Identification of depression using support vector machine with different connectivity

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Abstract. Patients with depression have shown attention bias and inhibition deficits of negative emotional valance. However, it is not clear how the distributed brain networks support the function of inhibition and whether the modulation altered in depression. Thirty-seven patients with depression and 37 matched controls were undertook the audio-visual emotion task-fMRI and whole-brain psychophysiological interaction analysis was employed to obtain three different types of connectivity features, including task-modulated connectivity (TMC), task-independent connectivity (TIC) and task-functional connectivity (TFC). Support vector machine method was used to classify depression and explore the relation of reaction time prediction. Results indicated decreased modulation related to frontoparietal cortex, increased in temporal lobe and sensorimotor system in depression. Moreover, TMC performed better in predicting RT, while TIC and TFC had better classification performance. This study reveals that aberrant modulation of neural response is widely associated with the inhibitory dysfunction in depression and support that different connectivity features provide supplementary information for underpinning the functional integration and its alterations of brain networks.

1. Introduction

Major depressive disorder (MDD) is complex mental illness characterized by emotion dysregulation and cognitive deficit, which accompanied by increased negative information and difficulties in disengaging from negative material [1, 2]. Numerous studies have revealed that MDD patients display poorer ability of recognition in facial [3, 4] and vocal emotional expressions [5]. Specifically, MDD tends to have longer reaction time (RT) of emotional valance [6] and show decreased activation in the dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (VMPFC) cortex [7], as well as increased activation in the amygdala (AMG) and anterior cingulate cortex (ACC) gyrus [8]. Previous studies have revealed the brain responses to specific stimuli for negative emotion in depression, which linked MDD with imbalanced frontoparietal and subcortical networks, as reflected by abnormal neural activity [9]. However, most of them focus on the regional brain activations during audio-visual emotional inhibition task, the potential aberrant functional interactions between regions in MDD remain unclear.

Psychophysiological interaction (PPI) method is referred as the main method to assess the modulated effects between two regions with different task conditions [10, 11]. Previous neuroimaging studies have revealed that reduced functional connectivity between the left amygdala and bilateral VLPFC in depression during emotion processing tasks [12]. Besides, MDD was reported to be mediated by medial
prefrontal cortex by using PPI analysis, especially functioning on rostral/dorsal ACC gyrus [2]. Whole-brain PPI analysis examines a broader range of functional relations of brain but the difficulty of the multiple-comparison may arise due to the coverage of brain regions increased [13]. Machine learning method can overcome this problem [14], in particular, support vector machine is widely used in disease diagnosis, prognosis, treatment response prediction and symptom prediction [15, 16]. Although it is known that MDD can be characterized by neural responses associated with the attentional bias to negative emotion, the relationship between functional dysregulation and behavioural index is poorly understood.

In this study, we implemented audio-visual emotional task fMRI for both MDD and healthy control (HC) groups and employed whole-brain analysis to extract three different types of connectivity features. Specifically, task-modulated connectivity (TMC) and task-independent connectivity (TIC) were obtained by psychophysiological interaction model, and task-functional connectivity (TFC) was computed by Pearson correlation analysis. Support vector classification (SVC) model was used to characterize MDD from HC and support vector regression (SVR) model was built to explore the relationships between TMC and RT in patients with depression. We hypothesize that different types of connectivity would measure complementary information of brain functions and have their advantages for characterizing MDD.

2. Methods and materials

2.1. Subjects

Over the course of the study, fMRI data from 74 participants consisted of 37 MDD and 37 matched HCs were analyzed (see Table 1 for details). Clinical states of the patients were evaluated using the 24-items Hamilton Depression Scale (HDMD) and the healthy control group were recruited from the community through advertisements. Written consent was obtained from each participant and all procedures were approved by the research ethical committee of School of Life Science and Technology at University of Electronic Science and Technology of China (UESTC).

Table 1. Demographics and clinical characteristics of patients with MDD and HC.

| Variables              | MDD Mean ± SD | HC Mean ± SD | p-value |
|------------------------|---------------|--------------|---------|
| Gender (M / F)         | 12 / 25       | 18 / 19      | 0.155a  |
| Age (years)            | 31.49 ± 12.12 | 36.57 ± 16.28 | 0.192b |
| Education (years)      | 14.30 ± 3.62  | 12.95 ± 2.77 | 0.076b  |
| Mean FD                | 0.08 ± 0.06   | 0.08 ± 0.05  | 0.738b  |
| Handness (Left / Right)| 0 / 37        | 0 / 37       | 1a      |
| RT(ms)                 | 802.60 ± 101.90 | 991.00 ± 227.40 | < 0.001*|

Abbreviations: a: chi-square test; b: Two-tailed two-sample t-test;

2.2. Experimental Design

In the experiment, sad face was combined with 2 sounds condition (laughing, crying), resulting in 2 different conditions (emotional congruent or incongruent). There were in total 30 Congruent trials and 30 Incongruent trials, and each trial was last for 4000, 6000 or 8000ms randomly. After presenting 1000ms cross and 1000ms background emotion picture, participants were asked to process visual stimuli projected on a screen behind them and press on MR-compatible response pad to sound on a keyboard with their both hand (one hand for laughing and the other for crying) while keep their eyes on picture. Stimuli was presented with the software Eprime.

2.3. fMRI Data Acquisition

MRI data were acquired using a 3.0T GE 750 scanner (General Electric, Fairfield, Connecticut, USA) equipped with high-speed gradients. An 8-channel prototype quadrature birdcage head coil fitted with
foam padding was applied to minimize the head motion. Foam pads and earplugs were used to minimize head movement and scanner noise. Functional images were acquired using a gradient-recalled echo-planar imaging (EPI) sequence. The parameters were as follows: repetition time/echo time = 2000 ms/30 ms, 90° flip angle, bandwidth = 250 Hz/pixel, 43 axial slices (3.2 mm slice thickness without gap), 64 × 64 matrix, 22 cm field of view. For each participant, a total of 190 volumes were obtained.

2.4. Data Preprocessing
Functional images were preprocessed using the Data Processing Assistant for fMRI (DPARSF 4.3) based on Statistical Parametric Mapping (SPM12). The main steps were as follows: (1) the first 10 volumes were removed; (2) the remaining 180 images were slice-timing corrected; (3) the corrected images were spatially realigned to adjust head motion, and coregistered to the anatomical image. (4) the deformation field maps were spatially normalized to Montreal Neurological Institute (MNI) EPI template. (5) the normalized images were resampled to 3×3×3 mm³ voxels and smoothed with 6mm FWHM Gaussian kernel. The BOLD signal for fMRI were extracted from 246 regions of interest (ROI) separately [17], in where brain regions can be divided into 7 networks, including frontal, temporal, parietal, insular, limbic, occipital, and subcortical networks.

2.5. GLM model and PPI Analysis
To examine the interaction effect of 2 condition trials in regions selective for audio-visual emotional congruence, the time courses of each ROI were first deconvolved with canonical hemodynamic response function (HRF), and multiplied pointly with the experimental conditions, then reconvolved with the HRF. As a result, a GLM model named gPPI [18] was built as follows:

\[ Y = \alpha + \beta_0 \times X_{\text{physio}} + \beta_1 \times X_{\text{psycho(incongruent)}} + \beta_2 \times X_{\text{psycho(congruent)}} + \beta_3 \times X_{\text{physio}} \times X_{\text{psycho(incongruent)}} + \beta_4 \times X_{\text{physio}} \times X_{\text{psycho(congruent)}} + \epsilon \]

Where \( Y \) is the time series of seed ROI, \( X_{\text{physio}} \) is another ROI’s time series, \( \alpha \) is the constant, \( \beta_{1-4} \) are the experimental regression terms and \( \epsilon \) is the residual term. The task-modulated connectivity (TMC) was defined as \( \beta_3 - \beta_4 \), measuring the modulated relationship between two regions under task interactions. The task-independent connectivity (TIC) was defined as \( \beta_0 \), capturing the intrinsic relationship between two regions without modulation [19]. Besides, the task-functional connectivity (TFC) between each ROI was calculated by Pearson correlation analysis, then Fisher-z transformation was performed to all connections. Consequently, a 246 × 246 TMC/TIC/TFC matrix for each subject was obtained, since the matrix is symmetrical, 30135 upper triangle elements of the matrix were extracted as connectivity features.

2.6. Classification and Prediction Based on Support Vector Machine
In order to avoid the over fitting problem, combined filter- and wrapper-based approaches and the 10-fold cross-validation (CV10) strategy were employed to obtained the optimal features set. Specifically, we performed two-sample t test as a filter-based method in training set and retained features with \( p \) value smaller than the threshold (\( p < 0.01 \), uncorrected). In case of minimizing the redundancy in biologically relevant in discriminative power among features, a wrapper-based method named SVM-RFE (SVM-RFE) with MRMR filter [20] was additionally employed. For each level of connectivity features, support vector machine (SVM) classifier with a linear kernel (\( C = 1 \)) was employed by using LIBSVM toolbox. The performance of a classifier was quantified by the accuracy (ACC), area under curve (AUC), sensitivity (SE), specificity (SP), and under receiver operating characteristic (ROC) in the testing set. A permutation test was implemented 5000 times with a threshold of \( p < 0.05 \) to judge the classifier’s statistical significance.

To further explore how different types of connectivity contribute to behavioral impulsivity level, a SVR model with a sigmoid kernel was employed to predict reaction time of depression patients, and the CV10 scheme was used in line with the previous procedure. The most discriminative classification features summed by each fold were used to construct the predictive model. After obtaining the predicted reaction time, we computed its correlations with the observed reaction time by using Pearson correlation.
analysis. The significance of the predictive model was assessed by using 5000 permutation tests with threshold of $p < 0.05$.

3. Result

3.1. Classification performance
Patients of MDD were characterized from HC based on different types of connectivity features using SVM model and the performance the classification in terms of ROC curves were shown in Figure 1 (see Table 2 for more details). In particular, TIC obtained best performance among all types of connectivity and achieved a classification accuracy of 82.14%, an AUC of 79.11%, a sensitivity of 75.68%, a specificity of 89.19%. Both TMC and TFC had comparable classification performance and achieved much higher than chance accuracy, with the accuracy = 0.7036/0.7482, AUC = 0.6289/0.7078, sensitivity = 0.7027/0.7838, specificity = 0.7027/0.7027, respectively.

![Figure 1. Characterizing MDD based on TMC/TIC/TFC using SVM model.](image)

| Feature types | ACC     | AUC     | SE      | SP      | p-value   |
|---------------|---------|---------|---------|---------|-----------|
| TMC           | 0.7036  | 0.6289  | 0.7027  | 0.7027  | < 0.0038* |
| TIC           | 0.8214  | 0.7911  | 0.7568  | 0.8919  | < 0.0001* |
| TFC           | 0.7482  | 0.7078  | 0.7838  | 0.7027  | < 0.0001* |

Table 2. Classification results using three types of connectivity features.

Abbreviations: p-value was measured by permutation test 5000 times using 10-fold cross-validation;

3.2. Altered TMC with high discriminative power in MDD
The most discriminative features were most frequently selected in all cross-validations due to the optimal feature differ from fold to fold. The left and right panels show decreased and increased TMC in MDD compared with HC, respectively (shown in Figures 2). The results indicated that the decreased TMC mainly involved in frontoparietal network and increased TMC related to sensorimotor network in MDD, and the areas contributed most for classifying MDD mainly included the left para-hippocampal gyrus-left middle temporal gyrus and left amygdala-left middle frontal gyrus. In particular, the most discriminative TIC and TFC features were located in temporal and subcortical network, which were quite different from TMC features.
3.3. Prediction Performance
The discriminative features were further investigated their correlation with the observed RT in MDD by SVR model and Pearson’s correlation analysis was employed to evaluate the prediction power (Figure 3). TIC and TFC failed to predict the RT of MDD, while TMC succeed. Specifically, TMC achieved high correlation of 0.44 between predicted and observed RT of depression with significance of $p = 0.0062$ ($p < 0.05$, FDR corrected).

![Figure 3. RT prediction based on TMC/TIC/TFC using SVR model.](image)

4. Discussion
It has been demonstrated that the attentional bias of negative emotions is largely associated with difficulties inhibition in depression.[21, 22]. The widely distributed networks of frontoparietal cortex and subcortical systems are crucial to emotion regulation and cognitive inhibition on functional communications in brain [23]. When it comes to depression patients, the response to cross-modal emotional stimuli is manifested as the dysfunction of superior temporal gyrus (STG) and inferior frontal gyrus (IFS) [24, 25]. In the context, we revealed decreased modulated connectivity within or across frontoparietal network and subcortical network, increased modulation related to sensorimotor network, providing new insight to understanding the abnormal modulation mechanism of MDD’s brain.

In addition, the classification models showed that depression can be characterized by the task-modulated connectivity under incongruent emotional valance. Additional features showed that important weights for discriminating depression from healthy controls are the local neural response as well as the network interactions within or between in the superior temporal gyrus, sensorimotor cortex, and lateral prefrontal areas [26, 27]. Particularly, our findings demonstrated that prefrontal lobes were attributed most to the discriminative power, which confirms that the frontoparietal network plays significant role in emotion inhibition.

It’s worth noting that different types of connectivity features had their own advantages in classification and behavior prediction. TIC obtained the highest accuracy in classification, while TMC performed better for behavior prediction. Previous studies have indicated that TIC/TFC are trait-like...
measures to reflect the intrinsic fluctuation, but TMC prefer to be state-like measure of the interactive modulation between regions [28]. Of note, the classification is a characteristic problem of requiring discriminative power to separate two groups while the RT prediction identifies features correlated with behavioral indicators [29]. Together, all connectivity features showed high performance in both classification and prediction, supporting that the functional interactions modulated by task can be used as potential biomarker to identify and evaluate depression.

5. Conclusion
In this study, we characterized the aberrant modulation of audio-visual emotional encoding in depression using support vector machine with different task-related connectivity. The results indicated that depression had impaired emotional modulation ability with the weak effect on frontoparietal to sensorimotor network and the hyperactivity between audio-visual and subcortical networks. Moreover, RT of depression can only be predicted by TMC but not TIC or TFC, indicating the aberrant modulation is largely association with the inhibition deficits of negative emotion in MDD. These results demonstrated that different types of connectivity measurement provide supplementary information for underpinning the functional integration and have implications for understanding the complex neural mechanisms in MDD.

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