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Convergent and Divergent Functional Connectivity Patterns in Schizophrenia and Depression

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Abstract

Major depression and schizophrenia are two of the most serious psychiatric disorders and share similar behavioral symptoms. Whether these similar behavioral symptoms underlie any convergent psychiatric pathological mechanisms is not yet clear. To address this issue, this study sought to investigate the whole-brain resting-state functional magnetic resonance imaging (MRI) of major depression and schizophrenia by using multivariate pattern analysis. Thirty-two schizophrenic patients, 19 major depressive disorder patients and 38 healthy controls underwent resting-state functional MRI scanning. A support vector machine in conjunction with intrinsic discriminant analysis was used to solve the multi-classification problem, resulting in a correct classification rate of 80.9% via leave-one-out cross-validation. The depression and schizophrenia groups both showed altered functional connections associated with the medial prefrontal cortex, anterior cingulate cortex, thalamus, hippocampus, and cerebellum. However, the prefrontal cortex, amygdala, and temporal poles were found to be affected differently by major depression and schizophrenia. Our preliminary study suggests that altered connections within or across the default mode network and the cerebellum may account for the common behavioral symptoms between major depression and schizophrenia. In addition, connections associated with the prefrontal cortex and the affective network showed promise as biomarkers for discriminating between the two disorders.

Introduction

Major depressive disorder (MDD) and schizophrenia are two of the most serious psychiatric disorders and share similar behavioral symptoms [1]. Some previous studies indicated that 59% of patients with schizophrenia met the DSM-III criteria for major or mild depression [2]. Similarly, other studies have suggested that patients with schizophrenia are 29 times more likely to have a lifetime diagnosis of MDD than the general population [3]. Symptoms and clinical findings, such as a depression factor [4,5,6], genetic risk [7], mild loss of brain volume [8], postnatal complications of brain development [9], lack of energy, anhedonia, and social withdrawal [10], often cause particular problems when attempting to differentiate between the two syndromes. Whether the similar behavioral symptoms underlie any convergent psychiatric pathological mechanisms is not yet clear, and few investigations have been performed to address this issue. Understanding the etiology and pathogenesis of schizophrenia and depression is a major challenge in the field of psychiatry [11]. Ciaran et al reported that the features of schizophrenia, especially those that are 'negative', exhibit many clinical similarities to the syndrome of depression [10]. Here, we speculated that schizophrenic and MDD patients share convergent dysfunctional connectivity patterns that account for their similar behavioral symptoms. Exploring the convergent and divergent functional connectivity patterns not only can enhance our comprehension of

the pathophysiology of major depression and schizophrenia, but may also facilitate the clinical identification of major depression and schizophrenia, which is currently based largely on self-reported symptoms and clinical signs.

In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) techniques have been widely used in the quantitative analysis of the brain in some neuropsychiatric disorders, including schizophrenia [12,13] and MDD [14]. Hypotheses regarding functional connectivity abnormalities have been proposed as physiological explanations of the behavioral syndromes of MDD patients [15,16]. Furthermore, rs-fMRI studies have detected resting-state network (RSN) alterations, specifically, abnormalities in the default mode network (DMN) [17,18], affective network [19], and visual cortical areas [14] in MDD patients. Similarly, hypotheses regarding functional connectivity abnormalities in schizophrenic patients have been investigated in many other neuroimaging studies [12,20]. For example, Whitfield-Gabrieli et al identified abnormal connectivity within the DMN in schizophrenic patients compared with healthy controls [20], and Salvador et al found that some regions of the DMN showed hyper-connectivity in schizophrenic patients [21]. These studies accelerated the search for pathophysiological mechanisms of MDD or schizophrenia and supplied some additional information for current clinical diagnostic systems which are mainly based on the patients' clinical manifestations

[14,22]. From the above-mentioned studies, we noticed that MDD and schizophrenia exhibited convergent abnormal connections associated with the same regions, such as the prefrontal lobe [17,23,24], thalamus [16,25], and hippocampus [26]. However, whether the two disorders share convergent, in addition to divergent, functional connectivity patterns has not been well investigated. The present study sought to investigate the whole-brain rs-fMRI of major depression and schizophrenia using multivariate pattern analysis.

Multivariate pattern analysis has generated great interest due to its capacity to identify potential neuroimaging-based biomarkers to differentiate patients from healthy controls at the individual subject level, as well as its ability to detect spatially distributed information to further highlight the neural mechanisms that underlie patients' behavioral symptoms [27,28,29,30], which can complete previous group-level statistical analysis studies. Recent studies have used multivariate pattern analysis to explore structural and functional alterations in schizophrenia or MDD, obtaining satisfactory correct classification rates [14,31]. In the current study, multivariate pattern analysis was further extended to the multiclass discriminative analysis of whole-brain resting-state functional connectivity in schizophrenic patients, MDD patients, and healthy controls to explore the convergent and divergent functional connectivity patterns of schizophrenia and MDD. Machine learning is an important aspect of multivariate pattern analysis. In the last few years, several learning techniques have been widely used in the multivariate pattern analysis of rs-fMRI, such as principal component analysis (PCA) [32], independent component analysis (ICA) [33], and the multivariate linear model [22]. However, these above-mentioned methods do not analyze the differences in functional connections, which are more significant in real-word discriminative analysis. In the current study, we first used intrinsic discriminative analysis (IDA) [34] in the multivariate pattern analysis of rs-fMRI data. IDA is a supervised linear dimensionality reduction method that explicitly exploits the knowledge of which types of features are critical for classification and tries to best differentiate different classes by maximizing the inter-class difference while minimizing the intra-class difference.

Due to the limited samples size, the leave-one-out cross-validation (Loocv) strategy was used during the dimensionality reduction process. When the dataset of features in the embedding space was obtained, support vector machines (SVMs) with a linear kernel function were employed to solve the classification problems [35]. Functional connectivity features with the highest discriminative power were further identified using a reconstruction technique.

Materials and Methods

Participants

This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, with knowing that the participants, including schizophrenic and MDD patients, belonged to a traditionally vulnerable population. Participants, including 19 MDD patients, 32 schizophrenic patients, and 38 healthy controls, were physically healthy as indicated by physical examinations performed before screening. All subjects provided their written informed consent after receiving a complete description of this study. The patients provided informed consent with accompany of their next of kin, and their capacity of providing informed consent was confirmed by clinical psychiatrists. Because the patients belong to a traditionally vulnerable population, their next of kin also provided informed

consent to participant in this study on behalf of them. MDD and schizophrenic patients were recruited from outpatient departments and inpatient units at the Second Xiangya Hospital of Central South University. All of the patients fulfilled the criteria for schizophrenia or MDD according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) [36], and confirmation of the diagnosis was made by clinical psychiatrists. Symptom severity for the schizophrenic patients was assessed with the Positive and Negative Syndrome Scale (PANSS) [37]. The depressive symptoms of the MDD patients were assessed with the 17-item Hamilton Depression Rating Scale (HDRS) on the days of the scans [38]. Exclusion criteria included acute physical illness, substance abuse or dependence, a history of head injury resulting in loss of consciousness, and a major psychiatric or neurological illness other than schizophrenia or depression. Similar exclusion criteria were adopted for healthy control subjects, who were recruited via advertisement and matched to the affected individuals with respect to age, gender, education level, and handedness (details are shown in Table 1).

Resting Experiment and Data Acquisition

fMRI scans were performed with a 1.5-T GE Signa System (GE Signa, Milwaukee, Wisconsin, USA) using a gradient-echo echo planar imaging sequence. The imaging parameters were as follows: TR = 2000 ms, TE = 40 ms, FOV = 24 cm, FA = 90°, matrix = 64×64, slice thickness = 5 mm, gap = 1 mm, slices = 20. During the experiment, the subjects were instructed to relax, keep their eyes closed, remain awake, and perform no specific cognitive exercises. Foam pads and earplugs were used to minimize head motion and scanner noise, respectively. Each functional resting-state session lasted ~6 minutes, resulting in 180 volumes.

Data Preprocessing

Image preprocessing was performed using the statistical parametric mapping software package (SPM8, Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). For each subject, the first five volumes of the scanned data were discarded due to magnetic saturation effects. The remaining volumes were corrected by registering and reslicing them to account for head movement. Then, the volumes were normalized to the standard echo planar imaging template in the Montreal Neurological Institute space. The resulting images were spatially smoothed with a Gaussian filter of an 8-mm full-width half-maximum kernel and then temporally filtered with a Chebyshev band-pass filter (0.01–0.08 Hz). The registered fMRI volumes were further divided into 116 regions according to the anatomically labeled atlas previously validated and reported by Tzourio-Mazoyer *et al* [39]. The atlas

Table 1. Demographic and clinical profiles of the participants in this study.

variable	MDD patients	Schizophrenia	Healthy controls
Gender (M/F)	11/8	25/7	27/11
Age (years)	26.65(±7.62)	24±5.66	24.44±4.45
Education (years)	12.41(±2.24)	11.15±2.50	13.65±2.78
PANSS score	––	80.06±16.55	––
HRSD score	25.43 (±6.34)	––	––

PANSS: Positive and Negative Syndrome Scale; HDRS: Hamilton Depression Rating Scale.
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divides the cerebrum into 90 regions (45 in each hemisphere) and divides the cerebellum into 26 regions (9 in each cerebellar hemisphere and 8 in the vermis).

Functional Connectivity

Regional mean time series were acquired for each individual by averaging the fMRI time series over all voxels within each of the 116 regions. For each regional mean time series, we performed further regression of the global mean signals and assessed the effects of translations and rotations of the head as estimated in the course of initial movement correction by image realignment. The residuals of the above regressions constituted the set of regional mean time series used for further functional connectivity analysis [40]. We then evaluated the functional connection between each pair of regions using Pearson's correlation coefficient, resulting in a 6670-dimensional feature vector for each subject.

IDA Algorithm and Intrinsicconnectomes

Suppose that there are N training samples sampled from k classes (each class has N_i, $(i=1,2,...,k)$ samples and $N = \sum_{i=1}^{k} N_i$) in the original high-dimensional space and that x_j^i in $\Re^D$ denotes the jth sample in the ith class.

We now consider the following matrixes:

$$H_M = \left[X_1^1 - \mu, X_2^1 - \mu, ..., X_{N_k}^k - \mu, \right] \in \Re^{D \times N}. \quad (1)$$

$$H_M^i = \left[X_1^i - \mu_i, X_2^i - \mu_i, ..., X_{N_i}^i - \mu_i, \right] \in \Re^{D \times N_i}, i=1,2,...,k. \quad (2)$$

where

$$\mu = \frac{1}{N} \sum_{i=1}^{N} \sum_{j=1}^{N_i} x_j^i. \quad (3)$$

$$\mu_i = \frac{1}{N_i} \sum_{j=1}^{N_i} x_j^i. \quad (4)$$

Suppose that $r = rank(H_M)$ and that the singular value decomposition of H_M is $H_M = U \sum V^T$, where U and V are orthogonal. Partitioning U, V, and $\sum$ results in the following:

$U = [U_r, \tilde{U}_r]$, where $U_r \in \Re^{D \times N}$ and $\tilde{U}_r \in \Re^{D \times (D-r)}$.

$V = [V_r, \tilde{V}_r]$, where $V_r \in \Re^{N \times r}$ and $\tilde{V}_r \in \Re^{N \times (N-r)}$.

$\sum = \begin{bmatrix} \sum 1 & 0 \\ 0 & 0 \end{bmatrix}$, where $\sum_1 \in \Re^{r \times r}$ is nonsingular.

Similarly, we suppose that $r^i = rank(H_M^i)$ and acquire U^i from the SVD of matrix H_M^i ($H_M^i = U^i \sum V^{iT}$).

After performing the above calculation, we can decompose x_j^i into the following form:

$$x_j^i = (I - U_r U_r^T) x_j^i + (U_r U_r^T - U_{r^i}^i U_{r^i}^i T) x_j^i + U_{r^i}^i U_{r^i}^i T x_j^i. \quad (5)$$

where I is the identity matrix.

This formula describes the three components of the original sample after being decomposed. It has been proven that these three components correspond to different properties. $(I - U_r U_r^T) x_j^i$ is a common component corresponding to the common nature of all the training samples, $(U_r U_r^T - U_{r^i}^i U_{r^i}^i T) x_j^i$ is a common component of all the training samples belonging to the same class, and $U_{r^i}^i U_{r^i}^i T x_j^i$ can be viewed as the difference of an individual in a particular class. Thus, the intrinsic model is established.

Eq. (5) can then be rewritten as the following formula when projecting the sample onto a lower d-dimensional space by using a $D \times d$ transformation matrix G.

$$G^T x_j^i = G^T (I - U_r U_r^T) x_j^i + G^T (U_r U_r^T - U_{r^i}^i U_{r^i}^i T) x_j^i + G^T U_{r^i}^i U_{r^i}^i T x_j^i. \quad (6)$$

The transformation matrix G can be obtained by solving the maximization problem of the following objective function:

$$\arg \max \frac{trace(G^T S_C G)}{trace(G^T S_I G)} = \arg \max \frac{trace(G^T X_C X_C^T G)}{trace(G^T X_I X_I^T G)}. \quad (7)$$

where

$$X_C = \left[(U_r U_r^T - U_{r1}^1 U_{r1}^1 T) x_1^1, ..., (U_r U_r^T - U_{r^i}^i U_{r^i}^i T) x_j^i, ..., (U_r U_r^T - U_{rk}^k U_{rk}^k T) x_{N_k}^k \right].$$

and

$$S_C = X_C X_C^T.$$

$$X_I = \left[U_{r1}^1 U_{r1}^1 T x_1^1, ..., U_{r1}^1 U_{r1}^1 T x_{N_1}^1, ..., U_{rk}^k U_{rk}^k T x_1^k, ..., U_{rk}^k U_{rk}^k T x_{N_k}^k \right].$$

and

$$S_I = X_I X_I^T.$$

The objective function is usually approximated as the following form because Eq. (7) does not often have a closed-form solution.

$$\arg \max trace(G^T S_I G)^{-1}(G^T S_C G). \quad (8)$$

The dimensionality reduction algorithm based on the above intrinsic discriminant criterion is called intrinsic discriminant analysis.

The optimal transformation vectors $g_1, g_2, ..., g_d$ are given by solving the following generalized eigenvector problem:

$$S_C g = \lambda S_I g. \quad (9)$$

However, S_I is argued to be singular when the number of training samples is smaller than the dimensionality. The perturbation technique was introduced to overcome this problem, that is, we changed Eq. (9) to the following form:

$$S_C g = \lambda(S_I + \Delta I)g. \qquad (10)$$

where Δ is a relatively small positive number and I is the identity matrix.

Obtaining the transportation vectors $g_1, g_2, ..., g_d$ corresponding to the d maximum eigenvalue solutions, the final transformation matrix G from the original sample space to the embedded space is formed as:

$$G = [g_1, g_2, ..., g_d]. \qquad (11)$$

The IDA algorithm procedure is formally stated as:

Step 1. Without loss of generality, we store the training samples of a certain class compactly in the original training data matrix X using order rearrangement, i.e., $X = \left[x_1^1, ..., x_{N_1}^1, x_1^2, ..., x_{N_2}^2 ..., x_1^k, ..., x_{N_k}^k \right]$.

Step 2. The SVD of H_M and H_M^i $(i = 1, 2, ..., k)$ is computed to obtain U_r and $U_{r^i}^i$. Then, S_C and S_I are computed using Eq. (7).

Step 3. The generalized eigenvector problem is solved, and the transportation matrix G is obtained.

The column vectors of G are called intrinsicconnectomes in subsequent discussion.

Multiclass Classification Based on Intrinsic Discriminative Analysis

The multivariate pattern analysis of fMRI is a challenging task due to the high dimensionality of the data. IDA was applied here to reduce the dimensionality of the original feature space. When the data set of features in the embedding coordinate were obtained, SVM with a linear kernel function was employed to solve the classification problem [35]. A one-against-rest strategy was used to design our classifiers [41]. For a k-class problem, the one-against-rest method constructs k SVM models. The ith SVM is trained with the training samples in the ith class with positive labels and other samples with negative labels. The final output of the one-against-rest method is the class that corresponds to the SVM with the highest output value. A Loocv strategy was employed to estimate the generalization ability of the classifiers. A flowchart of our method is shown in Fig. 1. To comprehensively investigate the discriminative ability of the IDA method, the classification performance of our IDA algorithm was compared with that of the PCA method.

Identification of Features with High Discriminative Power

We determined the functional connection features with the highest discriminative power via the reconstruction technique based on the performance of each one-against-rest classifier. Because each feature influences the classification by its weight, the larger the absolute magnitude of a feature's weight, the more it will affect the classification result. For each one-against-rest classifier, we obtained a weight vector in each Loocv experiment. The weight vector for this one-against-rest classifier was finally acquired by averaging the aforementioned weight vectors. We therefore obtained three weight vectors representing the features' discriminative power for each one-against-rest classifier. Because we performed the classification in the dimension-reduced subspace, to determine the original functional connections that make significant contributions to the classification, we then mapped back each weight vector to the original high-dimensional space. Thus, for all of the 6670 resting-state functional connec-

tions, we obtained the order of their contribution to the classification for each one-against-rest classifier. In the subsequent study, the top 5% of functional connection features with the greatest weights were extracted as the most discriminative functional connections. Region weight, representing the relative contribution of each region to the classification, was denoted by its occurrence number in the consensus functional connections.

Results

Intrinsicconnectomes

According to theoretical analysis, the columns of the transformation matrix G are called intrinsicconnectomes, and any functional connections can be represented as a combination of these intrinsicconnectomes. We displayed the first nine intrinsicconnectomes in Fig. 2.

Classification Results

As we described in the Materials and methods section, a total of 89 samples were used in the discriminative analysis in this work, and by using Loocv, our IDA method achieved an accuracy of 80.9% at the individual level (84.2% for MDD patients, 78.9% for healthy controls, and 81.3% for schizophrenic patients; details are shown in Table 2). The dimensionality of the embedding space was set using a grid search format [2, 88] with a granularity of 1. All of the results were reported based on the best parameter settings. To further validate the discriminative ability of the IDA method, we compared the IDA algorithm with the traditional PCA method, which achieved an accuracy of 79.8%. The best classification rates for the two methods, along with their associated dimensionality, are summarized in Fig. 3.

Functional Connections with High Discriminative Power

In this study, 5% consensus functional connections were identified for each one-against-rest classifier. Compared with the healthy controls, the MDD and schizophrenia patients showed convergent altered functional connectivity patterns related to the DMN (mainly containing the parahippocampal gyrus, precuneus, anterior cingulate cortex, hippocampus, thalamus, inferior temporal gyrus, posterior cingulate cortex, and medial prefrontal cortex), as well as the cerebellum. Several brain regions exhibited greater weights than others (i.e., the medial prefrontal cortex, anterior cingulate cortex, thalamus, hippocampus, cerebelum_7b, cerebelum_9, cerebelum_vermis10, and cerebelum_crus1). Those functional connections with high discriminative power were observed within or across the DMN and the cerebellum (Fig. 4), i.e., connections between the medial prefrontal cortex and the precuneus, thalamus, and inferior temporal gyrus; connections between the thalamus and the anterior cingulate cortex and hippocampus; as well as connections between the cerebellum and the medial prefrontal cortex, hippocampus, thalamus, and anterior cingulate cortex. Divergent functional connectivity patterns that make key contributions to the identification of schizophrenic and MDD patients were obtained by combining the MDD-against-rest classifier and the schizophrenia-against-rest classifier. Some consensus functional connections related to the prefrontal cortex, temporal poles, and amygdala were identified. Such connections included connections between the amygdala and the medial prefrontal cortex, parahippocampus, hippocampus, precuneus, and some cerebellar regions, as well as connections between temporal poles, amygdala, and medial prefrontal cortex (Fig. 5).
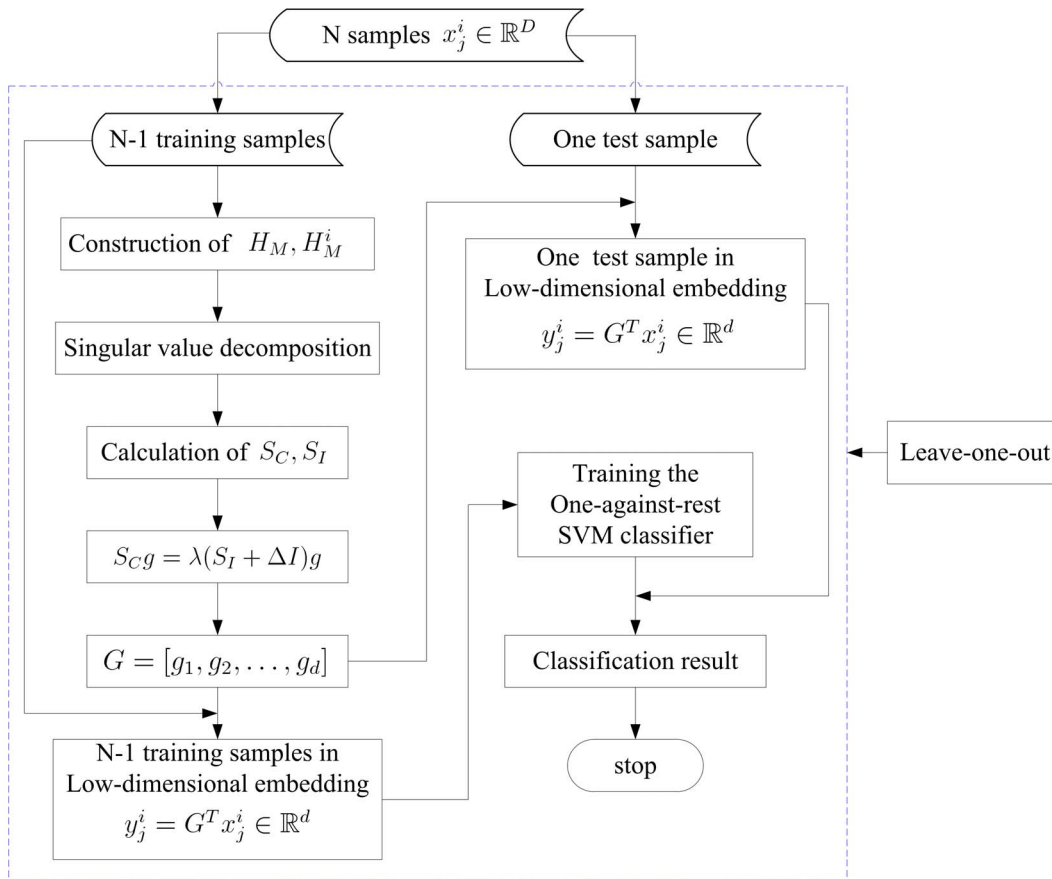
Figure 1. Flow chart of the intrinsicconnectome method.
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Discussion

The rs-fMRI technique is currently generated increasing interest because the imaging of baseline states is fundamental in understanding human brain functions [42]. In the present study, rs-fMRI was extended to the field of discriminative analysis of schizophrenia and depression to identify the potential convergent and divergent functional connectivity patterns associated with the two disorders. Selecting low-dimensional embedding of rs-fMRI acquired using IDA as classification features, we have designed a data-driven multiclass classifier and successfully extracted the significant discriminative functional connections that potentially underlie the spontaneous neural activities in the brains of MDD patients, schizophrenic patients, and healthy controls. Our preliminary study suggested that resting-state functional connections are promising for use in classifying schizophrenic patients, MDD patients, and healthy controls, and, accordingly, rs-fMRI could be potentially useful in revealing the convergent and divergent functional connectivity patterns associated with the two disorders.

In recent years, the multivariate pattern analysis method has been widely used in neuroimaging studies [28,30]. Compared with the group comparison methods, which have been previously used in some studies to explore abnormal function connectivity to differentiate patients from healthy controls, there are many benefits of using multivariate pattern analysis. First, group-level statistical methods are less helpful in diagnosis due to complex dysfunction in the entire brain in psychiatric disorders

[14,25,31,43]. Second, group-level methods are not helpful in clinical diagnosis at the individual subject level. In recent years, multivariate pattern analysis methods have been widely used in neuroimaging studies, as they can not only identify potential neuroimaging-based biomarkers with which to differentiate patients from healthy controls at the individual subject level, but they can also detect interesting spatially distributed information to further highlight the neural mechanisms underlying the behavioral symptoms of MDD and schizophrenia. Our previous studies have used multivariate pattern analysis to explore the resting-state functional alterations in schizophrenia and depression compared with the general population, obtaining satisfactory correct classification rates [14,31]. In the present study, we extended the multivariate pattern analysis method to the multiclass discriminative analysis of rs-fMRI to explore the convergent and divergent functional connectivity patterns in schizophrenic and MDD patients. To our knowledge, this study was the first to use the IDA algorithm in the discriminative analysis of rs-fMRI data, which may provide some useful insights into how to address the challenging problem of the dimensionality reduction of rs-fMRI data. IDA is a supervised linear dimensionality reduction. Compared with nonlinear algorithms, linear algorithms were suggested to be more insensitive to over-fitting problems, especially in case with a large number of dimensions and small sample sizes [44]. Another advantage of linear algorithms is that they can reveal potential neuroimaging-based biomarkers using the reconstruction technique. On the basis of their experimental results, Young Wang *et al.* suggested that IDA exhibited better perfor-
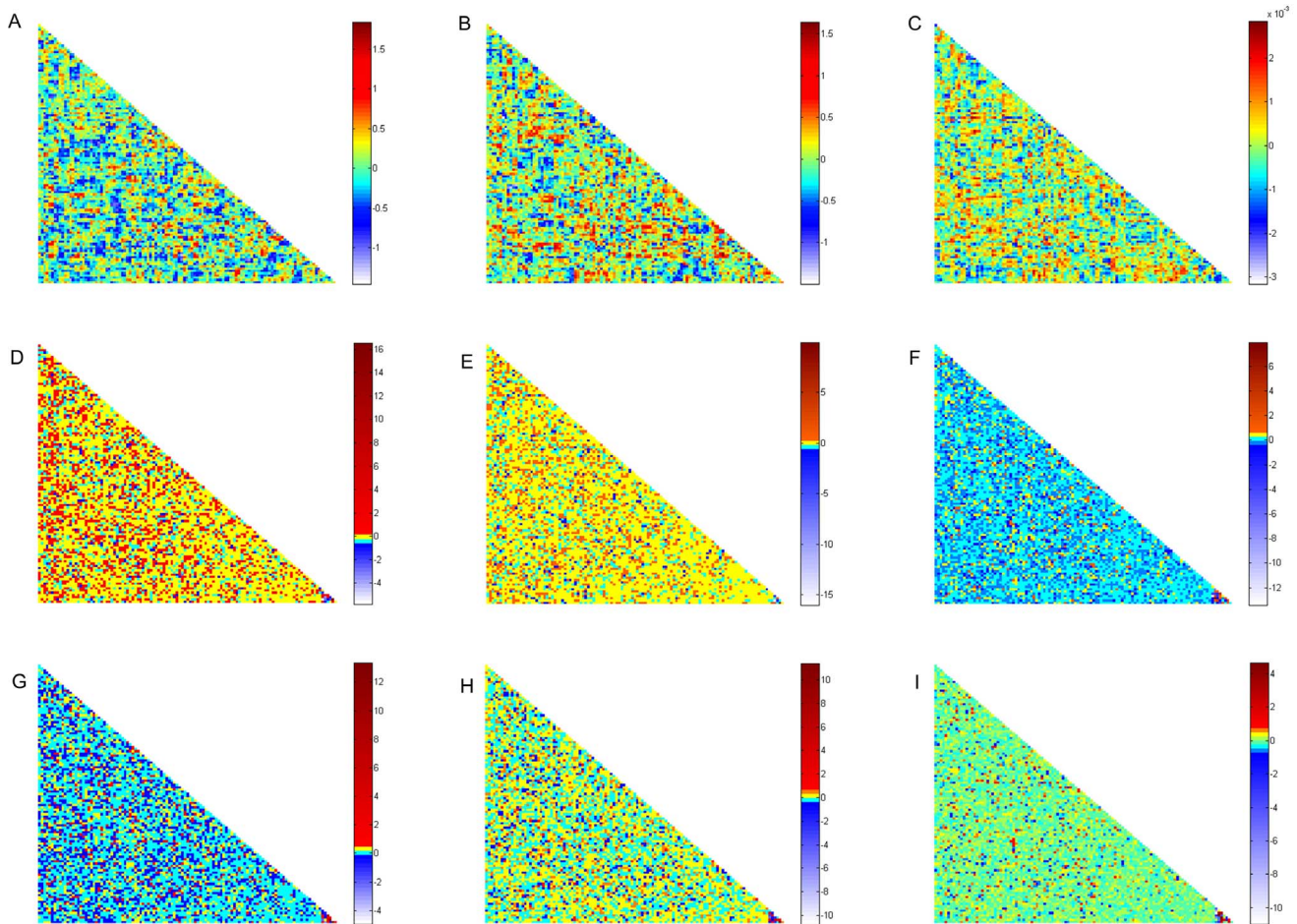
Figure 2. The first nine intrinsicconnectomes calculated by our method.
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mance than PCA [34]. Our experimental results also showed a slight superiority of IDA over the PCA method. The most likely explanation for the superiority of IDA in performance compared with the unsupervised PCA algorithm is that IDA explicitly uses data label information to supervise the implementation of

dimensionality reduction. In other words, IDA uses the knowledge of which types of functional connections are critical for discriminative analysis, which in theory can lead to better discriminative performance. In this aspect, IDA is more generalized and suitable in multi-class discriminative analysis. However, the difference
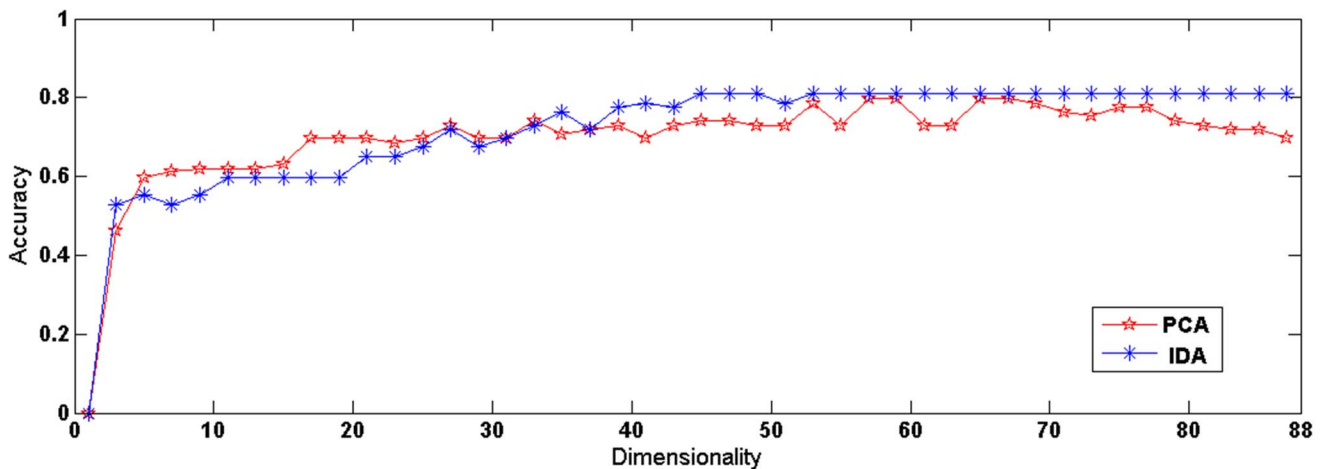

Figure 3. The curve of classification accuracy of the IDA and PCA methods.
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Table 2. Confusion matrix for results in leave-one-out cross-validation.

Classes	MDD	Healthy controls	Schizophrenia
MDD	84.2%	5.3%	10.5%
Healthy controls	13.2%	78.9%	7.9%
Schizophrenia	12.5%	6.2%	81.3%

The rows of this matrix indicate the groups of the subjects (ground truth), and the columns indicate the predictions by the classifier. The cells in each row contain the proportion of trials in which subjects responded with the category indicated by the column.

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between the two methods is, in practice, only one sample. Accordingly, it would be very important to evaluate the performance of the IDA method with a larger sample size using neuroimaging data in the future.

A number of previous studies have identified abnormalities in the function of the DMN in schizophrenia and MDD, such as abnormalities in the bilateral hippocampus [18], anterior cingulate cortex, thalamus, inferior temporal gyrus, and posterior cingulate cortex [14,16] in MDD patients, as well as abnormalities in the hippocampus [45], medial prefrontal cortex, anterior cingulate cortex [24], thalamus, and posterior cingulate cortex [46] in schizophrenic patients. Regarding the convergent functional connectivity patterns, regions with high discriminative power related to the DMN were consistent with these previous findings. The DMN is known to be involved in self-referential activity [47,48]. Furthermore, ample evidence suggests that the anterior cingulate cortex, a key component of the DMN, plays a distinctive role in cognitive functions and information processing [49,50]. Altered functional connections related to the anterior cingulate cortex have been implicated as a focus of dysfunction in MDD [16,18] and schizophrenic [23] patients. The hippocampus has been suggested to be critical in memory formation [51], and it is involved in the deficits in working memory observed in MDD [52] and schizophrenic [53] patients. Although schizophrenia and depression are conventionally viewed as two distinct disorders, similar symptoms are evident during the disease courses [54]. Ciaran et al suggested that depression and schizophrenia are not simply two independent illnesses, and moreover, that the neurobiology of depressive symptoms in schizophrenia may have similarities to that of depressive disorder [10]. Kohler et al suggested that frontal lobe dysfunction may account for the depressive symptom in schizophrenia [55]. Previous studies have also provided presumptive evidence for the common pathology of schizophrenia and MDD, particularly in the prefrontal cortex, for example, a reduction in grey matter volume, changes in glucose metabolism, and changes in blood flow have been reported in the prefrontal cortex in both schizophrenia [56,57] and MDD [58]. Accordingly, we assumed that convergent dysfunctions of the identified brain regions may reveal the convergent neuroimaging-based pathological mechanisms of depression and schizophrenia. Abnormalities in the cerebellum have been previously reported in schizophrenic and MDD patients [19,59,60]. A previous study also suggested that the cerebellum is involved in cognitive and emotional activities [61]. In our study, compared with the healthy controls, the connections between the cerebellum (cerebelum_7b, cerebelum_9, cerebelum_vermis10, and cerebelum_crus1) and some cerebral regions exhibited very high discriminative power in both the MDD and

schizophrenic patients. Therefore, we speculated that the convergent aberrant connections between the cerebellum and the cerebral cortex may contribute to part of the common behavioral symptoms in MDD and schizophrenia. Further work is required to clarify our speculation.

Resting-state functional connections between the amygdala and prefrontal cortex, hippocampus, and precuneus, as well as connections between the temporal poles and the amygdala and the prefrontal cortex, were found to be different between the MDD and schizophrenic patients. A large number of studies have reported that people with schizophrenia demonstrate dysfunction of the prefrontal cortex during the performance of working memory tasks [62,63]. Although other reports have suggested that people with major depression also display prefrontal cortex deficits [64], these deficits were reported to be not as severe as those found in schizophrenia [65]. A recent fMRI study suggested that the deficits in prefrontal cortex function are different in schizophrenia and MDD [66]. Consistent with this study, we predicted that schizophrenic and MDD patients exhibit different functional impairments in the prefrontal cortex. The affective network is known to be involved in mood regulation and affective processing [67]. The amygdala has a wide variety of functions, such as cognition, memory consolidation, and control of affective behaviors [68,69]. Morphometric and histological abnormalities have been reported in the amygdala of patients with schizophrenia [70]. Meta-analyses also showed volume reductions in the amygdala in patients with schizophrenia [70]. Other studies argued that abnormal connections related to the amygdala may affect the regulation of mood [71] and reflect dysfunctions in visceral monitoring, which is compromised in MDD [18]. However, our experimental results suggested that the amygdala was affected differently in schizophrenia and depression. Abnormalities in the amygdala in patients with these psychiatric diseases may be pathophysiologically explained as follows. On one hand, abnormalities of the amygdala constitute a universal phenomenon throughout the brain of psychiatric patients, which may account for the respective physiological mechanisms of MDD and schizophrenia. On the other hand, the functional integration of the amygdala is differently affected between the two disorders. A recent study revealed that fatty acid metabolism in the amygdala is different between MDD and schizophrenia [72], which partially substantiates our explanation. Moreover, with respect to the temporal poles, some studies suggested that their dysfunctions are associated with clinical symptoms in schizophrenia [73]. Both the amygdala and the temporal pole are coincidently located within the affective network (including the amygdala, temporal poles, pallidum, insula, and superior temporal gyrus). Accordingly, we speculated that the functional integration of the prefrontal cortex and the affective network may be differently affected in the MDD and schizophrenic patients. The difference may partially reflect the different emotional and cognitive behavioral symptoms seen between MDD and schizophrenic patients and may enable the development of neuroimaging-based approaches to distinguish the two patient groups. This preliminary speculation needs to be further investigated.

Limitations

Although the classification results of the present study are encouraging, several possible limitations still need to be considered. First, due to the limited sample size, it is important to test the classification performance of our methods and to confirm our findings with a larger sample size in the future. Second, global signal regression was applied in the data preprocessing for the consideration of removing potential sources of physiological noise.
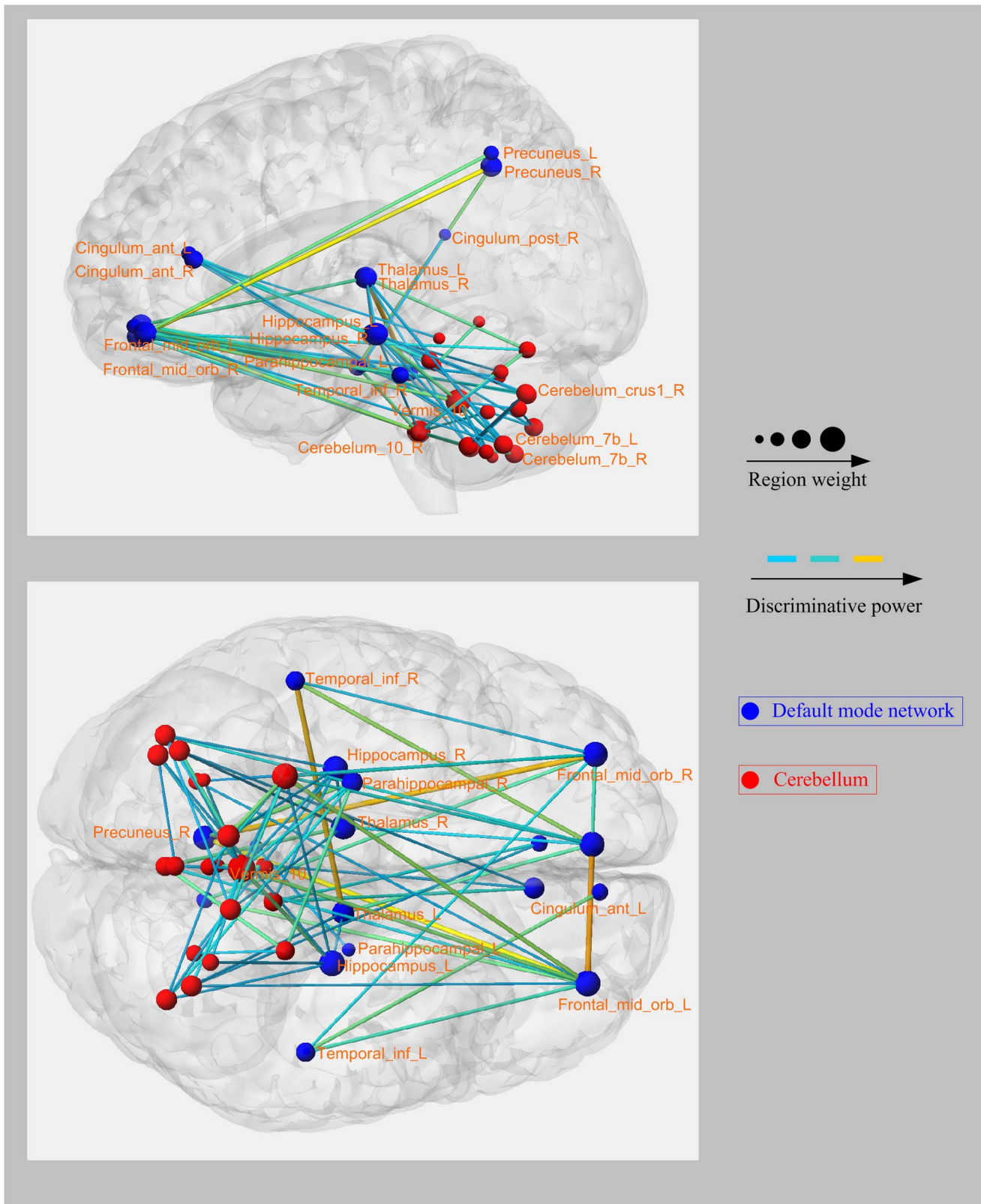
Figure 4. Left and bottom views of the convergent functional connectivity patterns with high discriminative power. Regions are color-coded by category. The line colors representing the discriminative power of the relative connections are scaled with their mean discriminative power in the leave-one-out cross-validation.
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Figure 5. Left and bottom views of the divergent functional connectivity patterns with high discriminative power. Regions are color-coded by category. The line colors representing the discriminative power of the relative connections are scaled with their mean discriminative power in the leave-one-out cross-validation.
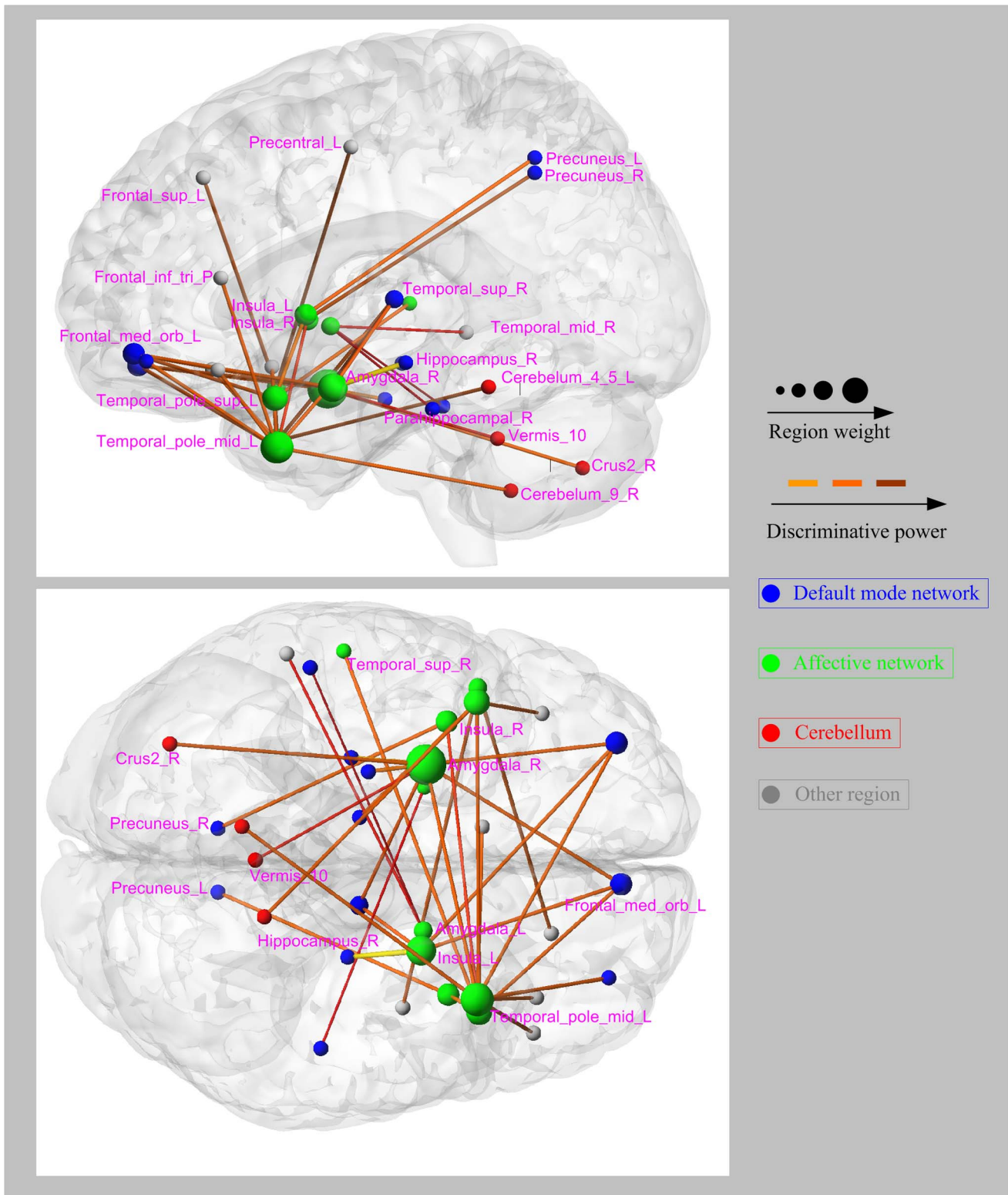doi:10.1371/journal.pone.0068250.g005

However, the success of this technique has been variable between studies. For example, Fox *et al* used global signal regression in functional connectivity analysis and suggested that this technique may remove several potential sources of physiological noise [74]. Therefore, there is much work being conducted in the use of global signal regression to correct for physiological confounders. Murphy *et al* suggested that this technique may result in a negative mean correlation value in functional connectivity analysis such that it may consequently change the inherent functional connectivity patterns [75]. Based on their experimental results, Saad *et al* suggested that this technique can induce false anti-correlations and even induce false between-group differences. Therefore, we performed the classification without removing the global signal. Keeping the parameters unchanged, the results showed that the overall classification accuracy did not differ from the previous accuracies.

Conclusions

In the present study, we designed a data-driven multiclass classifier based on the intrinsicconnectomes model and successfully extracted the significant discriminative functional connections that potentially underlie spontaneous neural activity in the brains of MDD and schizophrenic patients, which should shed new light on how to address the challenging problem of dimensionality reduction of rs-fMRI data. Moreover, this preliminary study suggested that rs-fMRI could be potentially useful in revealing the convergent and divergent functional connectivity patterns of schizophrenia and depression. Compared with the healthy controls, the MDD and schizophrenic patients both exhibited altered functional connections within or across the DMN and the cerebellum, which may account for the similar behavioral symptoms seen in the two disorders. In addition, our results demonstrated that the prefrontal cortex and the affective network played notable roles in distinguishing the MDD patients from the schizophrenic patients. Further work is required to clarify these findings.

Author Contributions

Conceived and designed the experiments: DH. Performed the experiments: YY HS LLZ. Analyzed the data: YY HS LLZ QM. Contributed reagents/materials/analysis tools: YY LLZ QM. Wrote the paper: YY.

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