Machine learning classifier using abnormal brain network topological metrics in major depressive disorder

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Resting state functional brain networks have been widely studied in brain disease research. However, it is currently unclear whether abnormal resting state functional brain network metrics can be used with machine learning for the classification of brain diseases. Resting state functional brain networks were constructed for 28 healthy controls and 38 major depressive disorder patients by thresholding partial correlation matrices of 90 regions. Three nodal metrics were calculated using graph theory-based approaches. Nonparametric permutation tests were then used for group comparisons of topological metrics, which were used as classified features in six different algorithms. We used statistical significance as the threshold for selecting features and measured the accuracies of six classifiers with different number of features. A sensitivity analysis method was used to evaluate the importance of different features. The result indicated that some of the regions exhibited significantly abnormal nodal centralities, including the limbic system, basal ganglia, medial temporal, and prefrontal regions. Support vector machine with radial basis kernel function algorithm and neural network algorithm exhibited the highest average accuracy (79.27 and 78.22%, respectively) with 28 features ($P<0.05$). Correlation analysis between feature importance and the statistical significance of metrics was investigated, and the results revealed a strong positive correlation between them. Overall, the current study demonstrated that major depressive disorder is associated with abnormal functional brain network topological metrics and statistically significant nodal metrics can be successfully used for feature selection in classification algorithms. *NeuroReport* 23:1006–1011 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Several functional neuroimaging studies have reported that major depressive disorder (MDD) is related to widespread local abnormalities, including morphology, function, and functional connection in some brain regions, which had been proposed as potential biomarkers in recent years, such as hippocampus [1], parahippocampal gyrus [2], posterior cingulate gyrus [3], and so on. It would be clinically useful to identify individuals and predict the treatment automatically to avoid self-reported symptoms. With those potential biomarkers, which are called feature in the classifier, the machine learning classification methods have been recently applied to identify individuals with depression and predict clinical outcome. Costafreda *et al.* [4] and Fu *et al.* [5] constructed classifiers using structural and functional MRI data, and tested them with normal controls and MDD patients, respectively, reporting accuracy rates of 67 and 86%. Gong *et al.* [6] investigated differences between the use of gray matter and white matter as classification features, and used support vector machine (SVM) algorithms to distinguish refractory and nonrefractory depressive disorder patients, reporting accuracy rates of 65.22 and 76.09%, respectively.

Brain networks are a widely used tool for identifying abnormal topological properties in whole-brain networks (for reviews, see Bassett and Bullmore [7]). Abnormal brain network topological metrics, which provided a new perspective of potential biomarkers for neurological disease diagnosis, had been found in various brain diseases, such as Alzheimer's disease [8], schizophrenia [9], and MDD [10]. However, little is known about how to use them effectively in clinical diagnosis. To our knowledge, there is no study showing that abnormal brain network topological metrics can be used in machine learning classification methods for the identification of MDD patients. Moreover, we need a standard and quantifiable scalar to evaluate the effectiveness of the metrics during the classification process.

In the current study, we hypothesized that resting state functional brain network topological metrics could be used as effective features in constructing a classifier,

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and that statistical analysis could be used to quantify the contribution of these metrics. To test this hypothesis, we collected resting state MRI data from 38 drug-naive, first-episode MDD patients and 28 normal controls to construct resting state functional brain networks. In addition, we calculated network metrics using graph-theoretical methods, and examined significant between-group differences using statistical approaches. Two hundred and seventy nodal metric values were used as classification features in six different classification algorithms. The statistical significance of metrics was used as the threshold for filtering features so that the performance of classifiers with different numbers of features could be evaluated. Moreover, the importance of 270 nodal metric values in the classifier was calculated using sensitivity analysis, and correlation analysis between feature importance and the statistical significance of metrics was investigated.

Materials and methods

Participants

A total of 66 participants were recruited, including 38 first-episode drug-naive MDD patients (15 males and 21 females), and 28 healthy controls (13 males and 15 females) (Table 1). All participants were inpatients at the Department of Psychiatry, First Hospital of Shanxi Medical University, clinically diagnosed with MDD by at least two experienced psychiatrists according to *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* [11]. The severity of MDD was rated using the 24-item Hamilton Rating Scale for Depression [12]. The controls were recruited from local communities. Written informed consent to participate in the study was obtained from all controls, and from the first-degree relatives of all patients, before inclusion in the study, which was approved by the Ethics Committee of the Chinese Academy of Medical Science.

Data collection and preprocessing

All participants underwent resting state functional MRI using a 3 T MR scanner (Siemens Trio 3 T scanner; Siemens, Erlangen, Germany). Image preprocessing was performed using DPARSF software (version 2.0; Yan Chao-Gan, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China). Participants exhibiting more than 1.0 mm of translation and 1.0° of rotation were excluded. After these corrections, the images were spatially normalized to Montreal Neurological Institute standard space according to the standard EPI template, then linearly detrended and band-pass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency physiological noise (for the details of scanning parameters, see Supplemental digital content 1, *http://links.lww.com/WNR/A217*).

Table 1 Demographics and clinical characteristics of the participants

	NC ($n=28$)	MDD ($n=38$)	P-value
Age (years)	17–51 (26.6±9.4)	17–54 (28.4±9.68)	$t=0.76$[a] $P=0.44$[a]
Sex (male/female)	13/15	15/23	$\chi^2=0.31$[b] $P=0.57$[b]
Handedness (R/L)	28/0	38/0	–
HAMD	NA	15–34 (22.8±13.3)	–

Data are presented as the range of minimum to maximum (mean±SD).
HAMD, Hamilton Depression Rating Scale; MDD, major depressive disorder; NA, nonapplicable; NC, normal controls.
[a]The t and P-values were obtained by two-sample two-tailed t-test.
[b]The χ^2 and P-value were obtained by two-tailed Pearson's χ^2-test.

Network construction and threshold selection

Node definition: In the current study, a prior atlas of automated anatomical labeling [13] was used to define the nodes. The brain was divided into 90 regions (45 for each hemisphere), with each region representing a node in the network. The mean time series for all voxels in each region was calculated as part of the time series of the corresponding node.

Edge definition: We computed partial correlation coefficients as edges in the network. Before the time series of nodes, we used multiple linear regression analysis with head motion profiles, estimated from the image realignment, to correct the effects of head motion. The residuals were then used to compute the partial correlation, producing a 90×90 correlation matrix. Finally, according to a predefined threshold, S, the correlation matrix was converted into a binary matrix.

Threshold selection: In the current study, sparsity, S, was used to set the threshold, which was defined as the ratio of the number of real existing edges divided by the number of maximum possible edges in the network. The threshold space is generated as $S \in (8\%, 32\%)$ and the interval was set as 1% throughout this study (for the details of threshold selection criterions, see Supplemental digital content 2, *http://links.lww.com/WNR/A218*).

Network metrics and statistical analysis

For each selected threshold, we analyzed three nodal metrics including the degree (k_i), betweenness centrality (b_i), and nodal efficiency (e_i) (for detailed mathematical definitions and interpretations of these network metrics, see Supplemental digital content 3, *http://links.lww.com/WNR/A219*).

Moreover, we calculated the area under the curve (AUC) for each metric, providing a summarized scalar for the selected threshold space. Previous studies have reported that the AUC metric is effective for detecting between-group differences in topological properties of brain networks.

A nonparametric permutation test was conducted for 270 metrics (90 nodes, three metrics per node) to determine whether there were significant between-group differences, and the results were ranked according to P-value.

Multiple linear regression was performed to remove the influence of sex and age (independent variables: AUC of metric; dependent variable: age and sex).

Classifier

To automatically identify the disease data, we used machine learning methods to construct a classifier. A total of 270 nodal metric values were selected as classification features, which were used in six algorithms, including SVM with linear kernel function (SVM-Linear), SVM with radial basis kernel function (SVM-RBF), linear discriminant analysis (LDA), neural network, decision tree (C4.5 algorithms), and logistic regression (for detailed algorithm descriptions and parameter settings, see Supplemental digital content 4, *http://links.lww.com/WNR/A220*).

To compare classifier performance alterations with different numbers of features, we used a range of *P*-values as significance thresholds. We used five threshold levels ($P < 0.005$, $P < 0.015$, $P < 0.05$, $P < 0.10$, and $P < 0.15$). The corresponding feature numbers were 4, 15, 28, 55, and 87.

A cross-validation method was used to evaluate the performance of models. We randomly selected 70% of samples as a training set and the remaining 30% as a test set. The accuracy rate of the test set was recorded. This procedure was repeated 100 times for each threshold. Cross-validation methods have been widely used in previous studies (for review, see Pereira *et al.* [14]).

Feature importance

Sensitivity analysis was used to calculate the change in variance of each feature in the target category. The normalized sensitivity provided a standard and quantifiable scalar to determine the importance of the features in the classifying process [15]. The method has been widely used in earlier studies and commercial software (for detailed mathematical definitions and interpretations, see Supplemental digital content 5, *http://links.lww.com/WNR/A221*).

Furthermore, we assessed the relationship between feature importance and statistical significance in the neural network model to determine whether statistical significance was an effective method for feature selection.

Results

Nodal metrics

We identified brain regions containing significant between-group differences in at least one node metric ($P < 0.05$, uncorrected). Compared with normal controls, MDD patients exhibited significantly increased centrality in some regions, including the limbic system (including the right hippocampus, right posterior cingulate gyrus, bilateral median cingulate, and paracingulate gyri), part of the basal ganglia (right putamen and right thalamus), and left angular gyrus, among others. Some of these regions belong to the default network, including the hippocampus and right posterior cingulate gyri.

Table 2 Regions exhibiting abnormal nodal metrics in major depressive disorder patients compared with controls

	P-value		
Brain regions	Degree	Betweenness centrality	Nodal efficiency
MDD < control			
Left fusiform gyrus	**0.016**	0.151	**0.047**
Left inferior frontal gyrus (orbital part)	**0.017**	0.179	**0.034**
Right cuneus	**0.025**	**0.001**	0.093
Right superior frontal gyrus (medial)	**0.035**	0.495	0.151
Right middle frontal gyrus (orbital part)	**0.049**	0.557	**0.025**
Left inferior frontal gyrus (opercular part)	**0.050**	0.295	0.141
Left calcarine fissure and surrounding cortex	0.058	0.547	**0.046**
Right inferior frontal gyrus (opercular part)	0.063	**0.048**	0.178
Right superior frontal gyrus (medial orbital)	0.082	0.848	**0.044**
MDD > control			
Right hippocampus	**0.001**	**0.005**	**0.003**
Left angular gyrus	**0.008**	0.284	**0.011**
Right posterior cingulate gyrus	**0.008**	0.167	0.007
Right thalamus	**0.008**	**0.004**	**0.008**
Right lenticular nucleus (putamen)	**0.014**	0.213	**0.023**
Right middle occipital gyrus	**0.021**	0.443	**0.027**
Right median cingulate and paracingulate gyri	0.070	0.482	**0.014**
Left median cingulate and paracingulate gyri	0.073	0.632	**0.048**

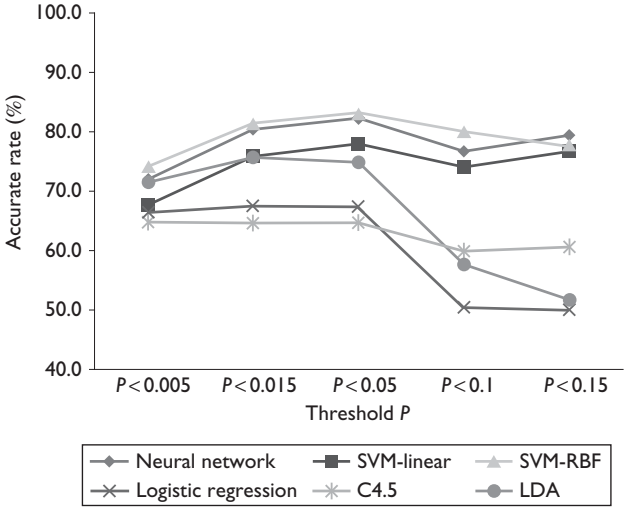
Regions were considered abnormal in MDD patients if they exhibited significant between-group differences ($P < 0.05$, uncorrected) in at least one of the three nodal metrics (bold font).
MDD, major depressive disorder.

Decreasing nodal centralities in MDD patients were predominantly located in several regions of medial occipital (right cuneus and left calcarine fissure and surrounding cortex), medial temporal (left fusiform gyrus) and prefrontal [left inferior frontal gyrus (orbital part), right superior frontal gyrus (medial), right middle frontal gyrus (orbital part), bilateral inferior frontal gyrus (opercular part), and right superior frontal gyrus (medial orbital)] regions. Most of the regions mentioned above, including the hippocampus, cingulate gyrus, lenticular nucleus, and thalamus, are components of limbic-cortical-striatal-pallidal-thalamic (LCSPT) tract (Table 2 and for illustration of cortical surface, see Supplemental digital content 6, *http://links.lww.com/WNR/A215*).

Classifiers

Two hundred and seventy nodal metric values were selected as classification features and tested in six classification algorithms. The results revealed that SVM-RBF and neural networks exhibited the best performance, with an average accuracy of five thresholds

Fig. 1



Average accuracy in six classification algorithms. To compare the changes in classifier performance with different feature counts, we selected the statistically significant *P*-values as a threshold. There were five threshold levels: $P<0.005$, $P<0.015$, $P<0.05$, $P<0.10$, and $P<0.15$ and the corresponding number of features were 4, 15, 28, 55, 87. SVM-Linear, support vector machine with linear kernel function; SVM-RBF, support vector machine with radial basis kernel function; C4.5, decision tree with C4.5 algorithms; LDA, linear discriminant analysis.

reaching 79.27 and 78.22%, respectively, and the highest accuracy reaching 83.00 and 82.38%, respectively (Fig. 1).

Comparing the five threshold values revealed that all the algorithms except LDA exhibited the highest accuracy with 28 features ($P < 0.05$). The results suggested that different models always had an optimized feature number.

Feature importance

Sensitivity analysis was carried out with the neural network model to determine the importance of its characteristics in the classifying process. The results showed that the metrics exhibiting significant between-group differences also exhibited high sensitivity on several measures (for detailed feature importance of 270 metric values, see Supplemental digital content 7, *http://links.lww.com/WNR/A216*).

Furthermore, we analyzed the correlation between normalized sensitivity (S_i) and statistical significance (*P*-value) for each metric. All three nodal metrics exhibited strong positive correlations (Fig. 2). The results suggested that stronger statistical differences were associated with greater contribution to the classifying process. Our results demonstrated that statistical significance can be used as an appropriate criterion for feature selection.

Discussion

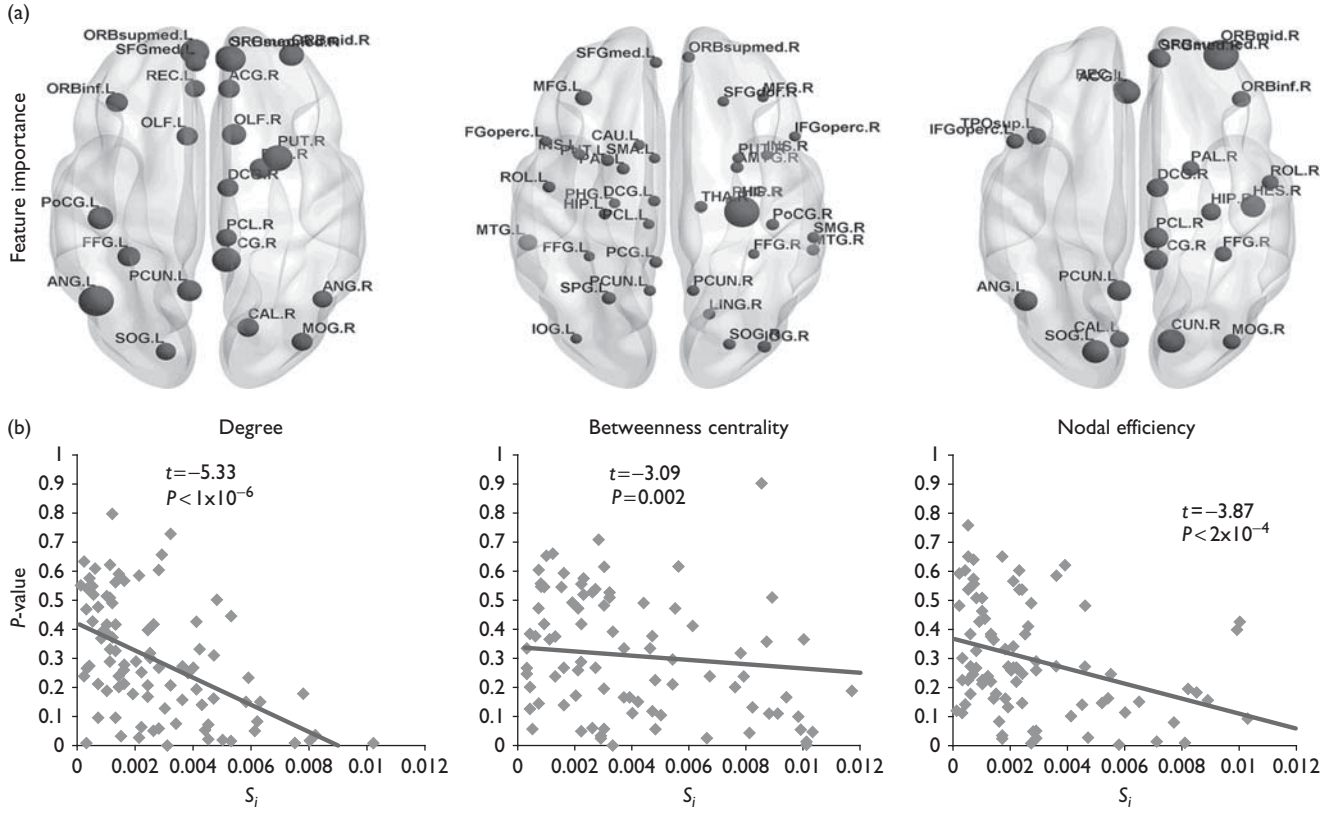
Most recent studies of the neural pathology of MDD implicate the LCSPT circuit (for review, see Sheline [16]). In the current study, some of the regions in this circuit exhibited significantly increased nodal centralities, including the limbic system (including the right hippocampus, right posterior cingulate gyrus, bilateral median cingulate, and paracingulate gyri), basal ganglia (right lenticular nucleus, putamen, right thalamus), and a part of the inferior parietal lobule region (right angular gyrus). The increased nodal centralities we observed in MDD patients indicate a strengthened role for coordinating whole-brain networks, possibly in response to the pathological disorder. Our research provides new evidence indicating pathological changes in the LCSPT circuit from a brain network perspective.

The current study revealed that most of the models exhibited the highest or second highest accuracy with 28 features ($P < 0.05$). In the classifier model, the optimized feature number P_{opt} is an important parameter for evaluating the model [17]. P_{opt} depends on the scale of the sample set, classifier rule types, distribution of the sample categories, effectiveness, and ordering of the selected features [18]. Previous studies have reported specific rules about P_{opt}. Jain and Waller [19] suggested the linear classification function P_{opt} could be calculated as $P_{opt} = (N/2) - 1$ assuming that all features have the same effect and a random order. N is the number of samples. The current findings are compatible with previous reports. Using simulation data, Hua *et al.* [20] compared seven kinds of classifier to find a different effect of error rate with different feature numbers, reporting highest accuracy with 28 and 30 features when the sample size was 50 in accord with the current findings.

Sensitivity analysis was carried out to determine the contribution of 270 nodal metric values in the classifier. The results revealed that the features of brain regions with significant between-group differences always provided strong contributions, including betweenness centrality in right hippocampus, right middle frontal gyrus, nodal efficiency in middle frontal gyrus (orbital part), right cuneus, and degree in left angular gyrus, right posterior cingulate gyrus, right superior frontal gyrus (medial part), right putamen. Previous studies reported that the abnormal morphology and function of these brain regions were related to MDD [1,21–23]. The current study provides machine learning evidence in support of this conclusion.

There are a couple of potential limitations in our study. First, the sample size is rather small and hence does not preclude the possibility that our result could have been affected by sample size. Second, as it was exploratory analysis, the statistical results of our network metrics were not corrected. Future studies should test a large sample of MDD patients to increase statistical power.

Fig. 2



Brain regions showing feature sensitivity (S_i) in the neural network algorithm and their relationship with statistical significance (P). (a) Nodes indicate the brain regions in which sensitivity was above 0.004. Node size indicates the value of sensitivity. The nodes were mapped onto the cortical surfaces using BrainNet viewer software (*http://www.nitrc.org/projects/bnv/*). (b) Scatter plot of the sensitivity of nodal metrics against statistical significance. There were strongly significant correlations with the three metrics (k_i: $P<1\times10^{-4}$; b_i: $P=0.002$; e_i: $P<2\times10^{-4}$).

Conclusion

In summary, the present study provides evidences that MDD is associated with abnormal functional brain network topological metrics, which could be used as effective features in constructing a classifier and that statistical significance can be used as an appropriate criterion to evaluate the effectiveness of the metrics during the classification process. Our research provided an initial step towards the use of brain network topological metrics. It would be clinically significant to identify individuals and predict the treatment automatically avoiding self-reported symptoms.

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Conflicts of interest

There are no conflicts of interest.

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