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Classification of Bipolar Disorder using Basal-ganglia-related Functional Connectivity in the resting state

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Abstract—**The emotional and cognitive symptoms of bipolar disorder (BD) are suggested to involve in a distributed neural network. The resting-state functional magnetic resonance imaging (fMRI) offers an important tool to investigate the alterations in brain network level of BD. The aim of this study was to discriminate BD patients from healthy controls using whole-brain resting-state functional connectivity patterns. The majority of most discriminating functional connectivities were between the basal ganglia and three core neurocognitive networks, including the default mode, executive control and salience networks. Using these resting-state functional connectivities between the basal ganglia and three core neurocognitive networks as the features, the clustering accuracy achieved 90%.**

I. Introduction

Bipolar disorder (BD) is a mood disorder with a prevalence of at least 1% and creates a considerable health care burden [1]. The hallmark symptoms of BD are extreme mood fluctuations known as depression and mania. The abnormal mood swings in BD patients influence their behaviors and cognitive function, such as sustained attention [2], psychomotor speed [3] and decision-making [4]. It has been proposed that these emotional and cognitive symptoms involve in a distributed neural network rather than an individual brain region [5]. Hence, investigating the alterations in the brain network level can be helpful to understand the pathophysiology of bipolar disorder.

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The resting-state functional magnetic resonance imaging (fMRI) has been used to map large-scale brain network by estimating the functional interactions between brain regions, namely, the functional connectivity. The functional connectivity between brain regions during resting state is the similarity of spontaneous fluctuations in the blood-oxygenation-level-dependent (BOLD) signal of fMRI [6]. Several studies have revealed that the resting-state functional connectivity maps mirror brain functional networks, including the sensorimotor, auditory, visual, executive control (ECN), and default mode (DMN) networks [7]. The whole-brain resting-state functional connectivity patterns have been used to identify cognitive states [8] and psychiatric disorders, such as major depression [9].

This study aims to discriminate BD patients from normal controls (NC) using whole-brain resting-state functional connectivity patterns. The functional connectivity was estimated between each pair of 90 functional regions of interests in the 14 resting-state networks, which were previously identified by independent component analysis [8]. We expected that BD patients may present a different connectivity pattern of the resting-state networks associated with the emotional and cognitive processing compared with NC. The altered connectivity patterns can be used as features to classify BD and NC.

II. Material and Method

A. Participants

This study was conducted under the approval of the Institutional Review Board of Taipei Veterans General Hospital. Fifteen patients with bipolar I disorder (mean age, 42.9 years; 10 men) were recruited from Taipei Veterans General Hospital. Clinical psychiatrists confirmed the diagnosis of all patients using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Before acquiring fMRI images, the depressive and manic symptoms of BD patients were rated using the Hamilton Depression Rating Scale (HAMD, 7.8±7.6) and the Young Mania Rating Scale (YMRS, 3.6±4.4), respectively. Sixteen age- and gender-matched normal controls (mean age, 43.4 years; 11 men) with no history of psychiatric illness, neurological or physical disorders, alcohol or drug dependence, or electroconvulsive therapy were also recruited. All participants were right-handed and gave voluntary and informed consent.

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B. Imaging data acquisition and preprocessing

Functional imaging was performed on a Discovery MR750 3T system (GE Healthcare, USA) at Taipei Veterans General Hospital. The whole brain volume was acquired in 43 axial slices using an echo planar imaging (EPI) sequence. The resting fMRI contained 200 volumes with the following parameters: slice thickness of 3.5 mm, interslice gap of 1 mm, repetition time (TR) of 2500 ms, echo time (TE) of 30 ms, flip angle of 90°, field of view (FOV) of 222×222 mm^2, and matrix size of 64×64. Each participant was scanned for approximately 500 s while resting in a supine position with eyes closed. Structural 3D T1-weighted images were obtained using a rapid acquisition gradient echo for each participant (TR = 12.2 ms, TE = 5.2 ms, flip angle = 12°, FOV = 256×256×168 mm^3, and matrix size = 256×256×168). The preprocessing of functional analysis was conducted using SPM8, including slice-timing, realignment, spatial normalization and smoothing.

C. Functional parcellation and functional connectivity matrix

We parcellated the normalized EPI images using 90 functional regions of interests (fROIs) which were generated from 14 functional networks by Shirer et al. [8]. The 14 functional networks, including the precuneus, basal ganglia, sensorimotor, auditory, high visual, primary visual, language, visual spatial, dorsal and ventral DMN, bilateral ECN, anterior and posterior SN, were extracted by independent component analysis. The regional time series in each of the 90 fROIs was obtained by averaging the fMRI time series over all voxels in the fROI. The influence of head motion, the confounding effects of CSF and white matter, and the global mean were regressed out to eliminate the effects of physiological noise [10]. Each regional time series was further temporally band-pass filtered (0.01-0.08 Hz) to reduce the effects of low-frequency drift and high-frequency physiological noise [11]. All filtered time series were subsequently used to estimate functional connectivity.

Functional connectivity between each pair of filtered time series for each participant was estimated using a Pearson correlation to construct a 90×90 correlation matrix. Fisher's r-to-z transformation was applied to the correlation matrix to ensure the normality of the correlation coefficients for subsequent statistics.

D. fROI-based representative connectivity matrix construction

To obtain the representative connectivity matrices for each group, we performed a one-sample t-test across all participants for each entry of the 90×90 correlation matrix (Fig. 1a). We selected top 500 entries (a network with a sparsity of 12%) [12] from the lower triangle correlation matrix that were most significant in each group to maintain the same connectivity density between groups. The significant *p* values of the top 500 entries were smaller than 0.0005 for BD group and 0.0001 for NC group, respectively (Fig. 1b). Any entry that was significant for both groups were excluded and set to be zero. Therefore, these criteria retained 202 entries of interest for each group. This resulted in between-fROI functional connectivity matrix with strong positive or negative correlations that were consistent across participants and unique to a particular group (Fig. 1c).

E. Network-based representative connectivity matrix construction

To investigate the BD-dominant functional network, we re-constructed the fROI-based representative matrix into a network-based representative matrix with 14×14 entries. We applied the 'winner-take-all' strategy to assign each entry of the network-based representative matrix to either BD or NC groups. If the number of retained entries of the fROI-based representative matrix in BD is twice as many as that in NC, we assigned the entry of the network-based representative matrix to BD group (Fig. 1d orange entries), and vice versa (Fig. 1d green entries). Otherwise, the entry of the network-based representative matrix was set to zero (Fig. 1d white entries). The diagonal elements of the network-based representative matrix stand for the intra-network connections, and the off-diagonal ones stand for the inter-network connections.

F. Classification of BD and healthy participants

We used an unsupervised clustering method, the hierarchical clustering, to detect dissimilarities of resting-state functional connectivity for classification of BD and normal controls. Hierarchical clustering is a means to carry out grouping in a data set based on a created cluster tree with multilevel hierarchy, where clusters at one level are joined as clusters at the next higher level. Hierarchical clustering consists of three major parts: (1) find the dissimilarity between each pair of feature vectors in the data set; (2) group the feature vectors into a binary and hierarchical cluster tree; (3) determine what level or scale of clustering by cutting the hierarchical tree. Many algorithms are available in regard to the calculation of dissimilarity and the creation of cluster tree [13]. In this study, we adopted the Euclidean distance to calculate the dissimilarity, which was defined by

$$d_{rs}^2 = (x_r - x_s)^T (x_r - x_s) \tag{1}$$

where d_{rs}^2 is the Euclidean distance between two featured column vectors x_r and x_s. In order to construct the cluster tree, we employed the Ward's method to measure the distance between two clusters which was defined by

$$d^2(p,q) = n_p n_q \frac{\left\| \bar{x}_p - \bar{x}_q \right\|_2^2}{(n_p + n_q)} \tag{2}$$

where $d^2(p,q)$ is the distance between two clusters of featured vectors, n_p and n_q are the numbers of featured

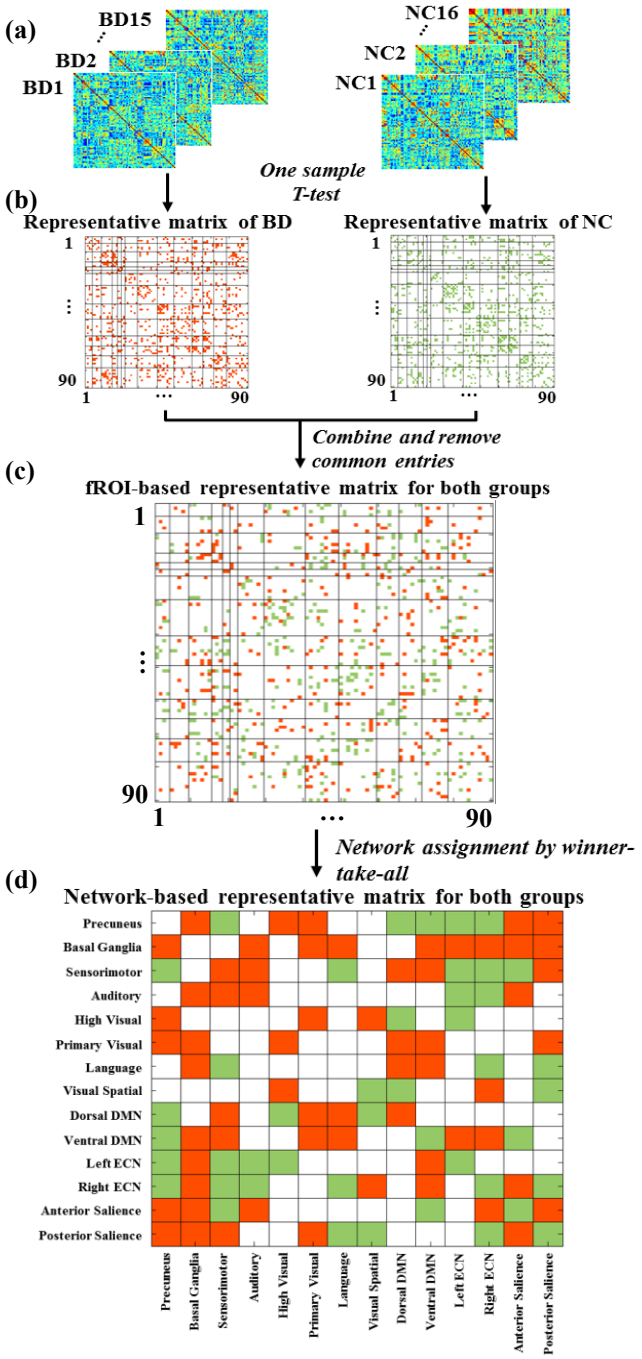

Figure 1. Identification of bipolar-related functional connectivity pattern. Each entry of the 90×90 correlation matrix across all participants (a) was performed one-sample *t*- test to obtain the representative connectivity matrices for each group (b). (c) The fROI-based representative matrix was obtained by combining the representative matrices of two groups and removing common entries. (d) The network-based representative matrx was obtained using 'winner-take-all' strategy.

vectors in cluster p and q, respectively, $\|\ \|_2$ is the Euclidean distance, $\bar{x}_p$ and $\bar{x}_q$ are the centroids of clusters p and q, respectively, which are defined by

$$\bar{x}_p = \frac{1}{n_p}\sum_{i=1}^{n} x_{pi} \quad \text{and} \quad \bar{x}_q = \frac{1}{n_q}\sum_{j=1}^{m} x_{qj} \tag{3}$$

where x_{pi} is the ith featured vector in cluster p and x_{qj} is the jth objects in cluster q.

The grouping procedure was initiated with N clusters (N is the total number of BD and NC) and any two clusters with the minimal values are grouped together into one cluster based on the Ward's method. These newly formed clusters then link to each other and to other featured vectors to create bigger clusters until all the featured vectors are linked together in a hierarchical tree. Finally, we cut the hierarchical tree into 2 clusters to classify BD patients and normal controls.

III. Results

A. *Functional networks related to basal ganglia presented a unique pattern in BD*

Along the column direction of the network-based representative matrix, BD patients presented the dominantly and consistently strong functional connectivities between the basal ganglia (the second column) and 9 functional networks (Fig. 1d). Three of 9 basal-ganglia-related functional networks, including the auditory, primary visual and language networks, were associated with the interaction with the external world. The remaining basal-ganglia -related functional networks, including the DMN (ventral part and precuneus), bilateral CEN, and anterior and posterior SN, were associated with the core neurocognitive functions. In the fROI-based representative connectivity matrix, there were 20 functional connectivities in these 9 basal-ganglia-related functional networks. These 20 functional connectivities were regarded as features to classify BD and NC.

The hierarchical clustering method correctly identified 84% of total participants (26 of 31 participants). The accuracy for BD patients was 87% (13 of 15 participants), and for healthy controls was 81% (13 of 16 participants).

B. *Significant different functional connectivity between the basal ganglia and three core neurocognitive networks in BD*

Eight of 20 basal-ganglia -related functional connectivities were significantly different between BD and NC groups (two-sample *t*-test, $p<0.05$ with FDR correction, see Fig. 2a). Five significantly increased functional connectivities were from the basal ganglia to the primary visual network (left thalamus), the ventral DMN (right parahippocampal gyrus), the left CEN (left parietal gyrus, precunues, and angular gyrus), and the anterior SN (left insula). Three significantly decreased functional connectivities were from the basal ganglia to the precuneus network (precuneus), the ventral DMN (right retrosplenial cortex and posterior cingulate cortex), and the right CEN (right caudate).

Using the 8 basal-ganglia-related functional connectivities with significantly difference between BD and NC groups as the features, the classification rate improved to 90% of total participants (28 of 31 participants). The hierarchical clustering method correctly identified 87% (13 of 15 participants) of BD patients and 94% (15 of 16 participants) of NC (Fig. 2b).

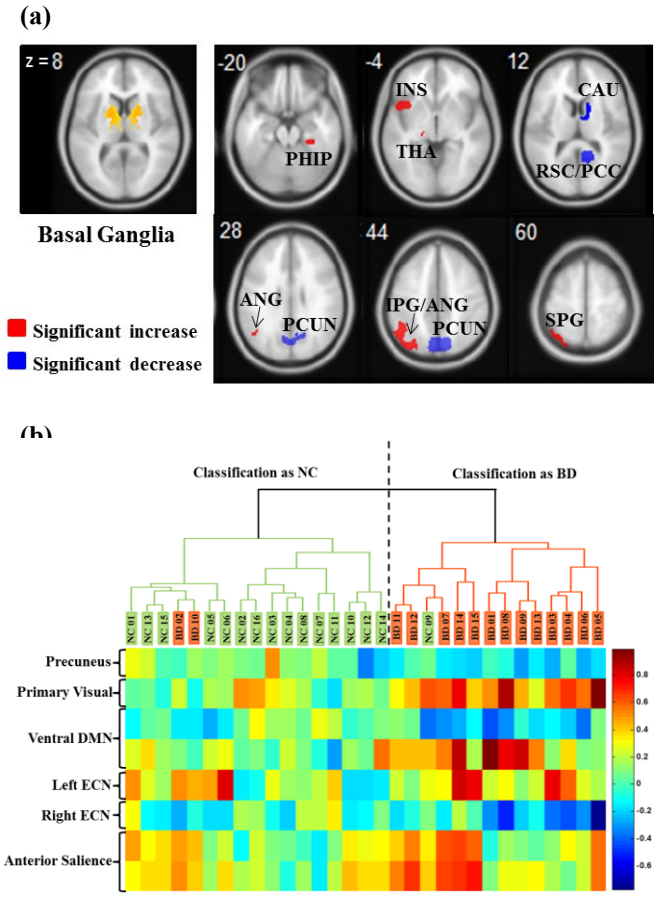

Figure 2. (a) Significant different functional connectivity realted to the basal ganglia in BD. (b) Using the 8 basal-ganglia-related functional connectivities with significantly difference between BD and NC groups as the classifier features, the classification rate improved to 90% of total participants.

IV. Conclusion

This study investigated the whole-brain resting-state functional connectivities of BD patients. We found that the basal-ganglia-related functional connectivity is predominant in BD patients, compared with healthy controls. Most of the basal-ganglia-related functional connectivities were linked to the core neurocognitive networks, including the DMN (ventral part and precuneus), CEN, and SN. Specifically, the functional connectivity significantly increased between the basal ganglia and left CEN, whereas that significantly decreased between the basal ganglia and the ventral DMN/precuneus in BD patients. The basal ganglia subserved in the emotional and cognitive processing which are related to the dopamine transmission. Changes in the basal-ganglia-related functional connectivity implicated that the dysregulated dopamine transmission resulted in the emotional and cognitive deficits of BD [14]. The basal-ganglia-related functional connectivities with significant difference between BD and healthy subjects can be used as features in hierarchical clustering to achieve 90% recognition rates.

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