Journal of Affective Disorders 217 (2017) 118–124

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Transdiagnostic differences in the resting-state functional connectivity of the prefrontal cortex in depression and schizophrenia

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ARTICLE INFO

Keywords:
Depression
Schizophrenia
Functional connectivity
Prefrontal cortex
Machine learning

ABSTRACT

Background: Depression and schizophrenia are two of the most serious psychiatric disorders. They share similar symptoms but the pathology-specific commonalities and differences remain unknown. This study was conducted to acquire a full picture of the functional alterations in schizophrenia and depression patients.
Methods: The resting-state fMRI data from 20 patients with schizophrenia, 20 patients with depression and 20 healthy control subjects were collected. A data-driven approach that included local functional connectivity density (FCD) analysis combined with multivariate pattern analysis (MVPA) was used to compare the three groups.
Results: Based on the results of the MVPA, the local FCD value in the orbitofrontal cortex (OFC) can differentiate depression patients from schizophrenia patients. The patients with depression had a higher local FCD value in the medial and anterior parts of the OFC than the subjects in the other two groups, which suggested altered abstract and reward reinforces processing in depression patients. Subsequent functional connectivity analysis indicated that the connection in the prefrontal cortex was significantly lower in people with schizophrenia compared to people with depression and healthy controls.
Limitation: The systematically different medications for schizophrenia and depression may have different effects on functional connectivity.
Conclusions: These results suggested that the resting-state functional connectivity pattern in the prefrontal cortex may be a transdiagnostic difference between depression and schizophrenia patients.

1. Introduction

Schizophrenia is a complex neuropsychiatric syndrome that is characterized by a constellation of symptoms, such as delusion and hallucination. Depression is an affective disorder that is characterized by the presence of a persistent negative mood state (Wang et al., 2012). They are two of the most serious psychiatric disorders and are treated as distinct entities. However, several clinical features, such as affective disruption and cognitive dysfunction, can be observed in both disorders (Anticevic et al., 2015). An alteration of the dopamine system is implicated in both depression and schizophrenia (Gradin et al., 2011). In addition, there is an increased risk of schizophrenia within the family with a proband with a mood disorder and vice versa (Berrettini, 2000; Bramon and Sham, 2001). It seems that the two diseases have generally overlapping pathophysiological aspects as well as disease-specific mechanisms (Guo et al., 2013; Dong et al., 2017). Until now, the clinical identification of the two disorders has largely been based on self-reported symptoms and clinical experiences. Objective indicators should be explored more fully.

In numerous studies, researchers have used neuroimaging techniques to study the brain's functional properties in people with mental disorders. Decreased frontal lobe activity, especially in the medial prefrontal cortex, was the most consistent finding in association with depression (Wang et al., 2012). In people with schizophrenia, abnormal connectivity within the default mode network was often identified (Whitfield-Gabrieli et al., 2009; Salvador et al., 2010). Previous study assessed transdiagnostic aberrations of default mode network in schizophrenia and depression patient (Schilbach et al., 2016). They identified a common reduction of the functional connectivity between precuneus and bilateral superior parietal lobe. In addition, the func-

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http://dx.doi.org/10.1016/j.jad.2017.04.001
Received 22 December 2016; Received in revised form 22 February 2017; Accepted 2 April 2017
Available online 04 April 2017

tional connectivity between the anterior and posterior nodes of the default mode network decreased specifically in schizophrenia. Since resting-state fMRI often acquires good compliance, it serves as a useful tool in the study of psychiatric disorders (Duan et al., 2015; Chen et al., 2016). Recently, studies used resting-state functional connectivity as the distinguishing feature to classify people as having schizophrenia (Shen et al., 2010; Arbabshirani et al., 2013; Cetin et al., 2015) or depression (Zeng et al., 2014; Patel et al., 2015) or as being a healthy control. One of the classification methods is a data-driven classification technique called multivariate pattern analysis (MVPA),[1] which can assess the contribution of multiple voxels simultaneously. The major advantage of MVPA is that it can detect subtle spatially distributed information. In psychiatric disorders, it may provide information to promote understanding of the neural mechanisms underlying the pathophysiology of disorders (Zeng et al., 2012).

In the current study, we explored disorder-specific differences in resting-state functional connectivity by testing whether the observed connectivity alterations are more pronounced in one patient group than the other. Human brain has some interconnection hubs to support fast communication. Alteration of their configuration may link to various neuropsychiatric diseases. Most previous studies used seed regions to identify the functional connectivity between brain areas. However, this method relies on a priori selection of the seed regions. This conduction may bring bias and is computationally demanding. Thus, a voxel-wise data-driven method, local functional connectivity density mapping (local FCD), which delineates the distribution of brain functional connectivity hubs in the local area (Tomasi and Volkow, 2010) and refines our understanding of the schizophrenia and depression connectopathy (Mehta, 2017), was used first with the resting-state fMRI data to evaluate the functional features among schizophrenia patients, depression patients and healthy controls. This conduction could provide us with the brain hubs in the local area which with different distribution between three groups. Then, MVPA was conducted on the FCD maps to differentiate among the groups. The whole-brain functional connectivity patterns of the most discriminative brain areas were further analysed. We predicted that people with schizophrenia and depression would exhibit an altered functional connectivity pattern in some brain areas, specifically the frontal lobe, and these changes may contribute to the clinical identification of the two diseases.

2. Methods

2.1. Participants

This study involved the recruitment of 20 depression patients, 20 schizophrenia patients and 20 healthy controls. The participants were matched on age, gender and years of education and provided written informed consent individually. Participants with a history of acute physical illness, substance abuse, head injury or neurological illness were excluded. The patients were all recruited from the inpatient and outpatient departments at Chengdu Mental Health Center and diagnosed according to the DSM-VI Axis I Disorder-Clinical Version (SCID-I-CV) by two clinical psychiatrists independently. The Positive and Negative Syndrome Scale (PANSS) was used to assess the symptom severity of schizophrenia patients. The Hamilton Depression Rating Scale (HDRS) was used to assess the depressive symptoms of the depression patients. Assessments of six depression patients were missing. All patients were on medication. More details are provided in the supplementary materials. This experimental procedure was approved by the Ethics Committee of Chengdu Mental Health Center in accordance with the Declaration of Helsinki.

2.2. Data acquisition and image pre-processing

Resting-state fMRI data were acquired using a 3 T MRI scanner (GE Discovery MR 750, USA) at the Center for Information in Medicine (CIM) of the University of Electronic Science and Technology of China (UESTC). The scan (8.5-min runs) used a gradient-echo echo-planar imaging sequence. The imaging parameters were as follows: repetition time $=2$ s, echo time $=30$ ms, flip angle $=90^{\circ}$, matrix size $=64\times64$, and in-plane voxel size $=3.75\times3.75\times4$ mm. A total of 255 volumes were collected for each subject. Each functional volume contained 35 slices.

Image pre-processing was completed in SPM 8 (http://www.fil.ion.ucl.ac.uk/spm8). To minimize the effects of scanner signal stabilization, the first five volumes of each subject were excluded from all analyses. The remaining images were slice-time corrected, realigned and spatial normalized ($3\times3\times3$ mm^3). The six head motion parameters were calculated for each subject. Participants with an excessive head motion (a maximum displacement exceeding 2 mm in any cardinal direction or a maximum spin exceeding 2 degrees) were excluded from the subsequent analyses. The six head motion parameters were further regressed as nuisance signal in the subsequent functional connectivity analysis. In addition, head motion differences among the groups were compared. This analysis was conducted by averaging the frame-wise displacement from every time point for each participant (Power et al., 2012). Then, the resulting images were temporally band-pass filtered (0.01–0.08 Hz) (Fox et al., 2005).

2.3. Local FCD analysis

We used local FCD analysis to identify efficient hubs in the brain. For any given voxel, the number of functional connections between the target voxel and its adjacent voxels was computed. First, Pearson correlations between the time courses of the voxel and its neighbour voxels were calculated. The significance of the functional connection was identified according to a given threshold. The voxels that had a significant functional connection to the target voxel were added to a mass surrounding the target voxel. Next, the functional connectivity between the target voxel and the adjacent voxels to the voxels in the mass were calculated. If the functional correlation coefficients were larger than the given threshold, these new voxels were also added to the mass. This conduction was repeated iteratively until the boundary of the mass was determined. The number of voxels in the mass was assigned to the target voxel. This calculation was performed for all voxels. Then, the individual map was created by dividing by the mean value of the map. The local FCD map was defined and then spatially smoothed with an isotropic Gaussian kernel (8 mm full width at half maximum (FWHM)).

In a previous study (Tomasi and Volkow, 2010), the threshold was generally set at 0.6. Here, to obtain reliable results, we used multi-threshold levels (range: 0.5–0.75 stepped by 0.05) to determine the significance of the functional connection. Thus, there were six local FCD maps for each subject.

2.4. MVPA

MVPA based on the local FCD maps was conducted to differentiate the depression and the schizophrenia groups. In the current study, we combined the searchlight algorithm and PCA to extract features (Liu et al., 2012). Local FCD maps of 0.6 threshold served as inputs and were divided into the training set and the testing set. In the training set, according to the searchlight algorithm, the values of the voxels in a 27-voxel spherical cluster were extracted. Then, PCA was applied. The eigenvector, which had energy larger than 99%, was reserved as the

[1] MVPA: multivariate pattern analysis
FCD: functional connectivity density
PANSS: The Positive and Negative Syndrome Scale
HDRS: The Hamilton Depression Rating Scale
GRF: Gaussian random field
OFC: orbitofrontal cortex

Table 1
Demographic and clinical profiles of the participants.

	Depression (M^1 ± SD)	Schizophrenia (M^1 ± SD)	Healthy control (M^1 ± SD)	Statistical evaluation
Age (years)	41.8 ± 14.2	40.3 ± 13.8	41.6 ± 13.6	$\chi^2 = 0.142$; df = 2; $p = 0.931$[a]
Gender	13F; 7M[2]	11F; 9M[2]	13F; 7M[2]	$\chi^2 = 0.564$; df = 2; $p = 0.754$[b]
Education level (years)	11.3 ± 2.6	10.9 ± 2.7	10.4 ± 2.9	$\chi^2 = 2.372$; df = 2; $p = 0.305$[a]
Handedness (%right)	100%	100%	100%	
PANSS: positive		12.9 ± 5.6		
PANSS: negative		18.0 ± 7.0		
PANSS: general		27.8 ± 5.3		
PANSS: total		58.7 ± 12.5		
HDRS	5.3 ± 1.3			

Abbreviations: M^1 = Mean value; SD = Standard deviation; M^2 = Male.
[a] Kruskal-Wallis test;
[b] Chi-square test.

final classification feature and assigned to the center voxel of the spherical cluster. This conduction had been done across the whole brain. Afterwards, a linear support vector machine (SVM) classifier was conducted using MATLAB software.

Leave-one-out cross-validation was performed to assess the overall accuracy of the classifier. In each cross-validation test, one sample was used as the test set, and the rest of the sample was used as the training set. The accuracy of each voxel was defined by averaging all the accuracies obtained from the validation tests. The resulting spatial accuracy map was used to detect brain regions that successfully differentiated the two patient groups. Clusters that had an accuracy of higher than 70% were considered to be meaningful.

2.5. Statistical validation of the MVPA results

To validate the MVPA results, group differences were evaluated using one-way ANOVA, after controlling for the effects of age and gender ($p < 0.01$ with a cluster size > 621 mm^3). To obtain reliable results, the regions in which the clusters exhibited a dominant difference in all 6 comparisons (responded to the six correlation coefficient thresholds) were identified as significant group differences.

In addition, only the brain areas within the areas identified in the MVPA were included in the subsequent analyses. They were regarded as meaningful brain areas and used as regions of interest (ROIs) in the functional connectivity analysis.

As 0.6 was always chosen as the threshold to determine local FCD (Tomasi and Volkow, 2010; Luo et al., 2014), *post hoc* Bonferroni comparisons were conducted for the local FCD maps with the same threshold in SPSS version 19 for Windows.

2.6. Functional connectivity analysis

After spatial smoothing (Gaussian kernel with an 8-mm FWHM), nuisance signal regression (head motion parameter, white matter, cerebrospinal fluid and global mean signals) and filtering (0.01 − 0.08 Hz) (Fox et al., 2005), the resulting images were used to calculate the Pearson's correlation coefficients between the time course of the ROI and the time course of all the other voxels in the brain. Fisher's transformation was used to convert the correlation coefficients to normally distributed z-scores.

In the second-level analysis, connectivity maps from three groups were entered a three-level ANOVA, after controlling for the effects of age and gender. Multiple comparison correction was performed based on Gaussian random field (GRF) theory. The GRF, however, may have a limitation for clusterwise inference. According to the suggestion from the previous study (Eklund et al., 2016), we further applied permutation test (Winkler et al., 2014) which was based on PALM package in DPABI (http://rfmri.org/dpabi) in the current study. Permutation number was 5000 and cluster forming threshold (z) was 2.3. A kind of acceleration method (few permutations) which is embedded in the PALM was used. This conduction was consider to be valid for any spatial autocorrelation function. Regions from the ANOVA that survived correction were further examined in post hoc Bonferroni analyses in SPSS version 19 for Windows.

To investigate whether imaging parameters in the patient groups correlated with illness severity measures, partial correlations between the average z-scores of the 27 voxels in a cube with the center at the peak values of the local FCD difference or the functional connection difference and clinical features (disease duration, PANSS and HDRS scores) were calculated. Age, gender and education level were treated as covariates.

3. Results

No subjects were excluded because of excessive motion. In addition, there was no significant difference in mean head motion among the three groups (one-way ANOVA, $F = 2.871$, $p = 0.065$). The demographic and clinical information for the participants is shown in Table 1.

3.1. Local FCD map

The average distribution of the local FCD for the six thresholds for each of the three groups is illustrated in the supplementary materials (Fig. S1). Regions located in the posterior cingulate gyrus, precuneus and occipital cortex had a high local FCD value. This pattern was consistent with that found in previous studies (Tomasi and Volkow, 2010; Chen et al., 2015).

3.2. MVPA

As shown in Fig. 1(a), the local FCD value in the prefrontal cortex, especially in the orbitofrontal cortex (OFC), had a discriminative effect, distinguishing patients with depression from those with schizophrenia. In terms of accuracy, 85% of schizophrenia and depression cases were correctly classified. The average accuracy was 79% with a specificity of 98% and a sensitivity of 60%.

3.3. Statistical validation of the MVPA results

One-way ANOVA was used to examine group differences. These differences are illustrated in Fig. 1(b). There were stable differences among the groups in the OFC, cerebellum and paracentral lobule (ANOVA $F(2, 57)$, $p < 0.01$ with a cluster size > 621 mm^3). We focused on the area located at the prefrontal cortex. Thus, the region located at the OFC (Montreal Neurological Institute coordinate: x = − 9, y = 48, z = − 21) was used as an ROI in subsequent analyses.

In addition, the nature of the differences was examined via *post hoc* pairwise comparisons. In OFC, the depression group exhibited a

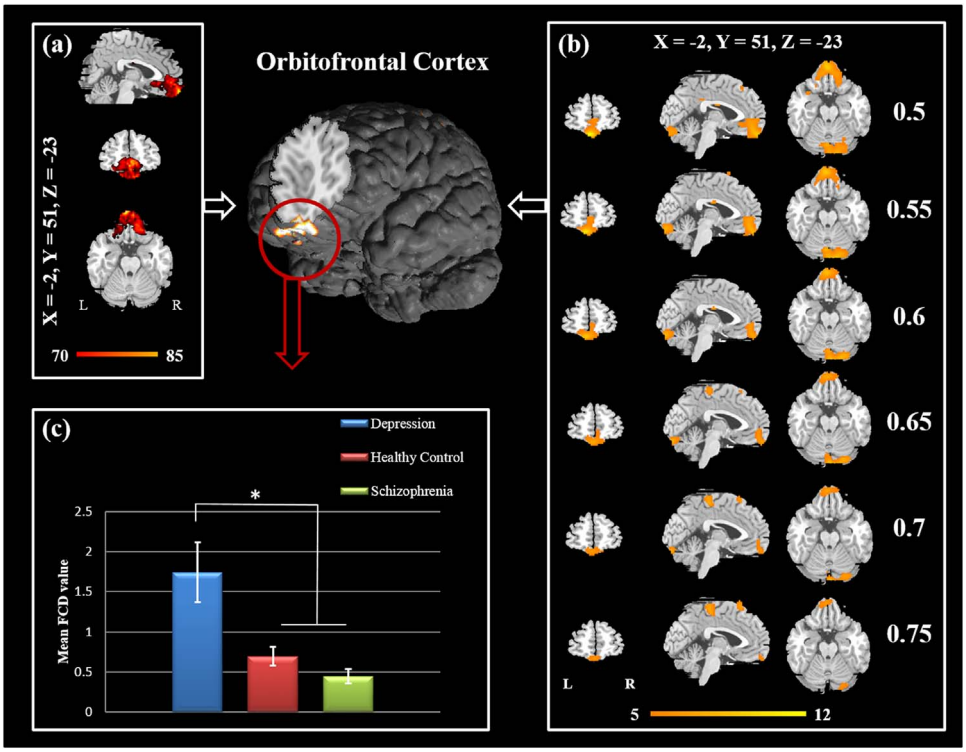

Fig. 1. Part (a) MVPA identified that the orbitofrontal cortex had a discriminative effect. The colour bar represents the accuracy level; part (b) Stable group differences of the six thresholds were found in the orbitofrontal cortex, pre- and post-central gyrus and cerebellum. The colour bar represents the F value; part (c) *Post hoc* pairwise comparisons found that the depression group exhibited a significantly higher local FCD value in the orbitofrontal cortex than the other two groups. L: left, R: right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

significantly higher local FCD value ($p < 0.05$). This pattern differed from both the healthy control and the schizophrenia groups (Fig. 1(c)).

3.4. Functional connectivity analysis

The spatial distribution of the functional connectivity map of each of the three groups is illustrated in Fig. 2(a) (one-sample *t*-test, $p < 0.05$, FDR corrected, cluster threshold > 621 mm^3). The group differences were obtained via one-way ANOVA) (Fig. 2(b)) (Table 2). Then, *post hoc* pairwise comparisons were conducted. The schizophrenia group exhibited significantly declined functional connection within the prefrontal cortex ($p < 0.05$). This pattern differed significantly from that of both the depression and the control groups (Fig. 2(c)).

The results of the same conduction without global mean signal regression are presented in the supplementary materials. It seemed that the global mean signal regression did not have a major impact (Fig. S2).

In addition, in the depression group, there was a correlation between the local FCD value in the OFC and HDRS score ($r = -0.5736$, $p = 0.032$). This correlation was not significant after correcting for the multiple comparisons. There was no significant correlation between the remaining clinical parameters.

4. Discussion

In the current study, we used a data-driven approach, specifically local FCD analysis combined with MVPA, to compare the resting-state functional connectivity among depression patients, schizophrenia patients and health controls. Our findings showed that local FCD in the OFC can differentiate depression patients from schizophrenia patients. Subsequent functional connectivity analysis indicated that the connection within the prefrontal cortex was significantly lower in people with schizophrenia. These results suggested that the functional connectivity pattern of the prefrontal cortex might be a diagnosis-specific alteration in schizophrenia and depression.

There is evidence of a failure in prefrontal cortex modulation in association with schizophrenia and depression. The prefrontal cortex always exhibits pronounced gray matter reduction in schizophrenia (Zipursky et al., 1992). Studies of depression treatment found that prefrontal TMS or ECT can have considerable clinical effectiveness (Lisanby et al., 2009). Functional neuroimaging showed that the prefrontal cortex exhibits hypoactivity in schizophrenia (Hill et al., 2004) and hyperactivity in depression (Northoff et al., 2011). In the current study, the OFC could distinguish patients with depression from those with schizophrenia successfully. The OFC receives almost all types of sensory stimuli from other cortical regions and evaluates them based on their associations with current needs (Sakurai, Gamo et al., 2015). The OFC is involved in sensory integration to represent the affective values of reinforces. This function is important for associative learning and reversal learning (Ongur and Price, 2000; Bissonette et al., 2013). Then, the OFC plays an important role in choosing objects as goals for future behaviours. In addition, previous neuroanatomical and neuropsychological studies proposed two distinct trends in relation to the OFC. The first is the medio-lateral distinction. The medial part of the OFC processes the rewards, while the lateral part processes punishments. The second is the posterior-anterior distinction. Complex or abstract reinforces are represented in the anterior part of the OFC, while primary reinforces are represented in the posterior part (Kringelbach and Rolls, 2004). Depression is mainly considered to be a mood disorder with deficits in hedonics and motivation. The affective deficit is the most significant deficit in depression (Pizzagalli et al., 2009). In the current research, people with depression exhibit the highest local FCD in the OFC, especially the medial and anterior parts, suggesting altered function in processing abstract, rewards in association with depression. Individuals with depression often have reduced self-reported and physiologically marked responses to reward stimuli (Bylsma et al., 2008) and frequently exhibit attenuated responsiveness to pleasant stimuli and monetary gains (Sloan et al., 2001). In addition, correlational analysis within a group of people with depression revealed

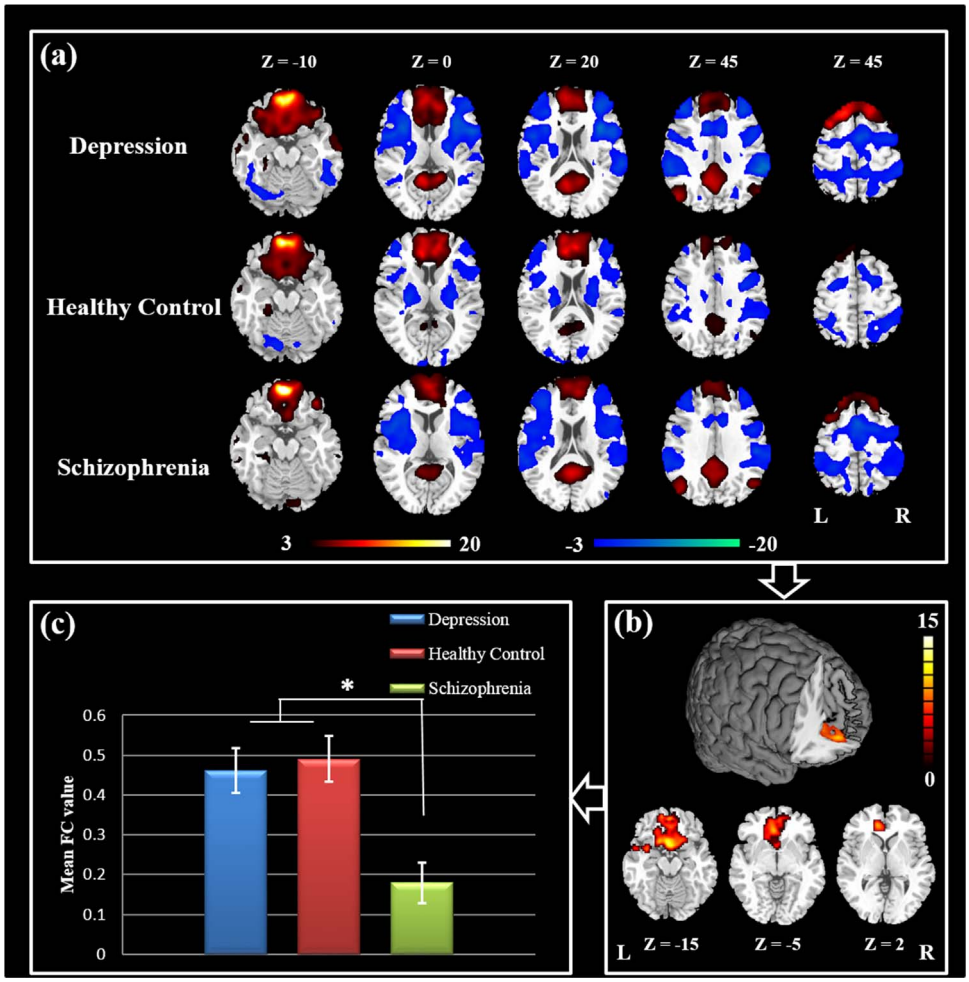

Fig. 2. Part (a) The spatial distribution of the functional connectivity map of the three groups, and the colour bar represents the T value; part (b) The functional connection within the prefrontal cortex exhibited significant group differences, and the colour bar represents the F value; part (c) *Post hoc* pairwise comparisons found that the schizophrenia group exhibited a significantly declined functional connection within the prefrontal cortex than the other two groups. L: left, R: right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

a negative association between the local FCD value in the OFC and HDRS score. In light of these findings, altered local FCD in the OFC may represent a disorder-specific aspect of depression.

In the current study, people with schizophrenia exhibited reduced functional connectivity in the prefrontal area. Previous studies found that among the regions implicated in the pathophysiology of schizophrenia, the prefrontal cortex is of great interest (van den Heuvel and Fornito, 2014). The reduced density of neuron (Enwright et al., 2016) and reduced protein levels (Pinacho et al., 2016) were often identified in the dorsolateral prefrontal cortex in schizophrenia patients. In addition, the reduced middle prefrontal cortex gray matter volume (Maat et al., 2016) and activation (Razafimandimby et al., 2016) identified in schizophrenia were often associated with social cognitive deficits. Functional connection within the prefrontal cortex was also decreased in schizophrenia and their unaffected first-degree relatives (Barbalat et al., 2011; Su et al., 2013). In detail, the prefrontal cortex can be subdivided into several sub-regions according to the different connections and functions. The OFC receives almost all kinds of sensory information and evaluates them (Bissonette et al., 2013). The medial prefrontal cortex is involved in emotion processing and social behaviour, and the dorsal lateral prefrontal cortex plays a crucial role in executive function (Chudasama, 2011). Moreover, the ventral lateral

Table 2
Brain regions with significant group differences of functional connection.

Brain regions	Cluster size	Center (MNI)			*F* value	*p*-value of permutation test[b]
	(voxels)[a]	x	y	z		
Anterior cingulate cortex Inferior frontal gyrus Olfactory cortex Gyrus rectus Superior frontal gyrus Medial frontal gyrus	1692	−2	34	−12	5.591	0.02

Abbreviations: MNI = Montreal Neurological Institute.
[a] The cluster size represents the number of voxels within the cluster.
[b] The *p*-value for a given cluster corresponds to the rank in the null distribution, which is composed by the maximum cluster size across all voxels for each permutation.

prefrontal cortex primarily is involved in visual, memory and language processing (Badre and Wagner, 2007; Grodzinsky and Santi, 2008; Petrides et al., 2012). The reduced interconnection within these brain areas may reflect the impaired executive function and social cognitive function in schizophrenia. In addition, schizophrenia is regarded as a disease of abnormal brain development. The maturation of connectivity in the local circuitry of the prefrontal cortex is slower than in any other brain region (Teffer et al., 2013; Ueda et al., 2015). The maturation period during which the structural and functional circuitry remodels through synaptic pruning extends to puberty (Stoneham et al., 2010). This period is easily affected by genetic and environmental damage, inflammation and stress, which cause cognitive deficits (Sakurai et al., 2015). If there are additional insults during puberty that exceed what the brain can tolerate, the system may shut down, resulting in a hyperdopaminergic status. Consequently, the person may experience hallucination, delusion and psychosis (Uhlhaas and Singer, 2013). Thus, the decreased functional connectivity in the prefrontal cortex in schizophrenia found in the current study may reflect the impaired remodelling process in this area associated with schizophrenia.

Our study had several limitations. First, the systematically different medications for schizophrenia and depression may have different effects on functional connectivity. This source of variance may have acted as a major confound in transdiagnostic analyses. In addition, the medicated patients were in stable condition, this may have an impact on the functional connectivity of cortical networks. Second, this work lacked related assessments, such as cognitive function, affective function and IQ assessment tests. These assessments should be included in future works. In addition, potential confounding effect which caused by head motion might exist since previous study identified a correlation between the reduced distant functional connectivity and high head motion. Finally, the relatively small sample may have yielded unreliable results. Our findings should be confirmed with a larger sample in the future.

In conclusion, the current study showed that the local FCD value of the OFC can differentiate depression patients from schizophrenia patients. People with depression exhibited higher local FCD in the OFC compared to those with schizophrenia, which suggested that there was altered function in abstract, reward processing in depression patients. Moreover, subsequent functional connectivity analysis indicated that schizophrenia patients showed significantly lower functional connection in the prefrontal cortex compared to depression patients and healthy controls. These findings, which resulted from combined functional connectivity analysis and machine learning, suggested that the functional property of the prefrontal cortex might be of great importance in the diagnosis of schizophrenia and depression and warrants greater attention.

Author disclosure

None.

Contributors

X C, L C, H H 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; X C, Y-C J 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; Y-J L, J-F L, M-J D, D-Z Y and C L had made a substantial contribution to the acquisition and interpretation of the data, then they gave final approval of the version to be published.

Role of the funding source

This study was supported by the National Nature Science Foundation of China (81471638, 81330032, 81571759), Special-Funded Program on National Key Scientific Instruments and Equipment Development of China (2013YQ490859), the Chinese Fundamental Research Funding for Central Universities (ZYGX2015J09), the Program for Changjiang Scholars and Innovative Research Team (IRT0910) and the 111 project (B12027).

Conflicts of interest

There is no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jad.2017.04.001.

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