



Integration of Handcrafted and Embedded Features from Functional Connectivity Network with rs-fMRI for Brain Disease Classification

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Abstract. Functional connectivity networks (FCNs) based on the resting-state functional magnetic imaging (rs-fMRI) can help to enhance our knowledge and understanding of brain function, and have been applied to diagnosis of brain diseases, such as Alzheimer's disease (AD) and its prodromal stage, *i.e.*, mild cognitive impairment (MCI). Traditional methods usually extract meaningful measures (*e.g.*, local clustering coefficients) from FCNs as (handcrafted) features for training the model. Recently, deep neural networks (DNNs) have been used to learn (embedded) features from FCNs for classification. However, few work explores to integrate both kinds of features (*i.e.*, handcrafted features from traditional methods and embedded features from DNN methods), although these features may convey complementary information for further improving the classification performance. Accordingly, in this paper, we propose a novel learning framework to integrate the handcrafted features from traditional method and embedded features from DNN method for classification of brain disease with rs-fMRI data. Experimental results on 174 subjects with baseline rs-fMRI data from the ADNI demonstrate the superiority of the proposed methods against several existing methods.

1 Introduction

The human brain is a complex structure, which contains multi-level and multi-functional substructure. Functional magnetic resonance imaging (fMRI) Neuroimaging technology provides a important tool to explore the mechanism and cognitive processing of the brain [1], and have been widely applied to analysis of brain disease, including Alzheimer's disease (AD) and its early stages, *i.e.*, mild cognitive impairment (MCI) [2]. Recently, function connectivity networks (FCN) based on resting-state fMRI (rs-fMRI) data, which characterizes the interaction between distributed brain regions, and thus help to better understand the pathology of brain diseases, have been widely applied to analysis of brain diseases [3].

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Recently, studies have successfully applied FCNs to the task of automated brain disease classification [4].

In these studies, each FCN is usually considered as a graph with each node denoting a brain region and edge corresponding to relation between nodes. Therefore, graph object provides a important way for exploring the association between brain functional deficits and the underlying structure [5]. In FCN classification task, traditional methods usually extract some meaningful graph measures (*e.g.* local clustering coefficients [6], regional homogeneity [3] and connectivity strengths [7]) from the FCNs as (handcrafted) features for training a learning model, and feature selection methods (*e.g.* t-test [6], LASSO [8]) were performed to select more discriminative features for improving the performance of the learning model. These studies have helped us to better understand pathology of the brain disease and improve the performance of brain disease diagnosis.

As a powerful learning method, deep learning technology, *e.g.*, convolutional neural network (CNN), is able to automatically learn (embedded) features from raw sensory data, has been successfully applied to many fields of medical image analysis [9], including computer-aided breast lesion detection [10], lung nodules [11] and histopathological diagnosis [12]. Recently, studies have applied deep neural network (DNN) methods to learning high-level features from FCNs for brain connectivity analysis. For example, (Jie *et al.*, 2020) [13] defined a unified CNN-based learning framework to extract hierarchical connectivities from FCNs for disease diagnosis based on rs-fMRI data. Compared with handcrafted feature based methods, deep learning based methods can achieve a good disease classification performance. However, few work explores to integrate both kinds of features (*i.e.*, handcrafted features from traditional methods and embedded features from DNN methods), although these features may convey complementary information for further improving the classification performance. Through this method the generalization error rate is low, the accuracy is high, and it can be applied to most classifiers without adjusting parameters.

Accordingly, in this paper, we propose a novel learning framework to integrate the handcrafted features from traditional method and embedded features from CNN method for classification of brain disease with rs-fMRI data. Figure 1 illustrates the proposed learning framework. Specifically, we first build the FCN of each subject using Pearson correlation coefficient (PCC) as connectivity measure. Then, based on constructed FCN, we extract the clustering coefficient as handcrafted features by using traditional graph object based method, and learn embedded features by using CNN-based method. Finally, we integrate two kinds of features for brain disease classification. Experimental results on 174 subjects with baseline rs-fMRI data from the ADNI demonstrate the superiority of the proposed methods against several existing methods.

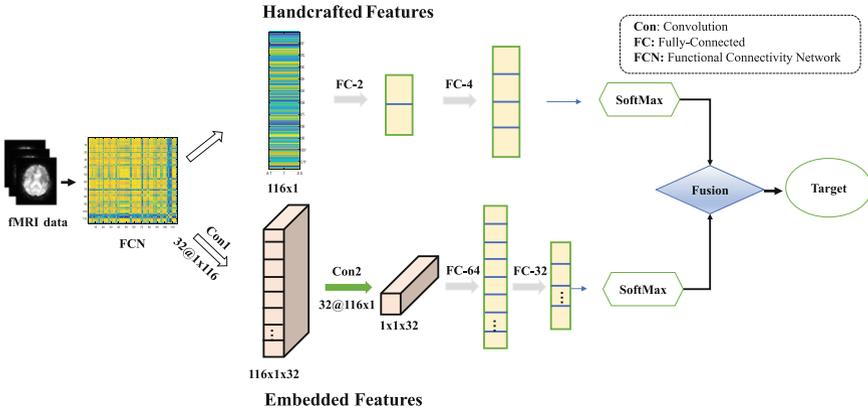


Fig. 1. Illustration of the proposed learning framework integrating handcrafted and embedded features of FCNs based on rs-fMRI data for brain disease classification.

Table 1. Characteristics of the studied subjects from ADNI (Mean±Standard Deviation). MMSE: Mini-Mental State Examination.

Group	HC	eMCI	lMCI	AD
Male/Female	20/28	20/30	27/18	16/15
Age	76.0 ± 6.8	72.4 ± 7.1	72.3 ± 8.1	74.7 ± 7.4
MMSE	28.8 ± 1.4	28.1 ± 1.6	27.1 ± 2.1	21.8 ± 3.3

2 Method

2.1 Subjects

In this study, we use 174 subjects with rs-fMRI data from the ADNI database¹, including 48 healthy controls (HCs), 50 early MCI (eMCI), 45 late MCI (lMCI) and 31 AD. Data acquisition was performed as follows: the image resolution is 2.29–3.31 mm for inplane, and slice thickness is 3.31 mm, TE = 30 ms and TR = 2.2–3.1 s. The clinical and demographic information of subjects is given in Table 1.

2.2 Image Preprocessing and Network Construction

Following [14], we use the standard pipeline to preprocess the rs-fMRI data, including (1) discarding the first 10 rs-fMRI volumes, (2) slice timing correction, and (3) head motion correction. The brain space of fMRI scans is partitioned into 116 regions-of-interest (ROIs) using the Automated Anatomical Labeling (AAL) template [15] with a deformable registration method [16]. The band-pass filtering is performed within a frequency interval of [0.025 Hz, 0.100 Hz]. The

¹ <http://adni.loni.usc.edu>.

BOLD signals from the gray matter tissue are extracted, and the mean time series of each ROI is calculated to construct the FC network.

Based on the mean time series of ROIs, we construct the FCN using PCC as measure of the functional connectivity between the ROIs. For each subject, a FCN is built with the nodes denoting brain ROIs and the strength of connections corresponding to the correlation coefficients.

2.3 Feature Learning

In order to improve the classification performance of brain disease with rs-fMRI data, we proposed to integrate the handcrafted features from traditional method and embedded features from CNN method, as illustrated in Fig. 1. In traditional method, the local weighted clustering coefficients are extracted from FCNs as handcrafted features, and followed by an efficient shallow networks, where a rectified linear unit (ReLU) is used as the activation function of each layer, and include two fully connected (FC) layers with 2 and 4 unites, respectively. In CNN method, there are two convolutional layers for feature extraction, and followed by two FC layers with 64 and 32 units, respectively. In the proposed framework, motivated by a recent work [17], we put two separated FC layers followed by a softmax layer on each learning network.

Handcrafted Feature Extraction. Considering our aim is to classify patients from HC, the local weighted clustering coefficients [18], which characterize the topological information of specific nodes and have been applied to brain disease classification [4], are extracted from constructed FCNs. Specifically, given the FCN (matrix) $F^n \in R^{N \times N}$ of the n^{th} subject, where N is the number of ROIs, the local weighted clustering coefficient of the i^{th} ROI is defined as follows.

$$c_i = \frac{2}{d_i(d_i - 1)} \sum_{j,q=1}^N (F_{ij}^n F_{jq}^n F_{iq}^n)^{\frac{1}{3}}, \quad (1)$$

where $d_i = \sum_{j=1}^N F_{ij}$ is the weighted degree of node i . These extracted local weighted clustering coefficients are considered as handcrafted features and applied to subsequent classification.

Embedded Feature Extraction. In this paper, we extract embedded features from the constructed FCNs by using CNN-based method. Specifically, we adopt the kernels with the size of $1 \times N$, and set the stride size along width and height dimension to $(1, 1)$. Therefore, the convolution along the width dimension is a feature mapping for each ROI, and characterize the connectivities of specific ROI. Then, we use the kernel with the size of $N \times 1$ and the stride of $(1, 1)$. Therefore, the convolution in this layer is a feature mapping for the whole FCN. The features obtained in this layer are used for subsequence classification.

2.4 Classification

Deep neural networks usually yield class probabilities using “softmax” function on the output of the neurons, *i.e.*,

$$p_i(y|x) = \frac{e^{\mathbf{z}_i}}{\sum_j e^{\mathbf{z}_j}} \quad (2)$$

where \mathbf{z}_i is the output of the i^{th} neuron. Finally, we integrate both kinds of features for classifying patients from HCs by computing the average value of the class probabilities produced by the shallow network and CNN method.

3 Experiment and Results

3.1 Experimental Setting

To investigate the performance of the proposed method, we perform two groups of experiments, including a binary classification task, *i.e.*, eMCI vs. HC classifications, and a multi-class classification task, *i.e.*, AD vs. IMCI vs. eMCI vs. HC classification, by using a 5-fold cross-validation. Specifically, for each classification task, the set of subjects is equivalently partitioned into five subsets. One subset is used as the testing set. The remaining four subsets are combined as training set. In addition, in each cross validation we select 15% training subjects as the validation data for tuning the parameters.

3.2 Methods for Comparison

We first compare the proposed method with the support vector machine (SVM) based methods denoting as baseline and SVM. In baseline method, we directly use the connectivity strengths of FCNs as features. In the SVM method, we extract the local weighted clustering coefficients from FCNs as features. For both methods, we perform the t-test method for feature selection and a linear SVM with default parameters for classification. Here, a one-to-all is used for multi-class classification task. In additional, we compare the method only using handcrafted features with the shallow network (denoted as handcraft), and method only using embeded features from the CNN (denoted as CNN).

3.3 Classification Performance

We evaluate the performance of all methods by computing the overall accuracy of all categories, and the accuracy of each category. Tables 2–3 presents the results of all methods in classification tasks. As we can see from Tables 2–3, our proposed method can achieve better classification performance compared with all competing methods. For example, the proposed method, respectively, achieves the ACC values of 78.4% and 57.1% for eMCI vs. HC classification and AD vs. IMCI vs. eMCI vs. HC classification, while the best overall accuracy

Table 2. Performance of all methods for eMCI vs. HC classification. ACC: Accuracy.

Method	eMCI vs. HC (%)		
	ACC	ACC _{HC}	ACC _{eMCI}
Baseline	57.1	48.1	65.6
SVM	63.6	50.0	75.0
Handcraft	65.7	50.7	77.6
CNN	72.5	68.7	75.7
Proposed	78.4	79.1	83.9

Table 3. Performance of all methods for AD vs. lMCI vs. eMCI vs. HC classification. ACC: Accuracy.

Method	AD vs. lMCI vs. eMCI vs. HC (%)				
	ACC	ACC _{HC}	ACC _{eMCI}	ACC _{lMCI}	ACC _{AD}
Baseline	30.6	20.0	38.9	30.0	33.3
SVM	35.0	22.0	69.5	21.0	6.7
Handcraft	47.9	22.6	65.6	73.3	77.8
CNN	48.5	64.7	59.5	25.0	26.7
Proposed	57.1	72.0	75.7	34.1	40.0

of competing methods is 72.5% and 48.5%, suggesting the effectiveness of our proposed method. In addition, the proposed method consistently outperforms the methods only using one kind of features (*i.e.*, handcraft and CNN), indicating that the both kinds of features can convey complementary information and should be integrated to further improve the classification performance.

Furthermore, to investigate the complementarity of two kinds of features, for each classification task, we extract and choose the maximum values of softmax function in each network (*i.e.*, the shallow network and CNN network) for testing subjects in the chosen first fold cross-validation. Figure 2 gives the obtained results. As we can see from Fig. 2, the predicted class probabilities predicted by the shallow network approach and CNN approach are complementary, indicating that two kinds of features can convey complementary information for jointly improving the classification performance.

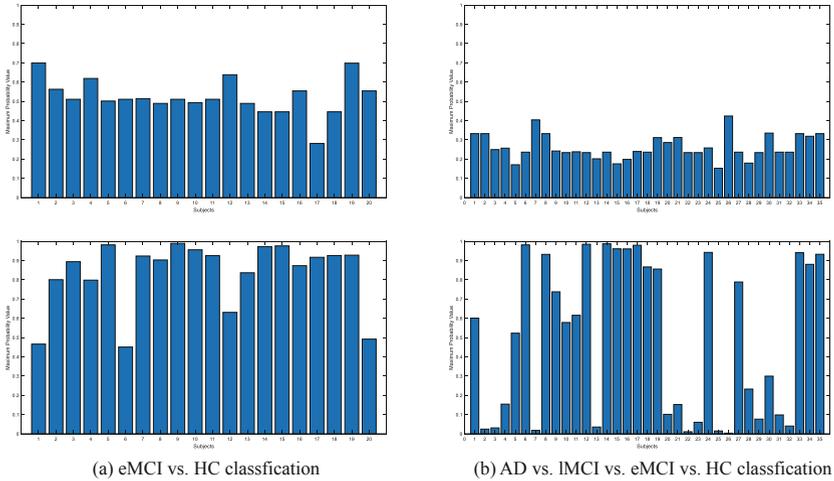


Fig. 2. Predicted maximum class probability value of testing subjects in the first fold cross-validation for the shallow network (up) and CNN (down)

4 Conclusion

In this paper, we propose a novel learning framework that integrates two kinds of features (*i.e.*, the handcrafted features from traditional method and embedded features from CNN method) for classification of brain disease with rs-fMRI data. Experimental results on 174 subjects with baseline rs-fMRI data from the ADNI show that the proposed method can achieve better classification performance than several existing methods.

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