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Multimodal Analysis of Structural and Functional MRI for Schizophrenia Diagnosis

Huixiang Zhuang[1], Yao Li[2], Ruihao Liu[2], Chaowei Wu[2], and Manhua Liu[1]*
[1] Dept. of Instrument Science and Engineering, School of EIEE, Shanghai Jiao Tong University, Shanghai, China
[2] Institute of Medical Imaging Technology, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China
*mhliu@sjtu.edu.cn

ABSTRACT

Schizophrenia (SZ) is one of the important brain diseases. Multimodal magnetic resonance (MR) images provide the important imaging biomarkers to detect the pathological changes in both brain function and anatomy for SZ diagnosis. In this paper, we propose a multi-modal image classification algorithm based on sparse coding and random forest to combine the structural and functional MR brain image analysis for SZ diagnosis. First, the structural and functional MR images are processed to extract the anatomical features and functional connectivity measures for representation. Second, for each modality, sparse coding is used for initial feature selection and the selected features are used as input for random forest (RF) models to calculate a proximity matrix for each modality. Third, the features from the two modalities are combined by linear combination of two proximity matrices into one matrix and the classical multidimensional scaling (MDS) is applied to the proximity matrix for dimensionality reduction. Finally, the reduced matrices are served as inputs for the RF models for multi-modal classification. Our proposed algorithm is tested on the structural and functional MRIs for classification of SZ and healthy controls. Both sparse coding and RF have capability of estimating the potential relationship among various features to reach an ideal group discriminating performance. Experimental results show the effectiveness of the proposed multimodal classification method for SZ diagnosis.

Keywords: Random forest, sparse coding, multi-modality, classification, manifold learning, schizophrenia

1. INTRODUCTION

Schizophrenia (SZ) is one of the important brain diseases which affects 3.8-8.4‰ people all over the world [1]. The typical clinical symptoms of SZ include cognitive dysmetria, altered perception, hallucination, motor activity impairment, language and cognition obstacle etc. It has been found in clinic that different types of symptoms are related to different morphological changes and functional dys-connections in brains. Magnetic resonance images (MRIs) can provide powerful imaging modalities to detect the brain changes and make discrimination between the healthy persons and the disorders. Multimodal brain MRIs can provide important imaging biomarkers of pathological changes from both functional and anatomical views for SZ diagnosis. Mass data across the multiple modalities require computational methods to make use of these data and achieve high efficiency and accuracy of classification [2]. Pattern recognition methods have been widely investigated for multimodal brain MR image analysis, with the advantages of handling with high-dimensional features [3-8]. However, most existing methods work on single modality. It is still challenging to consider the relationship of features within or across different modalities by multimodal MRI analysis for brain disease diagnosis.

Most of existing methods on multimodal brain image classification were proposed for prediction and diagnosis of Alzheimer's disease (AD) and mild cognitive impairment (MCI) [3-6]. The random forest (RF) based classification method was proposed to make use of multi-modal similarity to differ MCI patients from AD patients and healthy persons [3]. By combining proximity matrices in different modalities, an embedding was generated with the information from all features simultaneously. This combination method facilitates the collaboration of the multimodal MRIs. The multi-kernel linear support vector machine (MKL-SVM) were successfully applied for multimodal analysis which make use of multiple kernels to combine the multimodal features for AD diagnosis [4, 5]. In addition, multi-modality sparse representation-based classification was proposed for diagnosis of AD and MCI, which assigned different weights to the features of different modalities [6]. As for SZ diagnosis, RF was applied on single modality analysis such as functional connectivity measures extracted from resting-state functional MRI (rs-fMRI) [7] and cortical thickness from structural MRI (sMRI) [8]. From the previous studies, it is still challenging to combine the anatomical and functional MRIs for SZ diagnosis.

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sMRI and rs-fMRI provide complementary information for SZ diagnosis. Random forests provide consistent pairwise similarity measures for multiple imaging modalities, thus facilitating the combination of different types of image features. In this study, we have proposed a framework of multi-modality classification based on RF to combine cortical measures from sMRI and functional connectivity (FC) measures from rs-fMRI for improving SZ diagnosis. First, the sMRIs and rs-fMRI are processed to extract the features for representation. Second, sparse coding is used to select the discriminative features as input for RF models to compute a proximity matrix for each modality. Third, the multimodal features are fused by a linear combination of two proximity matrices into one matrix and the classical multidimensional scaling (MDS) is applied to the proximity matrix for the reduction of dimensionality. Finally, the reduced proximity matrix is the input to the RF models for multimodal classification and SZ diagnosis.

2. THE IMAGE DATASET AND FEATURE EXTRACTION

Both the structural and functional MRI scans used in this work are captured from two groups: 29 healthy controls from local community and 40 schizophrenia patients recruited from Shanghai Mental Health Center, China. All patients met the criteria of schizophreniaor schizophreniform disorder in Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V).

2.1 Data Acquisition

All sMRI and rs-fMRI data were collected on a 3.0-T Siemens Verio MR Scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil at the Shanghai Mental Health Center. During the process of scanning, the main parameters of imaging were as follows: blood oxygen level dependent (BOLD) images with echo time (TE)=30ms, repetition time (TR)=2000ms, slice thickness=4.0mm, voxel size=3.4$\times$3.4$\times$4.0mm, field of view (FOV)=220mm, matrix size=256$\times$256, and slice number=180. Anatomical T1-weighted images were acquired using a magnetic preparation fast gradient echo (MPRAGE) sequence with TE=3.65ms, TR=2530ms, FOV=256mm, slice thickness=1.0 mm, and slice number=224. Examples of the original MR images were displayed in Figure 1.

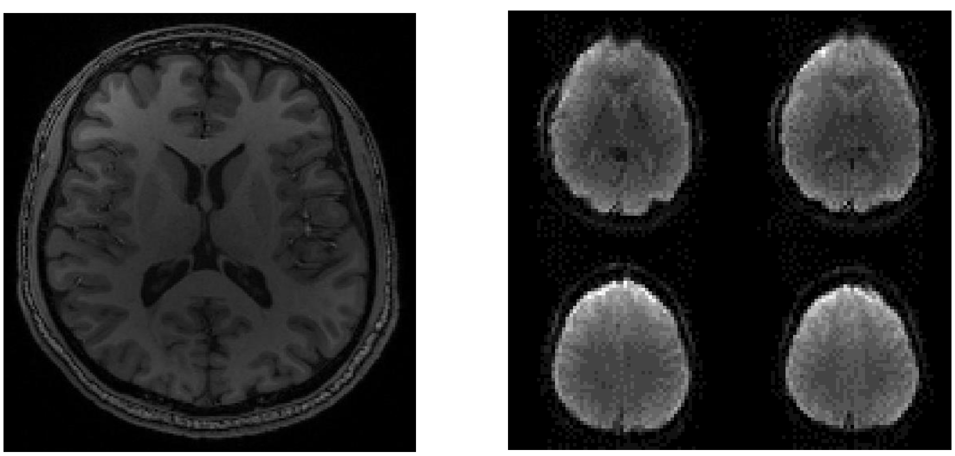

Figure 1. Examples of the original MR images (left: T1-weighted structural image; right: BOLD functional images)

2.2 Image Preprocessing

Freesurfer 6.0.0 (http://www.freesurfer.net/fswiki/DownloadAndInstall) [9, 10] is used for preprocessing of sMRI images. The software provides a complete pipeline of cortical and subcortical nuclei segmentation and surface reconstruction process. The T1-weighted MRIs of 69 subjects go through the fully automated pipeline for preprocessing. However, manual interventions are conducted for each subject to correct the potential errors in segmentation.

Preprocessing of fMRI data was conducted by SPM8 package (http://www.fil.ion.ucl.ac.uk/spm/software/do-wnload/), rest1.8 (http://restfmri.net/forum/index.php?q=rest) and DPARSF2.3 (http://rfmri.org/DPARSF) advanced edition under Matlab 2013a (Mathworks, USA). The parameters were initially set and the pipeline goes through automatically. After the preprocessing of realignment, normalization, smoothing, detrend and filtering on the BOLD images, features will be extracted from the processed images.

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2.3 Feature Extraction

Freesurfer calculated nine statistics for each segment based on different registration protocols. The statistical measures such as standard deviations derived from some of the other measures were excluded. We chose six of them as features in our study [11]. The six feature measures are: 1) cortical thickness; 2) gray matter volume (GMV); 3) surface area (calculated by computing the area of each triangle after tessellation); 4) mean curvature (computed by using the registration surface based on the folding patterns); 5) curvature index; 6) folding index. We chose the stats based on Destrieux atlas consisting of 74 regions of interest (ROIs) in each hemisphere [12]. 148 features of each type were acquired as a pair of 74 features from each hemisphere. The total number of features from sMRI is 888=148×6.

Functional connectivity matrix was constructed by applying an automatically labeled template, automated anatomical labeling (AAL), to parcellate the brain into 116 ROIs [13]. A Fisher's-Z transformation was further applied to the correlation matrices to improve the normality of the correlation coefficients. Since a value of FC revealed the connection between two different ROIs, 116 ROIs can generate 116×115÷2=6670 FC values.

3. PROPOSED MULTI-MODAL CLASSIFICATION ALGORITHM

An overview of the proposed multimodal classification algorithm is demonstrated in Figure 2. Sparse coding is to select the discriminative for each modality. Then the selected features are used to train the Random forests (RF) models. RF is applied twice in the proposed algorithm. The first RF is applied to compute proximity measures and the second RF is to make the final multimodal classification. Classical MDS is applied to the proximity matrix to generate embedded feature data in a lower dimension, which serve as the input of the latter RF.

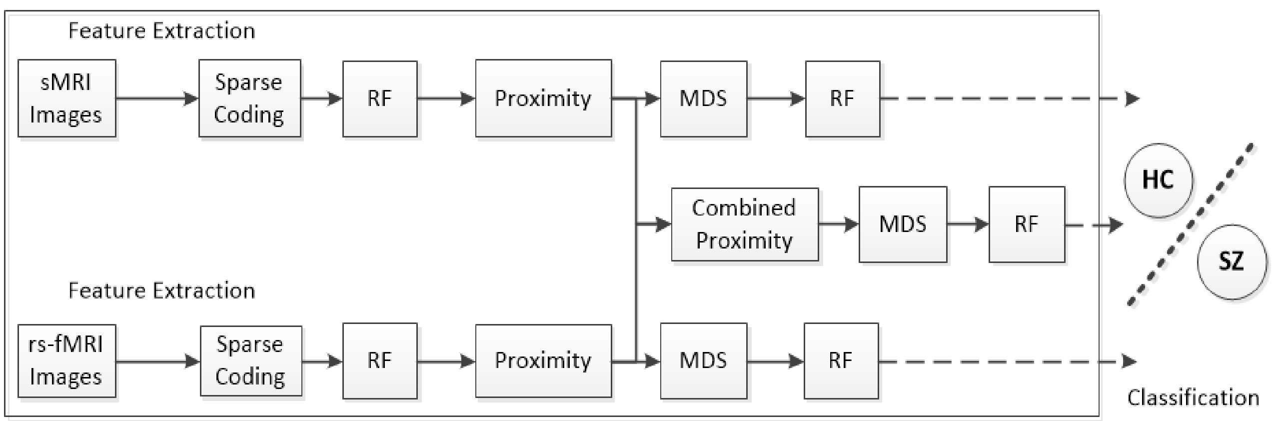

Figure 2. The framework of the proposed multi-modality classification algorithm.

3.1 Feature Selection Based on Sparse Coding

To avoid missing the important features for classification, we extract the features as many as possible from multi-modal MRI images. Traditionally, two-sample t-test was often used to select discriminative features. While this method completely ignored the correlations of imaging features and did not consider the discrimination of multiple variable combination. But the disease-induced abnormal changes often happen in multiple contiguous brain regions, instead of isolated voxels. To identify the informative biomarkers, a multivariate model is learned to consider the combinations of features over the distant brain regions for handling the multivariate interactions in feature selection. Accordingly, a sparse coding method with L1-regularization [14, 15] is applied to select the informative features for each modality. Sparse coding focus on the combination of multi-variable features to achieve a global significance. Let **A** represent a $P \times Q$ feature matrix where P and Q are the numbers of subjects and features in the matrix, respectively. The *pth* row of **A** is the feature vector of the image from the *pth* participant. y denotes the class labels of all participants with the *pth* element being the class label of the *pth* participant. Thus, a linear regression model can be used to generate the class outputs with a set of features as follows:

$$\mathrm{y} = \mathbf{A}\vec{\omega} + \varepsilon \quad (1)$$

where $\vec{\omega} = (\omega_1, \omega_2, \dots, \omega_Q)$ be a vector of coefficients assigned to the corresponding features, and ε is an independent error term. The class output can be characterized as the linear combination of features. One popular method to solve this

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problem is the least square optimization. When the number of features is large, sparsity is imposed on the coefficients to choose a small number of relevant features for classification. The L1-regularized sparse coding can be formulated as:

$$\vec{\omega} = \operatorname{argmin}_{\omega} \|y - \mathbf{A}\vec{\omega}\|_2^2 + \mathrm{z}\|\vec{\omega}\|_1, \ \ s.t. \vec{\omega}_i \geq 0, \forall i \tag{2}$$

where z is the sparsity regularization parameter which controls the amount of zero coefficients in $\vec{\omega}$. When the z value increases, the number of non-zero elements in $\vec{\omega}$ decrease to select more features. The non-zero elements in $\vec{\omega}$ indicate that the corresponding features are selected as relevant features for classification. Thus, the L1-regularized sparse coding method provides an effective multivariate regression model to select a subset of relevant features by taking into consideration both the correlations of features to the class labels and the combinations of individual features [16]. By adjusting the values of sparsity, various numbers of features can be selected without ranking. This method can jointly select the features from multiple contiguous brain regions based on the population difference.

3.2 Proximity-based Random Forest and Dimensionality Reduction by Manifold Learning

Random forest (RF) is an ensemble classifier of T decision trees in the forest. As to each decision tree in the forest, the training samples are randomly selected to establish the training set for the tree, which is known as bootstrap aggregation (bagging) [17]. All the terminal nodes can denote the category (SZ or HC in this study). Random forests combine bagging and random feature selection to provide a high classification performance as well as the estimation of importance for different variables. After training, the RF can generate proximity measures [18, 19]. Each of the N examples is represented by a feature vector, and all of them are passed down each tree in the forest. If examples i and j finish in the same terminal node of a tree, their proximity p_{ij} is increased by one. The final pairwise proximity measures are normalized by T, i.e., the total number of trees in the forest.

Furthermore, the proximity matrix of N×N is transformed into a distance matrix with each element $d_{ij} = 1 - p_{ij}$ [20]. Classical MDS is a dimension reduction method with the aim of generating manifolds that are optimal for the task of clinical group discrimination. It is applied on the distance matrix to generate a reduced coordinate embedding for the feature vectors based on eigenvalue calculation. The output of MDS contains the matrix of coordinates **X**, representing a k-dimensional embedding for the data.

3.3 Multi-modal Classification Based on Random Forest

After deriving the proximity matrix by RF, and RF is further used to make classification for single/multi-modality. To statistically evaluate the classification performance, the standard 10-folds cross-validation is performed in the experiments. Each time, 1 fold was used for testing, while the other remaining 9 folds were used as training set. To generate an embedding that simultaneously incorporated information from multiple modalities, a fused proximity matrix P was defined as a linear combination of the similarity matrices from the individual modalities P_i. Each modality was assigned a weighting factor α_i, such that $P = \sum_{i=1}^{2} \alpha P_i$, where $\sum_{i=1}^{2} \alpha = 1$. α_i is a weighting parameter optimized by grid search to ensure the optimal combination of multiple modalities for final classification.

4. EXPERIMENTAL RESULTS

In this section, we will present the experiments and compare the results in details. Sparse coding is conducted and the RF model is trained based on the feature matrix from each modality independently. The RF is implemented with the 'Treebagger' in Matlab 2014b to conduct forest training, proximity matrix calculation, and prediction. For training the RF model, we need to set the number of trees in the forest and the number of features randomly selected at each tree node. The number of trees is set to 300 based on the out-of-bag (OOB) classification error, which is stable with $T \gtrsim 100$. The number of selected features $d = \sqrt{D}$ for all experiments [21], where D is the available feature number in input dataset. From the RF, we obtained two separate proximity matrices from two modalities. Then we used classical MDS to reduce the dimension of each matrix. A goodness-of-fit value of 90% is set to determine an appropriate dimensionality of the transformed matrix. Then the RF classifier was trained based on the embedded features and 10-fold cross validation was applied. The parameters including sparsity z and weighting factor α_i are optimized based on training data. The rate of classification accuracy, sensitivity and specificity are computed to evaluate the classification performance.

The first experiment is to test the classification performances without using sparse coding for feature selection as shown in Table 1. From the results, the multi-modal classification performed the same as the single-modal classification of rs-fMRI (with accuracy 72.6%). The features of sMRI have no contribution on the multi-modal RF classifier. The results show that the performance without sparse coding is not very effective due to the redundant and noisy features.

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Table 1. Classification performance of single- and multi-modality without sparse coding.

Modality	Accuracy (%)	Sensitivity (%)	Specificity (%)
sMRI	62.6	85.0	31.7
rs-fMRI	72.6	87.5	51.7
Multi-modality	72.6	87.5	51.7

The second experiment is to test the classification performances without dimensionality reduction by MDS as shown in Table 2. From the results, we can see that combination of multi-modal features can improve the classification performance.

Table 2. Classification performance of single/multi-modality without MDS.

Modality	Accuracy (%)	Sensitivity (%)	Specificity (%)
sMRI	62.9	77.5	43.3
rs-fMRI	74.0	85.0	60.0
Multi-modality	79.8	92.5	63.3

The third experiment is to test the classification performances by the proposed multimodal classification algorithm using both the feature selection by sparse coding and dimension reduction by MDS. The single/multi-modality classification results are shown in Table 3. We also list k-dimension of the embedded features by MDS. From Table 3, we can observe that functional connectivity features are more effective than the cortical measures in classification. Combining these features significantly improve the classification performance.

Table 3. Classification performances of different modalities by the proposed method.

Modality	Accuracy (%)	Sensitivity (%)	Specificity (%)	k
sMRI	65.7	77.5	50.0	43
rs-fMRI	75.5	85.0	63.3	41
Multi-modality	81.2	92.5	66.7	48

Finally, we compare the proposed multimodal classification algorithm with the results without feature selection by sparse coding as in Gray et al. [3] and without dimension reduction by MDS as shown in Table 4. From the results, after applying sparse coding and MDS, the proposed algorithm achieves better performances than those without sparse coding and MDS. Feature selection and dimension reduction play important roles in the proposed algorithm.

Table 4. Comparison of multi-modal classification accuracy among the methods.

Method	Without sparse coding	Without MDS	The proposed method
Sensitivity (%)	87.5	92.5	92.5
Specificity (%)	51.7	63.3	66.7
Accuracy (%)	72.6	79.8	81.2

5. CONCLUSION

In this paper, we proposed a multimodal classification algorithm based on combination of sparse coding and RF for SZ diagnosis. Sparse coding is used for feature selection, while RF is used to generate proximity measures for feature combination of multi-modalities and MDS is applied to generate manifolds for optimal group discrimination. The proposed method has the advantages of discovering proper embedding of feature data and fully mining the relationship between features. The experiment results and comparison show the improvement of classification performance in the multimodal imaging data of sMRI and rs-fMRI.

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6. ACKNOWLEDGMENTS

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