Application of Graph Theory Features for the Objective Diagnosis of Depressive Patients with or without Anxiety: an Rs-fMRI Study

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Abstract. Purposes: To probe abnormality that may lead to anxiety in depressive patients. Procedures: This study investigated the graph theory features ahead of machine learning feature selection procedure. Classification methods were applied afterwards. Methods: Graph theory, statistical analysis and forward sequential feature selection were combined to find features. SVM classifier was also involved. Results: 1 global and 22 local features were found correlated with clinical anxiety factor. Conclusions: Anxiety is correlated with emotion and cognitive loop and other regions.

Introduction

Anxious depression is a common clinical subtype of major depressive disorder(MDD) [1]. Dysphoric mood, disturbed sleep, somatic complaints, altered interoceptive awareness, and increased morbidity are all anxiety characters [2-4]. Many resting state fMRI (rs-fMRI) studies have been searching for biomarker that can distinguish anxious and non-anxious depressive patients[5]. However, despite the plenty works features of graph theory were not completely discussed.

In present study, we involved in 22 non-anxious depressive patients and 21 depressive patients, abstracting 7 global and 9 local graph theory features of each individual as a primary feature vector. And then the combined feature selection method was applied to efficiently reduce the dimension of the features. Statistical analysis and classification was performed afterwards.

Methods

Subjects

Since this study focused on the anxiety in depressive patients, healthy control was not included [6]. Forty-three patients with MDD were recruited (including 22 patients without anxiety and 21 patients with anxiety). The initial diagnoses of depression were made according to DSM-IV. All the patients were included according to the criteria: (1) the Hamilton depression scale (HAMD) scores were over 17, (2) medicine naive for at

least 2 weeks, (3) without history of drug abuse or alcohol dependency, (4) no other mental illness, (5) anxiety/somatization factor scores below 7 were assigned as without anxiety, while anxiety/somatization factor scores over 7 were assigned as with anxiety. The 17-item HAMD Anxiety /Somatization factor includes six items: Anxiety (psychic), Anxiety (somatic), Somatic Symptoms (gastrointestinal), Somatic Symptoms (general), Hypochondriasis and Insight.

The study was approved by the Research Ethics Review Board of Nanjing Brain hospital in China. The demographic characteristics of the subjects were summarized in Table1.

Table 1. Demographic and Clinical data of the groups

Item/Group	Non-anxious	Anxious	*p*
Age	33.7±8.05	32.6±8.95	0.671
Education	13.5±2.92	13.7±2.50	0.800
Anxiety/somatization factor	5.91±1.54	9.14±1.39	0.0001*
HAMD	24.5±2.52	25.9±3.30	0.136
Subject number	22	21	

Data Acquisition and Preprocessing

All imaging data were collected by a Siemens verio scanner. Before the scans, subjects were instructed to close their eyes and not to think systematically. Image preprocessing was completed by the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox [7] and the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm).

Functional connectivity matrixes were extracted by the DPARSF analyzing steps using AAL template. The matrixes were sparse where the sparsity was determined by scaling from 0.1 to 0.9 with a step as 0.05, and making a permutation test of the two groups divided by clinical anxiety factor 7. Since the optimal sparsity of each individual differed from each other and small changes ranging from 0.3 to 0.6 of it may not lead to sudden deteriorate of the primary graph feature performance, the sparsity was determined by all members together and was not involved in the LOO strategy. The sparsity led to the least p-value (which represent the highest statistical significant between the two groups) should be optimal.

Computation of Graph Theory Features

We computed 7 global and 9 local graph theory features of each individual. Global measures representing the integration situation have only one value for each graph whereas local measures representing segregation signature have n values (n is the number of nodes in the graph) for each graph [8]. Six functional integration graph features were estimated, which are characteristic path length [9], global efficiency [10], density, density edge number, network walk and transitivity scalar [11]. Another global feature assortativity was an assessment of resilience. Three segregation graph features were also calculated, which are clustering coefficient [9], nodal efficiency and local efficient [10]. Six other nodal measures including nodal degree, nodal strength, eccentricity, nodal betweenness centrality vector, eigenvector centrality and walk length distribution [12], were applied to assess properties of brain regions. We used the Brain Connectivity Toolbox (www.brain-connectivity-toolbox. net). And the final feature number of each individual was 1051 (7 global + 116 × 11 local).

Statistical Analysis and Feature Selection

We took a permutation test of each feature and kept the features which showed significant discriminative power (with the resulted p-value of permutation test below 0.05). And then a Fisher coefficient feature selection was taken, which denotes the discriminative power of one feature [8]. The performance was estimated by the accuracy the classifier gained by adding features.

Classification and Correlation Test

Classification method was applied to the remaining subset of features in feature selection procedure. We chose supervised classifier SVM using a Leave-One-Out (LOO) method to confirm the generalization of this classification process.

Correlation test was also applied to probe the ability these features possess to differentiate depressive patients with or without anxiety.

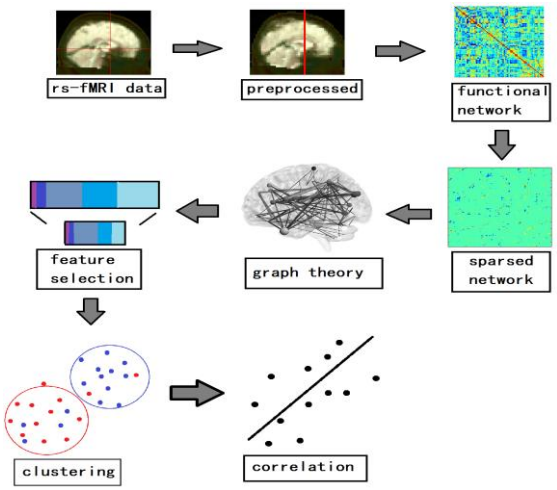

Figure 1. All the procedurals in this work

Results

Brain Network and Sparsity Decision

The data preprocessing, feature selection and classification process is shown in Fig. 1. Functional connectivity was calculated as correlation between AAL brain regions as the edges of brain network. And the resulted p-value changing with the sparsity was shown in Fig. 2. As is shown in the figure, the least p-value was resulted using sparsity 0.5. Thus we chose 0.5 as the optimal sparsity.

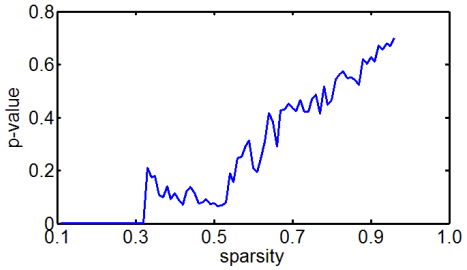

Figure 2. The p-value changes with sparsity.

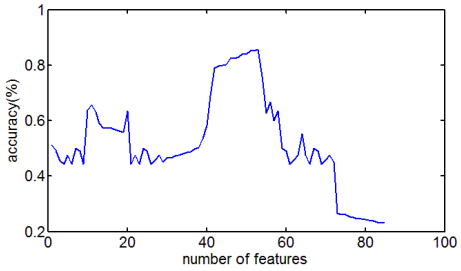

Figure 3. The accuracy changes in one LOO loop.

Table 2. The remaining features after the two feature selection procedure.

local graph feature	brain region	discriminative power
eigenvector centrality	Frontal_Sup_Medial_L	0.512438
nodal strength	Frontal_Sup_Medial_L	0.491747
clustering coefficient	SupraMarginal_R	0.460903
nodal betweenness centrality vector	SupraMarginal_R	0.460903
clustering coefficient	Rolandic_Oper_L	0.442652
nodal betweenness centrality vector	Rolandic_Oper_L	0.442652
eigenvector centrality	Temporal_Pole_Mid_R	0.429753
eigenvector centrality	Cingulum_Ant_R	0.427005
eigenvector centrality	Frontal_Mid_Orb_L	0.423196
eigenvector centrality	Fusiform_R	0.416208
eigenvector centrality	Frontal_Mid_Orb_R	0.413367
clustering coefficient	Pallidum_L	0.409213
nodal betweenness centrality vector	Pallidum_L	0.409213
clustering coefficient	Thalamus_L	0.393346
nodal betweenness centrality vector	Thalamus_L	0.393346
eccentricity	Cingulum_Post_L	0.391986

Feature Selection

The feature selection results were shown in Table 2. Only top 10% features were listed. The discriminative power was the mean value of the LOO repeat times. Only one global feature was found discriminative, which is global efficiency in Superior Frontal gyrus with the discriminative power as 0.07875. And 155 local nodal features of were found significant to the anxiety in depressive patients. Afterwards the classification accuracy achieved by adding features was shown in Fig. 3.

Classification Performance

By applying the LOO procedure the classification performance was able to be quantified. The percentage of false assignment of labels was counted to evaluate the accuracy of this classification procedure. The predictive accuracy, the sensitivity and the specificity was 0.8372, 0.8571, and 0.8182 respectively.

Correlation between Clinical Factor and Graph Features

The correlation of clinical factor and graph features were shown below in Table 3. The discriminative brain regions lie more in emotion-cognitive loop.

Discussion

In this study, we constructed a feature matrix using 7 global and 9 local graph theory features. We found out distinguishing features with a classification predictive accuracy as 0.8372 and the sensitivity as 0.8571, the specificity as 0.8182.

Intriguingly, the graph features correlated with anxiety factor we found lay mostly in emotion-cognitive loop. The Hippocampus regions and amygdala regions are believes to be necessary for the establishment of cognition and emotion, whose dysfunction may relate to the anxiety symptom [13]. It has been proved that the right prefrontal activation is associated with certain forms of anxiety [14]. Waugh et al. found out activation in temporal gyrus (during task recovery), and less activation of the cerebellum among

anxious patients [15]. The Andreescu et al's work suggest that anxiety maintain a "higher alert," scanning both in occipital areas and parietal areas [6]. Therefore, the abnormal observed in our study was believed to indicate impairments in intro-spective integration processing in anxious depression.

The feature selection procedure including statistical analysis and machine learning method was time consuming and efficient, since the features performed well in the classification and consistency measurements as shown in Fig. 3. Moreover, the discriminative power in our study can be quantified after the feature selection (Table 3).

Table 3. Correlation of clinical factor and graph features

Local graph features	Brain regions	Correlation coefficient	Statistical significance
degree	Cingulum_Ant_L	-0.314	0.016
	Occipital_Sup_L	0.307	0.019
	Occipital_Sup_R	0.405	0.002
clustering coefficient	Supp_Motor_Area_R	-0.290	0.027
	Frontal_Sup_Medial_L	-0.325	0.013
nodal efficiency	Occipital_Sup_L	0.263	0.046
	Occipital_Sup_R	0.372	0.004
eccentricity	Cingulum_Post_L	0.333	0.011
	Hippocampus_R	0.356	0.006
	Amygdala_L	0.272	0.039
	Calcarine_L	0.338	0.009
	Lingual_R	0.317	0.015
	Occipital_Sup_L	0.352	0.007
	Occipital_Inf_R	0.317	0.015
	Temporal_Mid_L	0.274	0.037
	cerebellum	0.327	0.012
	cerebellum	0.281	0.033
nodal betweenness centrality vector	Supp_Motor_Area_R	-0.290	0.027
	Frontal_Sup_Medial_L	-0.325	0.013
eigenvector centrality	Occipital_Sup_L	0.280	0.033
nodal strength	Occipital_Sup_L	0.347	0.008
	Occipital_Sup_R	0.378	0.003

Conclusions

In present work we applied an advanced feature selection method on graph features, and result in fine accuracy of differing anxious depressive patients with nonanxious depressive patients. The discriminative features mostly lay in emotion-cognitive loop, which we suggest played an important role in the depressive anxiety machanism.

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