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