Subspace Classification of Attention Deficit Hyperactivity Disorder with Laplacian Regularization

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Abstract. Attention Deficit Hyperactivity Disorder (ADHD) is a common nerobehavioral disease in school-age children. Its accurate diagnostic methods have drawn widespread attention in recent years. Among them, neurobiological diagnosis methods are proved as a significant way to identify ADHD patients. By employing some neurobiological measures of ADHD, machine learning is treated as a useful tool for ADHD diagnosis (or classification). In this work, we develop a Laplacian regularization subspace learning model for ADHD classification. In detail, we use resting-state Functional Connectivities (FCs) of the brain as input neurobiological data and cast them into the subspace learning model which is carried out in an existing binary hypothesis testing framework. In this testing framework, under a hypothesis of the test subject (ADHD or healthy control subject), training data generates its corresponding feature set in the feature selection phase. Then, the feature set is turned to its projected features by the subspace model for each hypothesis. Here, a Laplacian regularization is employed to enhance the relationship of intra-class subjects. By comparing the subspace energies of projection features between two hypotheses, a label is finally predicted for the test subject. Experiments show, on the ADHD-200 database, the average accuracy is about 91.8% for ADHD classification, which outperforms most of the existing machine learning and deep learning methods.

Keywords: ADHD classification · Subspace learning · Laplacian regularization · Binary hypothesis

1 Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurobehavioral disease in school-age children. It is characterized by inattention, excessive activity, and lack of self-control [1]. Many individuals who suffered from ADHD persist in the symptoms during their adulthood [2]. Current clinical diagnosis is with the direct observation of patients, which mainly depends on the subjective scores from various Hamilton scales [3]. Some questionnaires are taken for children to investigate their multiple performances in life, and then clinicians judge the disease status. However, such a diagnostic method is highly subjective and requires experienced clinicians. It frequently causes

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misdiagnosis for patients with mild symptoms. Therefore, the objective ADHD diagnosis becomes more attractive. Various objective methods have been proposed, wherein ADHD classification with Machine Learning (ML) and Deep Learning (DL) has made great developments in recent years.

Nowadays, well-developed imaging approaches, e.g., structural Magnetic Resonance Imaging (sMRI), functional Magnetic Resonance Imaging (fMRI), Positron Emission Computed Tomography (PET), and Electroencephalogram (EEG) [4, 5], provide plenty of objective data for diagnosis. Among these approaches, fMRI has more advantages in detecting psychological disorders. It monitors the Blood-Oxygen-Level-Dependence (BOLD) signals to discover the dynamic change in brain regions. With a series of data operations, more advanced biosignals can be extracted from the BOLD signals. Here, Functional Connectivity (FC) has received increasing attention by revealing the dysfunctions of the brain network [6]. Therefore, given a set of resting-state fMRI data, we focus on the FC analysis for ADHD classification.

Machine learning is an effective method to distinguish ADHD patients from healthy control subjects [7, 8]. The ML-based ADHD classification methods mainly include three phases, i.e., feature selection, feature extraction, and label decision. In feature selection, some recognizable biosignals are selected from a huge number of biosignals as their typical ones. Some feature selection algorithms are recommended such as Support Vector Machine Recursive Feature Elimination (SVM-RFE) [9], Least Absolute Shrinkage and Selection Operator (LASSO) [10], and Elastic Network [11]. Feature extraction contributes to the model design for capturing high-level features from selected features, where dimensionality reduction is a common and effective approach [12–14]. For example, a feature extraction framework is proposed with the forward-backward learning strategy to obtain low-dimension subspaces for FC data [15]. Label decision is another crucial phase to impact the classification performance. Many well-designed classifiers, e.g., logistic regression, random forest, and decision tree, are incorporated for ADHD classification. Most existing machine learning methods are carried out in a training-and-test framework. However, it may hinder the further promotion of classification accuracy. In practice, the features of test subjects often cannot be well included in the feature space of training data (a.k.a. training subjects) due to ADHD databases of small size. As a result, a binary hypothesis framework is presented to overcome this problem. For example, a binary hypothesis testing approach with dual subspace clustering is deployed and achieves a remarkable ADHD classification performance [16].

Besides, deep learning has been successfully applied in ADHD classification. Different from ML-based methods, the classification via deep learning integrates the aforementioned three phases as a whole. It flexibly learns the high-level features from various biosignal sets [17, 18]. As we know, a Convolutional Neural Network (CNN) is exploited to extract FC features through a fully connected network and then achieves an acceptable classification result [19]. Later, a three-dimensional CNN (3D-CNN) model [20] further uses various fMRI data to comprehensively analyze the local spatial abnormal patterns of ADHD patients. Moreover, another 3D-CNN variant is provided for the feature training, which adopts the linear discriminant analysis for classification [21].

Affected by recent research progress, we propose an ADHD classification method by Laplacian regularized subspace learning and binary hypothesis testing. The Laplacian

approach enhances the relationship of intra-class subjects in the learned subspace. Under the binary hypothesis framework, the subspace energy is exploited as a measure for the label prediction of the test subject. Experiments show, on the ADHD-200 database, the average classification accuracy is about 91.8%, which outperforms most of the existing ML-based and DL-based methods.

2 Material and Method

2.1 Image Data Preprocessing

In our work, all resting-state fMRI data is from the ADHD-200 consortium (http://fcon_1000.pro-jects.nitrc.org/indi/adhd200/). ADHD-200 database is an open-source database of fMRI scans and contains the corresponding clinical characteristics of ADHD and healthy control subjects. We use four datasets of the ADHD-200 database to investigate our ADHD classification method. These datasets are from New York University Medical Center (NYU), NeuroImage (NI), Kennedy Krieger Institute (KKI), and Peking University (PU), respectively. Their detailed information is given in Table 1.

In ADHD data processing, we obtain the time course value of BOLD signals from the connectome website (http://www.preprocessed-connectomes-project.org/adhd-200/). The preprocessing steps include removing of first four time points, slice time correction, motion correction (first image taken as the reference), registration on $4 \times 4 \times 4$ voxel resolution in Montreal Neurological Institute (MNI) space, filtration (bandpass filter with 0.009 Hz–0.08 Hz) and smoothing via 6mm FWHM Gaussian filter. According to the Automatic Anatomical Label-116 template, we select the first 90 brain regions as regions of interest to establish the FC network. FCs are generated from the Pearson correlation coefficients between regional BOLD signals. Later, a Fisher's r-to-z transform is utilized to transform the sampling distribution of correlation coefficients for normality.

Table 1. Information about used ADHD-200 datasets

Site	Age	Female	Male	Control	ADHD	Total
NYU	7–18	77	145	99	123	222
KKI	8–13	33	46	61	22	83
NI	11–22	17	31	23	25	48
PU	8–17	52	142	116	78	194
PU_1*	8–17	36	48	62	24	86

*PU_1 is the first sub-dataset of PU.

2.2 Binary Hypothesis Testing Framework

The core idea of binary hypothesis testing is to use the FCs of the test subject (without seeing its label) to affect the FC selection of training data. During the feature selection phase, the typical FCs of training data can be got under the true hypothesis of the test subject, while the obscure ones are under the false hypothesis. Sequentially, we adopt the Laplacian regularized subspace learning model in the feature extraction phase. It respectively provides their subspace energies under different hypotheses as a measure for the label prediction of the test subject. Finally, by comparing these two energies, the label of the test subject under the true hypothesis is effectively identified. Its ADHD classification framework is shown in Fig. 1.

We design a binary hypothesis framework still within three phases, i.e., feature selection, feature extraction, and label decision. At the very beginning, we employ the label hypothesis of the test subject as healthy control ($\mathcal{H}_0$) or ADHD patients ($\mathcal{H}_1$). In the feature selection, both FCs of training and test data is applied to calculate the reliability of FCs via SVM-RFE. By sorting all feature reliability values in descending order, two rank sets ($\boldsymbol{R}^{\mathcal{H}_0}, \boldsymbol{R}^{\mathcal{H}_1}$) are obtained under different hypotheses. Then, the first k-th FCs of training data is pruned to form the selected feature sets ($\boldsymbol{X}^{\mathcal{H}_0}, \boldsymbol{X}^{\mathcal{H}_1}$), which are correspondingly guided by ($\boldsymbol{R}^{\mathcal{H}_0}, \boldsymbol{R}^{\mathcal{H}_1}$). In the feature extraction, optimal subspace projection matrices ($\tilde{\boldsymbol{P}}^{\mathcal{H}_0}, \tilde{\boldsymbol{P}}^{\mathcal{H}_1}$) are achieved through our Laplace regularized subspace learning model. Thus the projected feature sets of ($\boldsymbol{X}^{\mathcal{H}_0}, \boldsymbol{X}^{\mathcal{H}_1}$) are provided as ($\tilde{\boldsymbol{X}}^{\mathcal{H}_0}, \tilde{\boldsymbol{X}}^{\mathcal{H}_1}$) with

$$\begin{cases} \tilde{\boldsymbol{X}}^{\mathcal{H}_0} = (\tilde{\boldsymbol{P}}^{\mathcal{H}_0})^T \boldsymbol{X}^{\mathcal{H}_0} \\ \tilde{\boldsymbol{X}}^{\mathcal{H}_1} = (\tilde{\boldsymbol{P}}^{\mathcal{H}_1})^T \boldsymbol{X}^{\mathcal{H}_1} \end{cases}, \tag{1}$$

We introduce an energy comparison strategy in the label decision. To avoid the energy fluctuation influence impacted by the input selected features, an energy normalization operation is performed as

$$E^{\mathcal{H}_i} = \frac{||\tilde{X}^{\mathcal{H}_i}||_F^2}{||X^{\mathcal{H}_i}||_F^2}, \quad i \in \{0,\ 1\}, \tag{2}$$

where $E^{\mathcal{H}_i}$ is the normalized energy. Thus, we get the label prediction of the test subject by

$$\tilde{\mathcal{H}}_{true} = \begin{matrix} \mathcal{H}_1,\ \Delta E < 0 \\ \mathcal{H}_0\ \ otherwise \end{matrix}, \tag{3}$$

where $\Delta E = E^{\mathcal{H}_1} - E^{\mathcal{H}_0}$ is the energy difference between two hypotheses. Since in practice, the mean value of selected features (a.k.a. selected FCs) that share the same label is approximately zero, the subspace energy can be viewed as a scatter measure for intra-class subjects. As a result, Eq. (3) is adopted to test the scatter measures between different hypotheses.

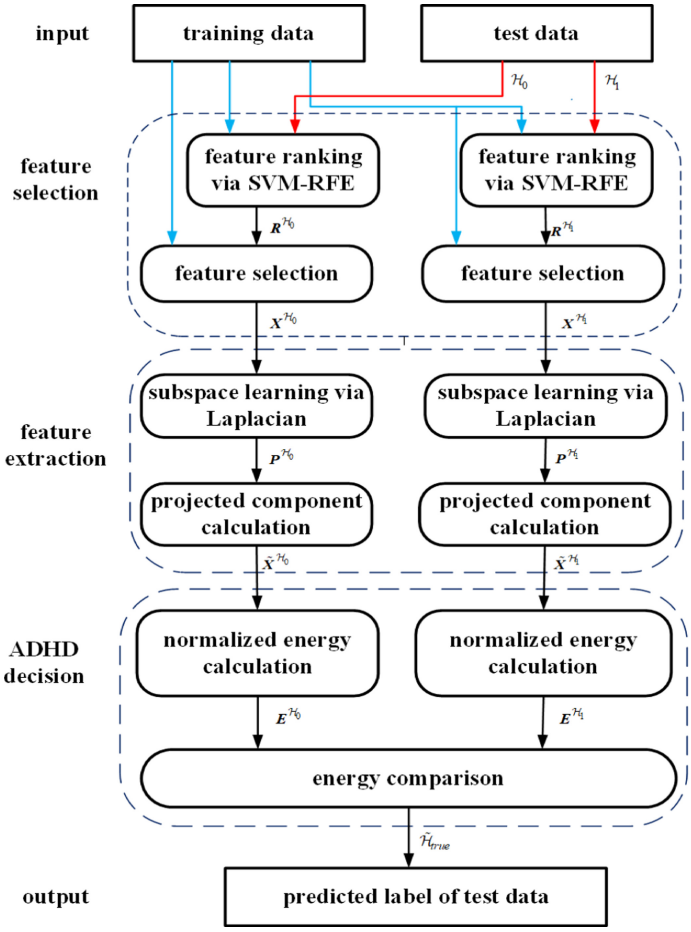

Fig. 1. Framework of proposed ADHD classification.

2.3 Laplacian Regularized Subspace Learning

Given the selected FCs as $\boldsymbol{X} = [\boldsymbol{X}_a\ ,\ \boldsymbol{X}_c]$, where $\boldsymbol{X}_a$ and $\boldsymbol{X}_c$ are the corresponding FCs of ADHD and healthy control subjects respectively, we firstly define the graph Laplacian matrix among the FCs. It is described as

$$\boldsymbol{L} = \boldsymbol{D} - \boldsymbol{W}, \tag{4}$$

where $\boldsymbol{W}$ is an adjacency matrix, $\boldsymbol{D}$ is a degree matrix with its diagonal elements as the row sum of $\boldsymbol{W}$ by $d_{ii} = \sum_j w_{ij}$. We set the adjacency matrix $\boldsymbol{W}$ as a block diagonal matrix with

$$\boldsymbol{W} = \begin{bmatrix} \boldsymbol{W}_a & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{W}_c \end{bmatrix}, \tag{5}$$

where $\boldsymbol{W}_a$ and $\boldsymbol{W}_c$ are the adjacency matrices for the ADHD and healthy control groups respectively. Moreover, the matrices $\boldsymbol{W}_a$ and $\boldsymbol{W}_c$ are formulated with the full binary conjunction in their categories.

Thus, we give the Laplacian regularized subspace learning model as

$$\tilde{\boldsymbol{P}} = \arg\min_{\boldsymbol{P}^T\boldsymbol{P}=\boldsymbol{I}} ||\boldsymbol{P}^T\boldsymbol{X}||_F^2 + \lambda tr(\boldsymbol{P}^T\boldsymbol{X}\boldsymbol{L}\boldsymbol{X}^T\boldsymbol{P}), \tag{6}$$

where $\boldsymbol{P}$ is a subspace project matrix, λ is a weighted coefficient and $\boldsymbol{I}$ is an identity matrix. The projected energy of $\boldsymbol{X}$ is deployed in the first term of Eq. (6), while the second term requires the projected features close to each other in the same category during the dimension reduction.

To solve the problem in Eq. (6), we rewrite it as

$$\tilde{\boldsymbol{P}} = \arg\min_{\boldsymbol{P}^T\boldsymbol{P}=\boldsymbol{I}} tr(\boldsymbol{P}^T\boldsymbol{X}\boldsymbol{A}\boldsymbol{X}^T\boldsymbol{P}), \tag{7}$$

where the complex matrix $\boldsymbol{A}$ is defined as $\boldsymbol{A} = \boldsymbol{I} + \lambda\boldsymbol{L}$. Finally, the optimal project matrix $\tilde{\boldsymbol{P}}$ is obtained as

$$\tilde{\boldsymbol{P}} = eig_r(\boldsymbol{X}\boldsymbol{A}\boldsymbol{X}^T), \tag{8}$$

where symbol $eig_r(.)$ denotes the eigenvalue decomposition to give the eigenvectors with the first r minimal eigenvalues.

3 Experiment Results

We conduct a series of performance evaluations on the ADHD datasets of Table 1. The classification accuracy is achieved by Leave-One-Out Cross Validation (LOOCV). In each test iteration, one subject is got from the database as the test subject, while the rest subjects are used as training data. As for the parameter setting, we choose the selected feature number $k = 110$ by SVM-RFE. The subspace dimension r is set as $r = 105$ for each dataset. Moreover, we further set $\lambda = 0.1$ to balance the term values in Eq. (6).

3.1 Subspace Dimension and Analysis

We first evaluate the accuracy performance with the subspace dimension variation in Fig. 2. It is observed that the highest accuracy is approximate with the subspace dimension $r = 105$. Meanwhile, the subspace dimension is not seriously reduced compared with the selected features of $k = 110$. The selected features now have limited redundant information. It also proves our selected feature number is fit for this subspace learning model. In this case, the task of subspace learning is to remove noise from input data rather than to reduce the feature number. As a result, this operation enhances feature discrimination to achieve remarkable accuracy.

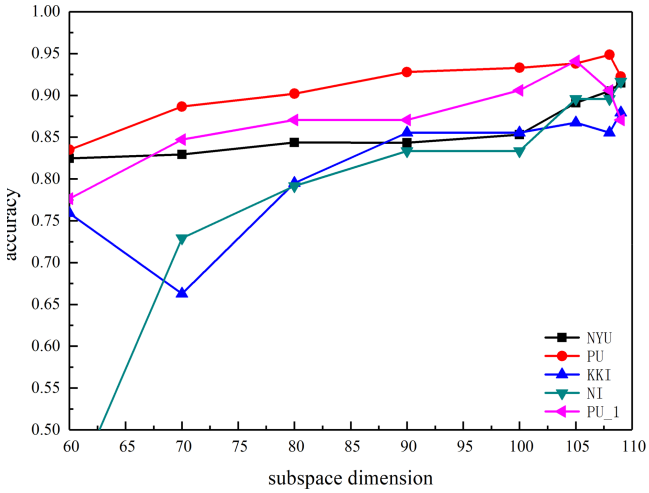

Fig. 2. Accuracy with subspace dimension

3.2 Classification Comparison

Various ADHD classification measures, including specificity, sensitivity, and accuracy, are given in Fig. 3. Our method reaches an average accuracy of 91.8%. In Fig. 3, the accuracy of KKI is the lowest. It is because of the subject imbalance problem, where the number of ADHD patients is seriously less than that of healthy controls. Conversely, NI's accuracy is acceptable for its balance subjects, though its dataset is of the smallest size. PU has the best classification performance. It benefits from its large dataset. With the subject number increasing, the subspace can be learned more effectively to contain reliable information about ADHD.

We further compare our method with other advanced ones in Table 2, including several ML- and DL-methods [19, 20, 22–25]. It shows our method outperforms these methods. Our method provides an alternative way to use binary hypothesis testing instead of the traditional training-and-test approach. With this strategy, the FCs of test data participate in the feature selection procedure. The subspace learning method then gives an effective scatter measure to make the sequential energy detection. Therefore, it can reliably deal with the classification task on different datasets, which significantly enhances the system robustness compared to the existing ML- and DL-based methods. Here, we also refer to a recent binary hypothesis method named dual-space learning with binary hypotheses (Dual-SP-BH) [25]. Since the dual spaces are employed for feature projection, it obtains an unsatisfied performance on NI. However, our method only learns one subspace to simplify the projection operation such that it brings better performance.

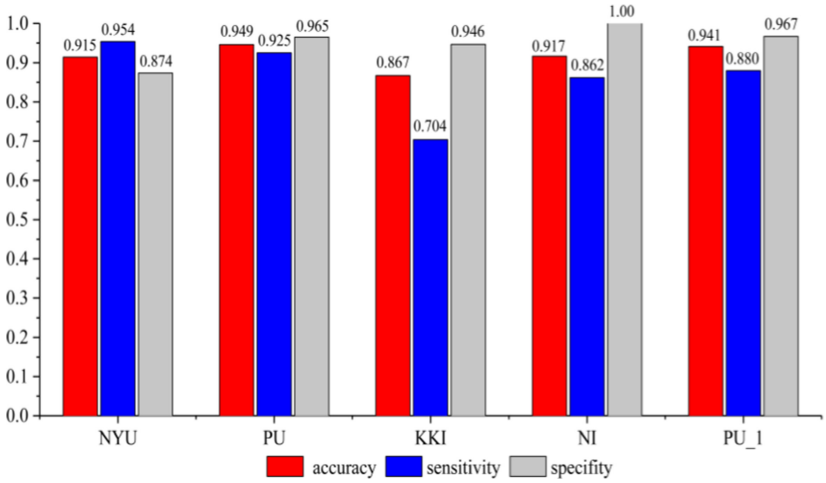

Fig. 3. Comparison of group classification on various datasets

Table 2. Accuracy comparison with various methods (%)

	NYU	PU	PU_1	KKI	NI	Average
Fusion fMRI [22]	52.7	–	85.8	86.7	72.9	–
FCNet [23]	58.5	–	62.7	–	60.0	–
3D-CNN [20]	70.5	63.0	–	72.8	–	–
Deep fMRI [19]	73.1	–	62.7	–	67.9	–
Deep Forest [24]	73.2	64.9	–	82.7	72.0	–
Dual-SP-BH [25]	**92.4**	92.3	89.4	85.5	81.2	88.2
Our method	91.5	**94.9**	**94.1**	**86.7**	**91.7**	**91.8**

3.3 ROC Analysis

We adopt Receiver Operating Characteristic (ROC) and Area Under Curve (AUC) to further evaluate our method. For the ROC measure, it is a balanced result for True Positive Rate (TPR) and False Positive Rate (FPR), describing a given confusion matrix. The indicators of TPR and FPR are computed as

$$\begin{cases} TPR = \dfrac{TP}{TP + FN} \\ FPR = \dfrac{FP}{FP + TN} \end{cases}, \tag{9}$$

where TP is the true positive, TN is the true negative, FP is the false positive, and FN is the false negative. Meanwhile, the value of AUC is defined as the area under the ROC curve. The higher the AUC is, the better classification performance our model is.

The ROC curves are depicted in Fig. 4 and Fig. 5 for the datasets of large and small sizes, respectively. In Fig. 4, NYU and PU datasets are tested. It is observed that their ROC values are rapidly converged to 1 with FPR increasing. Their AUC values are both above 0.9. It shows that the proposed classification method has a good performance on large datasets. As for the small datasets in Fig. 5, including KKI, NI, and PU_1, their ROC curves slowly increase compared with those in Fig. 4. Most of their AUC values are below 0.9 due to their small dataset size. Interestingly, the AUC on NI is even better than those on KKI and PU_1, though the size of NI is the smallest. We note that the data in KKI and PU_1 suffer from the subject imbalance problem. It seems such a factor seriously impacts the ADHD classification performance.

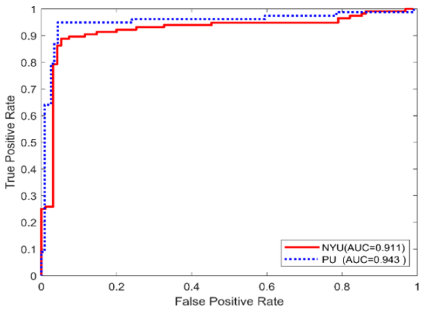

Fig. 4. ROC curves on large datasets

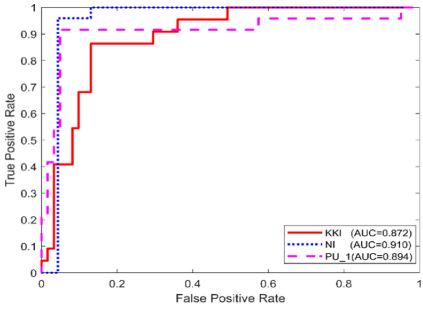

Fig. 5. ROC curves on small datasets

4 Conclusion

We propose an ADHD classification method by Laplacian regularized subspace learning and binary hypothesis testing. The binary hypothesis approach fully exploits the FC

information on test data. Meanwhile, the Laplacian regularized subspace learning well obtains the subspace energies under different hypotheses and thus effectively gives the label prediction of test data. In our experiments, the average classification accuracy of ADHD is 91.8%. It outperforms most of the existing machine learning and deep learning methods.

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