2014, 2013). The ability to discriminate self from others is the foundation of self-reflection that is necessary to generate insight (Dimaggio et al., 2009). Insight means the awareness of the illness (Palaniyappan et al., 2011). It shows a negative relationship with recovery. The functional connection between the right PI and pre- and postcentral gyrus was linked to a decreased degree of insight in schizophrenia patients in the current study, thus suggesting the importance of the right PI in schizophrenia patients.

The right dAI exhibited increased functional interactions with the bilateral pre- and postcentral gyrus. The dAI receives sensory input from the PI. The PI seems to be involved in coding the physical properties of stimuli, whereas the dAI seems to participate in reflecting on the subjective experience of it (Frot et al., 2014; Meier et al., 2015). The finding of altered functional interactions between the PI and dAI and the pre- and postcentral gyrus suggest the damaged integration of the sensorimotor signals that contribute to self-disorder in schizophrenia. The bilateral inferior parietal lobes are important nodes of the central executive network (Menon, 2011). The decreased functional connection between the right dAI and the bilateral inferior parietal lobe may suggest disrupted right dAI modulation of the central executive network, which has often been identified in schizophrenia (Moran et al., 2013). Previous studies have identified that the insular cortex of the right hemisphere is the main input brain area of exteroceptive bodily signals and visceral corporeal signal information (Craig et al., 2000). This is consistent with our findings that the significant relationship was only identified in the right hemisphere.

Our data must be interpreted based on several limitations. First, all patients in the current study were on medication. Previous studies have found that antipsychotic medication may have an impact on the functional connectivity of cortical networks (Lui et al., 2010). Thus, medication might affect the results. Second, the present study did not include task-related fMRI data. The insula is involved in salience processing. Task-free data can elucidate the intrinsic neural predisposition of the brain, while task-related BOLD signals might act differently. By combining the resting-state and task-related fMRI, we may obtain a more detailed picture of

the function of the insula. The last consideration is the seed identification of the insula. Abnormalities in insular volume in schizophrenia have been consistently reported. Thus, we defined the insular cortex according to the AAL in the current study, which may cause some deviations. However, we conducted the functional connectivity analysis based on the intersections of each of the insula subregions across subjects. This operation might compensate to some extent.

In conclusion, the right dAI and PI in schizophrenia patients exhibited altered functional connections with the primary sensorimotor area, and these altered functional properties were correlated with altered self-experience in patients. The results suggested that the insula, especially the right PI, could be highly important in the pathological mechanism of schizophrenia.

Contributors

X C, M-J D, D-Z Y, C L had made a substantial contribution to the conception and design the experiment and drafting and revising the article, then they gave final approval of the version to be published; H H, M Y had made a substantial contribution to the analysis and interpretation of the data, and revising the article critically, and then he gave final approval of the version to be published; B-K B, H X, Y-X L had made a substantial contribution to the acquisition and interpretation of the data, t, then they gave final approval of the version to be published.

Conflict of interest

There is no conflict of interest.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2016.09.006.

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