Classification of Borderline Personality Disorder based on Spectral Power of Resting-State fMRI

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Abstract— **Borderline personality disorder (BPD) is a serious mental illness that can cause significant suffering and carries a risk of suicide. Assigning an accurate diagnosis is critical to guide treatment. Currently, the diagnosis of BPD is made exclusively through the use of clinical assessment; no objective test is available to assist with its diagnosis. Thus, it is highly desirable to explore quantitative biomarkers to better characterize this illness. In this study, we extract *spectral power* features from the *power spectral density* and *cross spectral density* of *resting-state fMRI* data, covering 20 brain regions and 5 frequency bands. Machine learning approaches are employed to select the most discriminating features to identify BPD. Following a *leave-one-out cross validation* procedure, the proposed approach achieves 93.55% accuracy (100% specificity and 90.48% sensitivity) in classifying 21 BPD patients from 10 healthy controls based on the top ranked features. The most discriminating features are selected from the *0.1~0.15Hz* frequency band, and are located at the *left medial orbitofrontal cortex*, the *left thalamus*, and the *right rostral anterior cingulate cortex*. The high classification accuracy indicates the discriminating power of the *spectral power* features in BPD identification. The proposed machine learning approach may be used as an objective test to assist clinical diagnosis of BPD.**

Index Terms- **borderline personality disorder (BPD), functional magnetic resonance imaging (fMRI), spectral power, feature selection, classification**

I. Introduction

Borderline Personality Disorder (BPD) is a serious and complex mental illness characterized by unstable moods, behavior, and relationships [1]. It affects about 1.6% of Americans age 18 or older [2]. Research on the possible causes and risk factors for BPD is still at a very early stage and its underlying mechanisms remain unclear. Furthermore, BPD is often either underdiagnosed or misdiagnosed [1]. A major limitation to accurate diagnosis is that current BPD diagnosis is based on a person's self-reported symptoms and a clinical assessment by a mental health professional. There is no objective test which can diagnose the disease or verify a clinical assessment. Therefore, it is highly desirable to explore quantitative, robust and interpretable biomarkers for BPD, which would facilitate the clinical diagnosis and help in gaining knowledge about the physiological basis of the illness.

Neuroimaging studies have reported some consistent findings about structural and functional changes of the brain associated with BPD, mainly at the fronto-limbic regions. For example, magnetic resonance imaging (MRI) studies have found a reduced volume of the *hippocampus*, *amygdala orbitofrontal cortex* (OFC), and *anterior cingulate cortex* (ACC) in BPD patients [3, 4]. Functional MRI (fMRI) studies have also shown abnormal brain activity and connectivity at these regions using experimental paradigms that elicit a response to facial expressions [3, 4]. These findings suggest the potential of imaging based brain patterns as biomarkers for BPD identification. However, neuroimaging literature to date has two shortcomings. First, these studies examined each brain region separately without considering the combination effect of different regions. Second, these studies made inferences at the group level based on traditional statistical hypothesis, which do not provide information about the predictive ability of the patterns when applying to new subjects.

To overcome these limitations, we apply machine learning based pattern recognition and classification techniques, which can analyze multiple brain regions at the same time. Machine learning techniques are now routinely applied to analyze brain imaging data for the identification and predication of various brain diseases, such as schizophrenia, epilepsy, major depressive disorder, etc. However, the applications of such techniques to explore imaging-based biomarkers for BPD have not been sufficiently investigated. A recent study reported 80% accuracy in classifying 25 BPD patients from 25 healthy subjects using structural MRI patterns combined with Support-Vector-Machine classifier [5]. However, no classification result has ever been reported using fMRI data.

Motivated by the above considerations, we explore spectral-spatial fMRI features for BPD identification by machine learning approaches. The key contributions of this work are two-fold: selection of *spectral power* features and machine learning based classification. First, we extract *spectral power* features from the *power spectral density* (PSD) and *cross power spectral density* (CPSD) of resting-state fMRI (rs-fMRI) data covering 20 brain regions and 5 frequency bands. PSD describes how the strength of a signal is distributed in the frequency domain while CPSD describes how the strengths of two signals are shared in the frequency domain. The s*pectral power* is the sum of the PSD or CPSD values in a frequency band, which represents the total power

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in that band. To the best of our knowledge, this feature set has never been studied for BPD identification. Second, we have designed a machine learning based feature ranking and classification scheme. The feature ranking algorithm helps to select a small subset of most discriminating features, based on which a classifier is trained to distinguish BPD patients from healthy controls.

II. METHODS

Signal processing approaches are used to extract spectral-spatial features from rs-fMRI data. A *leave-one-out cross validation* (LOO-CV) [6] procedure is strictly followed during feature selection and classification. Each time, 30 subjects are used for feature selection and classifier training, while the other one subject is used for testing the classification accuracy. The procedure is repeated 31 times until all subjects have been used as testing subject once. The systematic framework of the study is shown in Figure 1. Details of each part are explained below.

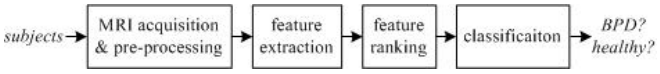


Figure 1. Framework of the study

A. Subject

Twenty-one BPD patients (7 male) aged 20 to 45 (mean 29 ±7.1), and 10 healthy control subjects (4 male), aged 19 to 45 (mean 27 ±7.5) participated in this study. None of the control subjects met criteria for a psychiatric or neurological disease or had any major medical illnesses. All the patients met the *DSM-IV-TR* criteria [7] for BPD diagnosis. In order to reduce confounds associated with diagnostic comorbidity, the patients included in this study do not have a history of any psychotic disorder, bipolar disorder, major depressive disorder with psychotic features, obsessive-compulsive disorder, generalized anxiety disorder, social phobia, or post-traumatic stress disorder. All the subjects gave written informed consent before entering the study. The study was approved by the University of Minnesota Institutional Review Board.

B. MRI data acquisition & pre-processing

Structural and functional MRI data were acquired at the University of Minnesota's Center for Magnetic Resonance Research using a Siemens 3T TIM Trio scanner. Whole-brain anatomical images were acquired using a T1-weighted high-resolution magnetization prepared gradient echo (MPRAGE) sequence: TR = 2530ms; TE = 3.65ms; TI = 1100ms; flip angle = 7 degrees; 1 mm slices, FOV = 256, voxel size 1x1x1 mm; GRAPPA =2. The six-minute resting-state fMRI scans were obtained using 180 contiguous echo planar imaging (EPI) whole brain volumes with TR = 2000ms; FOV = 256; voxel size 3.43x3.43x3.43 mm; 34 slices; 64x64 matrix, during which subjects were instructed to relax, try not to think about anything in particular, and remain awake with their eyes closed.

FreeSurfer [8] was used to process the T1 data including brain extraction and parcellation of data into a standard set of anatomically-based regions of white and grey matter. FreeSurfer output was visually inspected; when any errors were identified (N=2) they were manually corrected on a slice-by-slice basis. The processed T1 data was registered to the rs-fMRI data using *bbregister*. The rs-fMRI processing was mainly conducted using tools from the FMRIB software library [9]. Initial processing included brain extraction and motion correction. A denoising procedure was applied incorporating RETROICOR [10] to remove physiological noise caused by cardiac and respiratory cycles as well as any linear trends. Correction for magnetic field inhomogeneity-induced geometric distortion was conducted using the field map. FreeSurfer-generated regions of interest (ROIs) for lateral ventricles (cerebrospinal fluid; CSF) and white matter (WM) were aligned to rs-fMRI data using FLIRT [9]. Mean BOLD time series within these ROIs were extracted using *fslmeants*. We performed a regression of each other voxel's time series on eight nuisance variables: WM time series, CSF time series, and the six motion parameters. Data scrubbing was performed following [11] excluding any volume with a DVARS value exceeding 8 and/or a framewise dependent (FD) value exceeding 0.5, along with the previous volume and the two following volumes. Averaged time series from 20 FreeSurfer-based ROIs including: left and right *rostral*-ACC, *amygdala, thalamus, insula, caudal-ACC, medial-OFC, precuneus, posteriorcingulate, hippocampus* and *parahippocampus,* were used for further analysis.

C. Feature extraction

Spectral power of the rs-fMRI data is used as the feature for BPD classification. First, the PSD of the fMRI signal from each of the 20 regions, and the CPSD for each of the 190 region pairs were estimated using Welch method [12]. Next, define 4 frequency sub-bands: *B1 (0.01~0.05Hz), B2 (0.05~0.1Hz), B3 (0.1~0.15Hz), B4 (0.15~0.2Hz),* and a total band *B5 (0.01~0.2Hz).* The *spectral power* of PSD for each band is defined as the sum of the PSD within each band.

$$P_{PSD}(i,j) = \sum_{f \in B_j} PSD(i,j), \quad i = 1,\ldots,20. \; j = 1,\ldots,5. \tag{1}$$

where i and j are the indices for regions and bands, respectively. The size of the P_{PSD} feature set is 20 regions * 5 frequency bands = 100.

Similarly, the *spectral power* of CPSD is defined as the sum of CPSD within each band for each region pair.

$$P_{CPSD}(i,j) = \sum_{f \in B_j} CPSD(i,j), \quad i = 1,\ldots,190. \; j = 1,\ldots,5. \tag{2}$$

where i and j are the indices for region pairs and bands, respectively. The size of the P_{CPSD} feature set is 190 region pairs * 5 frequency bands = 950.

D. Feature ranking

Feature selection is an important and necessary step to prevent classifier overfitting, especially when the sample size is smaller than the dimensionality of the feature space, as in this application. Feature selection not only provides more cost-effective and more accurate predictors, but also helps in locating the most relevant frequency ranges and brain regions that contribute to the discrimination. In this study,

we employed the *minimum redundancy maximum relevance* (mRMR) criteria [13] to rank the P_{PSD} and the P_{CPSD} feature sets. The mRMR algorithm selects features according to the maximal statistical dependency criterion based on mutual information *I*. Mutual information based feature selection aims at finding a feature set *S* with *m* features $\{x_i\}$, which jointly have the largest dependency on the target class c.

$$\max D(S,c), \quad D = \sum_{x_i \in S} I(x_i;c) / |S|. \tag{3}$$

Features selected according to the maximal dependency criterion could have large redundancy. When two features highly depend on each other, the respective class-discriminative power would not change much, if one of them was removed. Therefore, the following minimal redundancy condition can be added to select mutually exclusive features:

$$\min R(S), \quad R = \sum_{x_i, x_j \in S} I(x_i,x_j) / |S|^2. \tag{4}$$

Finally, an operator $\Phi(D,R)$ is defined in terms of dependency *D* and redundancy *R*. The mRMR criterion solves the optimization problem given by:

$$\max \Phi(D,R), \quad \Phi = D - R. \tag{5}$$

E. Classification

We employed the Gaussian Mixture Model (GMM) [6] classifier to distinguish the patients from the controls, based on the top ranked *spectral power* features. GMM classifier classifies a sample $\mathbf{x}$ to the class C_i that yields the largest posterior probability $P(C_i \mid \mathbf{x})$. According to Bayes' Theory,

$$P(C_i \mid \mathbf{x}) = \frac{P(\mathbf{x} \mid C_i)P(C_i)}{P(\mathbf{x})} = \frac{P(\mathbf{x} \mid C_i)P(C_i)}{\sum_i P(\mathbf{x} \mid C_i)P(C_i)} \tag{6}$$

where $P(\mathbf{x} \mid C_i)$ is called the class likelihood; $P(C_i)$ is the relative probability for each class and is called the prior probability. Since the denominator $P(\mathbf{x})$ is the same for both classes, the decision rule becomes:

$$choose \begin{cases} C_1, & if\ P(\mathbf{x} \mid C_1)P(C_1) > P(\mathbf{x} \mid C_2)P(C_2) \\ C_2, & if\ P(\mathbf{x} \mid C_1)P(C_1) < P(\mathbf{x} \mid C_2)P(C_2) \end{cases}. \tag{7}$$

Assume the features are normally distributed within each class:

$$P(\mathbf{x} \mid C_i) = (\exp[-\frac{1}{2}(\mathbf{x} - \mathbf{m_i})^T \mathbf{S_i}^{-1}(\mathbf{x} - \mathbf{m_i})]) / \sqrt{(2\pi)^d \cdot |\mathbf{S_i}|} \tag{8}$$

where *d* is the dimension of the feature space; $\mathbf{m_i}$ is the mean vector of class C_i and $\mathbf{S_i}$ is the corresponding covariance matrix; N_1 and N_2 are the total number of samples in classes C_1 and C_2, respectively. Estimates of $\mathbf{m_i}$, $\mathbf{S_i}$, and the prior probability $P(C_i)$ can be obtained using maximum likelihood (ML) method for each class.

$$\hat{\mathbf{m}}_\mathbf{i} = \sum_{\mathbf{x} \in C_i} \mathbf{x} / N_i \tag{9}$$

$$\hat{\mathbf{S}}_\mathbf{i} = \sum_{\mathbf{x} \in C_i} (\mathbf{x} - \hat{\mathbf{m}}_i)(\mathbf{x} - \hat{\mathbf{m}}_i)^T / N_i \tag{10}$$

$$\hat{P}(C_i) = N_i / (N_1 + N_2) \tag{11}$$

III. Experimental Results

A. Classification Results

The performance of the proposed feature selection and classification scheme was evaluated using: *accuracy*, *specificity* and *sensitivity*, which represent the percentage of correctly classified subjects, controls and patients, respectively.

In Table I, we list the classification results using P_{PSD} and P_{CPSD} features, respectively. Besides GMM, two other commonly used classifiers: *linear discriminant analysis* (LDA) [6] and *k-nearest neighbor* (kNN) [6] are also tested for comparison. The highest classification accuracies are achieved using GMM classifiers with top 9 features ranked by the mRMR algorithm, for both feature sets. 19 out of 21 BPD patients and all the 10 control subjects are correctly classified while 2 patients are misclassified as controls.

TABLE I. Clssification Results with P_{PSD} and P_{CPSD} Feature Sets, using *LDA*, *kNN* and *GMM* Classifiers

feature	classifier	# of feats.	accuracy	specificity	sensitivity
P_{PSD}	*LDA*	10	0.8065	0.6	0.9048
	kNN	1	0.8065	0.9	0.7619
	GMM	**9**	**0.9355**	**1**	**0.9048**
P_{CPSD}	*LDA*	3	0.8387	0.7	0.9048
	kNN	1	0.8065	1	0.7143
	GMM	**9**	**0.9355**	**1**	**0.9048**

B. Feature Analysis

To explore the brain locations and frequency ranges that are most related to the discrimination between controls and patients, we show the region and frequency distributions of top P_{PSD} and P_{CPSD} features with P-value <=0.005 in Figures 2 and 3, respectively. Note that each P_{PSD} feature is associated with one frequency band and one ROI while each P_{CPSD} feature is associated with one frequency band and two ROIs. The histograms are obtained by counting the number of occurrences of each region and each band based on all P_{PSD} and P_{CPSD} features with P-value <=0.005.

From Figure 2, we observe that the most discriminating brain regions are the bilateral *thalamus*, the bilateral *precuneus*, *right rostralACC* and *left medialOFC*. These regions are key regions which have been shown to have structural and functional abnormalities in BPD patients. Other brain regions do not show significant spectral power difference between groups. In Figure 3, we observe that top ranked features exist in all frequency band between 0.01~0.2 Hz, and *B3 (0.1~0.15 Hz)* occurs as the highest occurrence.

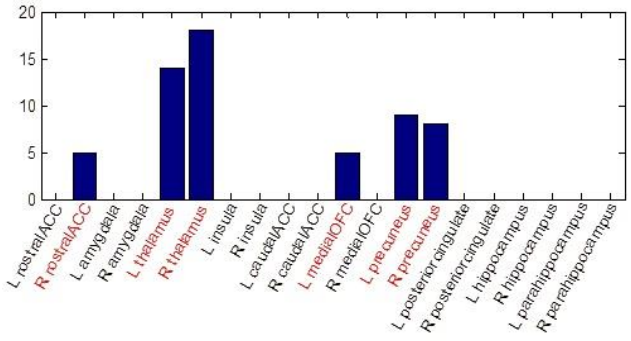


Figure 2. Number of occurrences of the 20 regions based on all P_{PSD} and P_{CPSD} features with p-value <=0.005.

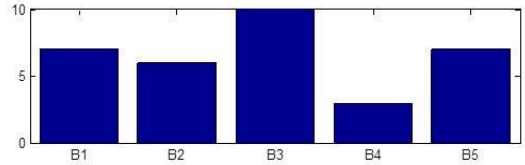
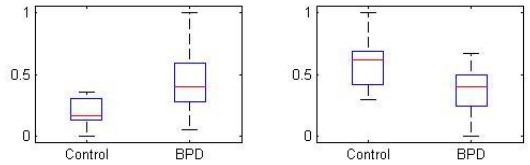


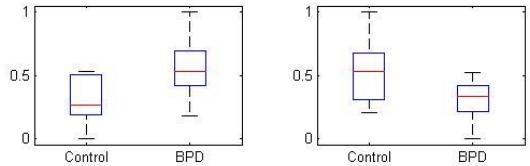
Figure 3. Number of occurrences of the 6 frequency bands based on all P_{PSD} and P_{CPSD} features with p-value <=0.005.

Furthermore, we show the boxplots of top two P_{PSD} and P_{CPSD} features with lowest p-value in Figures 4 and 5, respectively. All the 4 features were selected form the 0.1~0.15Hz frequency band. The patient group shows an increased P_{PSD} at the *left medialOFC* and a decreased P_{PSD} at the *left thalamus*. Patients also show an increased P_{CPSD} between the *right rostralACC* and the *left medialOFC* regions, as well as a decreased P_{CPSD} between the *left thalamus* and the *right precuneus* regions.



(a) (b)

Figure 4. Boxplots of top 2 P_{PSD} features: (a) left medialOFC, [0.1, 0.15 Hz], p-value = 0.0038, (b) left thalamus, [0.1, 0.15 Hz], p-value = 0.0039



(a) (b)

Figure 5. Boxplots of top 2 P_{CPSD} features: (a) right rostralACC-left medialOFC, [0.1, 0.15 Hz], p-value = 0.0028, (b) left thalamus-right precuneus, [0.1, 0.15 Hz], p-value = 0.0033

IV. Conclusions

In this study, we explore spectral-spatial fMRI patterns for BPD identification. Specifically, *spectral power* was extracted from the PSD and CPSD of rs-fMRI data, covering 20 ROIs and 5 frequency bands. Machine learning based feature ranking and classification approaches were employed to distinguish BPD patients from healthy controls. We identified several key regions and a frequency range which show significant spectral power difference between groups. Based on the top ranked features, 93.55% overall classification accuracy is achieved in discriminating 21 BPD patients from 10 healthy control subjects, following the LOO-CV procedure. High accuracy indicates potential of the identified *spectral power* features to become biomarkers for BPD identification. The feature ranking and classification scheme may be used to design a computer tool for assisting clinical diagnosis of BPD.

A limitation of this study is the small sample size (31 subjects). Sample size is especially important in light of heterogeneity of BPD. Therefore, the results of this work need to be interpreted with caution and need to be validated in future studies. Future work will be directed towards exploring other types of imaging patterns and more efficient feature selection and classification algorithms for BPD identification and tracking changes with treatment.

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