



Research article

Predictive brain networks for major depression in a semi-multimodal fusion hierarchical feature reduction framework

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ABSTRACT

Major depressive disorder (MDD) is characterized by dysregulation of distributed structural and functional networks. It is now recognized that structural and functional networks are related at multiple temporal scales. The recent emergence of multimodal fusion methods has made it possible to comprehensively and systematically investigate brain networks and thereby provide essential information for influencing disease diagnosis and prognosis. However, such investigations are hampered by the inconsistent dimensionality features between structural and functional networks. Thus, a semi-multimodal fusion hierarchical feature reduction framework is proposed. Feature reduction is a vital procedure in classification that can be used to eliminate irrelevant and redundant information and thereby improve the accuracy of disease diagnosis. Our proposed framework primarily consists of two steps. The first step considers the connection distances in both structural and functional networks between MDD and healthy control (HC) groups. By adding a constraint based on sparsity regularization, the second step fully utilizes the inter-relationship between the two modalities. However, in contrast to conventional multi-modality multi-task methods, the structural networks were considered to play only a subsidiary role in feature reduction and were not included in the following classification. The proposed method achieved a classification accuracy, specificity, sensitivity, and area under the curve of 84.91%, 88.6%, 81.29%, and 0.91, respectively. Moreover, the frontal-limbic system contributed the most to disease diagnosis. Importantly, by taking full advantage of the complementary information from multimodal neuroimaging data, the selected consensus connections may be highly reliable biomarkers of MDD.

1. Introduction

Major depressive disorder (MDD), which is characterized by low self-esteem, loss of interest in normally enjoyable activities, low energy, decreases in productivity and recurrent thoughts of self-harm or suicide, is the second largest cause of disability worldwide [1]. According to a recent report by the World Health Organization (WHO), the number of subjects with depression has increased by nearly 20% during the previous decade, and the current lifetime estimated prevalence of MDD worldwide is 17%. However, in most developed countries, half of the patients with MDD who suffer from depression are undiagnosed or untreated, and in less-developed nations, this percentage soars to between 80 and 90% [2]. Thus, early diagnosis is urgently needed for treating people at a risk of developing MDD.

To address this need, potential biomarkers of depression that can effectively predict and diagnose the disease have been evaluated in many neuroimaging studies [3–5]. Neuroimaging techniques, including magnetic resonance imaging (MRI), diffusional tensor imaging (DTI), positron emission tomography (PET) and functional MRI (fMRI), have the capacity to diagnose and predict the prognosis of patients with MDD. Extensive studies investigating multi-modality multi-task methods have been recently performed, and these methods have achieved excellent performance by fully utilizing complementary information from multiple modalities [6–9].

MDD is a heterogeneous illness, and its symptoms are associated with a dysregulation of a distributed neuronal network encompassing widespread regions that are associated with emotional and cognitive functions [10–13]. The dysregulation of distributed neuronal networks

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can be expressed by functional connectivity brain networks and structural connectivity brain networks. Functional connectivity brain networks can generally be investigated by group-level statistical comparisons and multivariate pattern analyses [14–16]. However, these methods cannot be applied to characterize the disease-associated structural networks because these connections are defined by the Pearson correlation coefficients between the interregional volume/cortical thickness across subjects within a group. Therefore, it may be challenging to utilize information from structural networks to predict and diagnose diseases may be challenging. However, the concept of multimodal fusion provides the following useful information: Structural networks could be employed as supplementary information, rather than a principal factor, in disease diagnosis. Structural and functional networks have been shown to be related at multiple temporal scales [17]. Brain areas are connected by white matter axons, and both are believed to be influenced by common tropic, developmental, and maturational influences [18–23]. The remarkable homogeneity between functional and structural networks indicates that functional connectivity networks can be considered the primary choice for the “principal part” in multimodal fusion. However, notably, the pattern of multimodal fusion in our paper is inconsistent with conventional multi-modality multi-task methods. Structural networks were introduced only to obtain supplementary information for feature reduction but were not applied in the following classification procedure. We named this approach “semi-multimodal fusion”.

In this paper, we propose a hybrid feature reduction framework to better capture complementary information from multiple modalities by preserving the relationship between the feature vectors derived from the functional and structural connections. To solve the inconsistent dimensionality of the features between the functional and structural networks, we replicated the feature matrix of the structural networks. Our proposed method is a hybrid feature reduction framework composed of two steps. The initial feature filtering is performed during the first step. In this process, we considered both the significance obtained by two-sample *t*-tests comparing functional connections and the distance of structural connections between the MDD and healthy control (HC) groups. The “wrapper” feature selection is performed during the second step, and we added a new constraint to preserve the inter-modality relationship based on the original *k*-support norm to enforce the sparseness of the selected features from the functional connections. The *k*-support norm is a key statistical method for improving the predictive performance when the sample size is substantially smaller than the dimensionality of the features while the underlying signal is known to be sparse [24]. Finally, a support vector machine (SVM) was applied to predict the classification label based on the selected functional connections.

2. Materials and methods

2.1. Study sample

This study was conducted at the Department of Psychosomatics and Psychiatry, ZhongDa Hospital, Southeast University. Written informed consent was obtained from each participant according to the Declaration of Helsinki, and all procedures were approved by the medical ethics committee of ZhongDa Hospital, Southeast University. In total, 56 antidepressant-free patients with MDD and 55 demographically similar HCs were recruited for this study. Detailed descriptions of all participants are presented in the supplementary material (S1). The demographic and clinical characteristics of the patients with MDD and the HCs are presented in Table 1.

2.2. Image acquisition

Imaging data were acquired using a 3-T Siemens scanner with a 12-channel head coil. High-resolution 3-dimensional T1-weighted 3D scans

were recorded in a magnetization prepared rapid gradient echo sequence (TR/TE = 1900/2.48 ms; FA = 90°; acquisition matrix = 256 × 256; FOV = 250 × 250 mm²). The whole brain resting-state fMRI data were acquired using a gradient-recalled echo-planar imaging pulse sequence (TR/TE = 2000/25 ms; FA = 90°; acquisition matrix = 64 × 64; FOV = 240 × 240 mm²; total volumes = 240). During the 8-min resting-state fMRI scan, the participants were instructed to keep their eyes open, relax, lay still in the scanner and refrain from falling asleep.

2.3. Structural connectivity networks

The VBM analyses were performed using Statistical Parametric Mapping (SPM8: <http://www.fil.ion.ucl.ac.uk/spm>). The preprocessing flow is consistent with the standard VBM DARTTEL procedure, and the detailed steps are presented in the supplementary material (S2). We constructed the structural connection matrix using the following steps. First, we generated ninety cortical and subcortical ROIs, excluding the cerebellum, by applying the automated anatomical labeling (AAL) parcellation scheme. Pearson correlation coefficients between the volumes within each ROI across subjects were calculated. Therefore, two structural connectivity networks (MDD groups vs. HC groups) were generated using the aforementioned approaches. After removing 90 diagonal elements, we extracted the lower triangle elements of the correlation coefficients (CCs) as features; the feature space was spanned by $(90 \times 89)/2 = 4005$ -dimension feature vectors. Therefore, the 4005-dimension feature vectors M_S^{MDD} and M_S^{HC} were constructed for the MDD and HC groups, respectively.

2.4. Resting-state functional networks

2.7 The resting-state fMRI data were analyzed using SPM8 software and the CONN-fMRI Functional toolbox [25]. The preprocessing flow is consistent with the standard processing procedure, which is implemented in CONN-fMRI, and the detailed preprocessing steps are presented in the supplementary material (S3). We constructed a functional connection matrix using the following steps. We parcellated all brain maps into 90 cortical and subcortical ROIs, excluding the cerebellum, by applying the AAL parcellation scheme. Pearson correlations between the mean time courses of each pair of ROIs were calculated. Therefore, for each subject, we obtained a resting-state functional network captured by a 90×90 symmetric matrix. We extracted the lower triangle elements of the CCs as features, and the feature space was spanned by $(90 \times 89)/2 = 4005$ dimension feature vectors.

2.5. Semi-multimodal fusion hierarchical feature reduction framework

An overview of our proposed MDD diagnosis pipeline is illustrated in Fig. 1. Our proposed hybrid feature reduction framework comprised two steps. First, the initial feature filtering step was performed, followed by a modified sparsity regularization.

2.5.1. Feature filtering procedure

Flow path of the feature filtering procedure was as follows: (1) we generated the differential structural network feature vector ΔM_S by subtracting the features in M_S^{HC} from the corresponding features in M_S^{MDD} , i.e., $\Delta M_S = M_S^{MDD} - M_S^{HC}$; (2) we sorted all 4005 features in ΔM_S in descending order according to their absolute values; (3) a two-sample *t*-test was performed to determine whether each of the 4005 features of the functional connectivity network was significantly different between the patients of MDD and the HCs. All 4005 features were ranked according to their significance level; (4) to integrate the anatomical and functional connectivity information extracted from T1 and the rs-fMRI, an overlapping pattern was used to select the features; (5) we selected the top-ranked *c* features from the different modalities, where *c* was set based on the rule that the value of the *c*-th feature in

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