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Phenotypic Integrated Framework for Classification of ADHD using fMRI

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Abstract - Attention Deficit Hyperactive Disorder (ADHD) is one of the most common disorders affecting young children, and its underlying mechanism is not completely understood. This paper proposes a phenotypic integrated machine learning framework to investigate functional connectivity alterations between ADHD and control subjects not diagnosed with ADHD, employing fMRI data. Our aim is to apply computational techniques to (1) automatically classify a person's fMRI signal as ADHD or control, (2) identify differences in functional connectivity of these two groups and (3) evaluate the importance of phenotypic information for classification. In the first stage of our framework, we determine the functional connectivity of brain regions by grouping brain activity using clustering algorithms. Next, we employ Elastic Net regression to select the most discriminant features from the dense functional brain network and integrate phenotypic information. Finally, a support vector machine classifier is trained to classify ADHD subjects vs. control. The proposed framework was evaluated on a public dataset ADHD-200, and our classification results outperform the state-of-the-art on some subsets of the data.

Keywords**:** ADHD, Density Clustering, Affinity Propagation, Elastic Net.

1 Introduction

The brain can be envisioned as a large and complicated network controlling the complex systems of the body. While coordinating bodily function, the brain regions continuously share information, and regions exhibiting temporal correlation are said to be *functionally connected*. Research studies have shown that neurological disorders such as Alzheimer's disease, epilepsy, ADHD can alter the functional connectivity of the brain network [1], [2]. Accurate identification of altered functional connectivity induced by a neurological disorder is thus an important task and may highlight the underlying mechanism of the disorder. Recently, resting state functional MRI (fMRI) has emerged as a promising neuroimaging tool to investigate functional activity of brain regions. In particular, fMRI has been employed to identify the connectivity alterations induced by neurological disorders such as epilepsy, schizophrenia, and ADHD.

ADHD is one of the most common neurological disorders found in young children, affecting 5-10% of children [3]. Like many other neurological disorders, the mecha-

nism underlying ADHD is still unknown [4]. ADHD has received significant research focus, including studies employing fMRI to investigate functional connectivity alterations in ADHD: [5] proposed a functional-anatomical discriminative region model for the identification of discriminant features and pattern classification of ADHD, and evaluated Elastic Net [6] based feature selection. Dey *et al.* [4] employed attributed graph distance measures for classification of ADHD, and similarly [1] investigated different graph based measures to assess their discriminative power. Tabas *et al.* [7] proposed a variant of Independent Component Analysis (ICA) to characterize the differences between control and patients, employing fMRI data. The studies show encouraging results, and demonstrate that machine learning techniques hold promise for the analysis of neuroimaging data.

In this paper, our motivation is to study functional connectivity alterations induced by ADHD. However, unlike previous work that relies on the image data alone, we integrate phenotypic data (such as age, gender, and IQ scores) in our machine learning framework to identify discriminant features to classify individuals as ADHD or non-ADHD (control). Our framework has several stages. In the first stage, the functional connectivity between brain regions is determined using the Affinity Propagation (AP) clustering algorithm [8]. Instead of requiring number of clusters in advance, AP takes a measure of similarity between data points and initial preference for each point for being cluster centroid. We propose a novel method to find these cluster centroids through a matrix derived from the Density Peaks (DP) algorithm by Rodriguez and Laio [9]. To our knowledge, this is the first paper to apply DP for classification of fMRI. Next, we select discriminant features through Elastic Net (EN) regression, which combines shrinkage with grouped selection of variables. Finally we employ a support vector machine classifier to classify between control and ADHD. We demonstrate that the integrated phenotypic information in our framework improves performance.

This work makes several contributions. First, we propose a novel method to initialize the AP clustering algorithm by employing the Density Peaks approach. Second, we demonstrate the importance of phenotypic information for classification of control vs. ADHD based on functional connectivity between brain regions. In addition, our experimental results outperform the previous state-of-the-art for three test datasets of the publically available ADHD 200 data.

2 Data

The resting state fMRI data used in this study is from the NeuroBureau ADHD-200 competition [11]. The data consists of resting state functional MRI data as well as different phenotypic information for each subject. There was a global competition held for classification of ADHD subjects, and the consortium has provided training and an independent test dataset for each imaging site. For this study we employed datasets from four sites: Kennedy Krieger Institute (KKI), NeuroImage (NI), New York University Medical Center (NYU) and Peking University (Peking). All sites have a different number of subjects. Also, imaging sites have different scan parameters and equipment, which makes the dataset complex as well as diverse. This data

has been pre-processed as part of the connectome project [12] and brain is parcellated into 90 regions using the Automated Anatomical Labelling[13] atlas. A more detailed description of the data and pre-processing steps appears in [11]. We have integrated phenotypic information of age, gender, verbal IQ, performance IQ and Full4 IQ, for all sites except from NeuroImage, for which phenotypic information is not available.

3 Methods

Our framework consists of the following modules: functional connectivity calculation, feature selection, phenotypic integration and classification. A block diagram of the methodological framework is presented in Figure 1 and described below.

3.1 Dataset balancing: In our study, datasets from two imaging sites are imbalanced, e.g. for Peking (61 Control vs. 24 ADHD) and for KKI (61 Control vs. 22 ADHD). This imbalance may hamper the performance of a classifier, which may overly focus on the majority class. One approach might be to apply random over-sampling of the minority class or under sampling the majority class to balance the training dataset, but these strategies have been shown to have suboptimal performance [14]. Instead, we employ Synthetic Minority Over-sampling Technique (SMOTE) [10] to create synthetic minority samples. Consider $I_A \in I$, where I is the total set of individual subjects, and I_A is the set of minority ADHD subjects, and we denote an individual sample in I_A as $\boldsymbol{x}_i$. We can synthesize additional minority subjects as

$$\boldsymbol{x}_s = \boldsymbol{x}_i + (\hat{\boldsymbol{x}}_i - \boldsymbol{x}_i) \times r \tag{1}$$

where $\hat{\boldsymbol{x}}_i$ is a randomly chosen subject from K-nearest neighbours of $\boldsymbol{x}_i \in I_A$, $\boldsymbol{x}_s$ is a synthetic subject and r is random number such that $r \in [0,1]$.

3.2 Functional connectivity: Functional connectivity can be estimated by correlation of time-domain signals [1], [4], as well as clustering [2], [15]. We propose a hybrid framework which employs Affinity Propagation (AP) clustering [8] and the Density Peaks (DP) algorithm [9] for functional connectivity estimation.

One of the most appealing properties of AP clustering is that it does not require an initial number of clusters. Instead, it takes a measure of similarity between data points. AP clustering is a message-passing algorithm where each data point is simultaneously considered as potential centroid and as being part of any cluster. Messages are passed between all data points until robust clusters and their centroids emerge. There are two kinds of messages passed between data points, namely responsibility and availability messages. The responsibility message $r(i,j)$ is sent from region i to a potential centroid candidate j, reflects the accumulated strength for how well suited region j is to serve as cluster centroid for region i, taking into consideration all other potential cluster centroids for the region. The availability message $a(i,j)$ is sent from a potential centroid candidate j to region i, and reflects the accumulated strength for how well suited it would be for region i to select region j as its centroid. Availability messages for all regions are initialized as

$$a(i,j) = 0 \tag{2}$$

and the responsibility is calculated as

$$r(i,j) = S(i,j) - \max_{j',j' \neq j} \{a(i,j') + S(i,j')\} \tag{3}$$

with the availability message as

$$a(i,j) = \min\{0, r(j,j) + \sum_{i',\ i' \neq \{i,j\}} \max\{0, r(i',j)\}\} \tag{4}$$

where S in Equation 3 is the similarity measure between brain regions which is initialized as

$$S(i,j) = -\sqrt{\sum_{k=1}^{t} \left(\frac{(i_k - j_k)^2}{\sigma_k^2}\right)} \tag{5}$$

where σ_k is the standard deviation of k^{th} dimension and t is the time points of regions. Instead of requiring an initial guess for number of clusters, the AP clustering algorithm requires a preference value p assigned for each region as the initial probability of being a cluster centroid. Selection of the preference value impacts the number of clusters produced [8], [15]. The value may be assigned to be median or minimum of similarities [8]. However, in this study we propose a novel method to initialize the preference value. We propose to estimate this initial strength for each region as being cluster centroid through the Density Peaks algorithm [9]. The density peak algorithm proposes that the cluster center can be identified as the points that have higher local density and are at larger distance from points with higher density. We initialize the preference for each region as

$$p(i) = \frac{\rho_i\, \delta_i - \min(\rho_i\, \delta_i)}{\max(\rho_i\, \delta_i) - \min(\rho_i\, \delta_i)} \times (N-1) + c \tag{6}$$

where $N = 90$, $c = N/6$, ρ_i is the density of region i calculated as

$$\rho_i = \sum_j^N f(d_{ij} - d_c) \tag{7}$$

where d_c is a cut-off distance controlling the number of neighbors of i, and f is

$$f(x) = \begin{cases} 1, & if\ x < 0 \\ 0, & otherwise \end{cases} \tag{8}$$

and δ_i is calculated as

$$\delta_i = \min_{j:\rho_j > \rho_i} d_{ij} \tag{9}$$

After initializing p, the availability and responsibility messages are updated, until robust clusters and their centroids emerge. From the AP clustering algorithm results, we construct a matrix M as

$$M_l(i,j) = \begin{cases} 1, & if\ i\ and\ j\ are\ \ in\ same\ cluster \\ 0, & otherwise \end{cases} \tag{10}$$

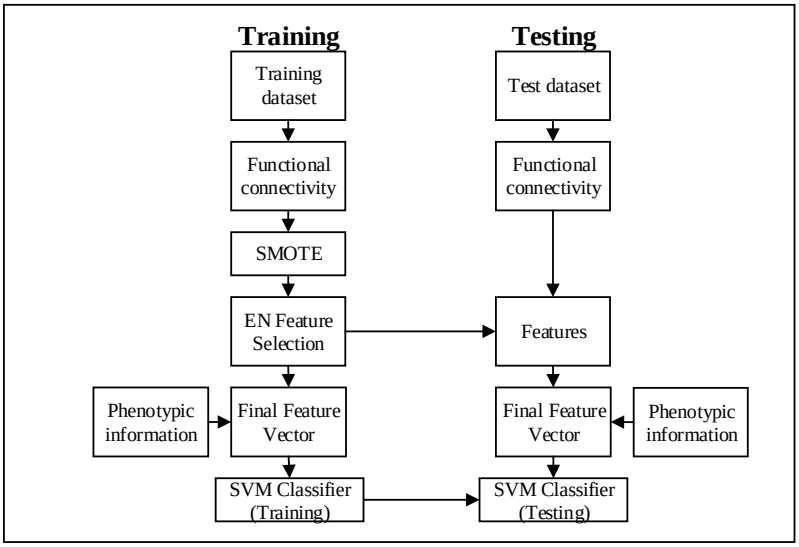

Fig. 1. Flowchart of proposed framework.

The cut-off distance d_c in Equation 7 impacts clustering by varying the preference value computed in Equation 6, yielding different clustering results. To address this issue, the AP clustering algorithm is run multiple times to yield multiple M matrices, with varying d_c so that the average number of neighbors is around 2% to 8% of the total number of points. Through these multiple runs of clustering, we produce K number of M matrices and calculate a functional connectivity matrix,

$$FC(i,j) = \frac{1}{K}\sum_{l=1}^{K} M_l(i,j) \tag{11}$$

This matrix represents the functional connectivity of a subject, such that each entry in $FC(i,j)$ represents an estimate of probability that the i^{th} and j^{th} regions belong to the same functional connectivity. The constructed functional connectivity matrix of Equation 11 has a dimensionality of 4005 ($90 \times 90/2$) unique features. The high dimension of the matrix may degrade the performance of classifier (the well known "curse of dimensionality" problem). Therefore, there is a need to select discriminant features.

3.3 Discriminant feature selection: The functional connectivity matrix may contain highly correlated features. We therefore investigate Elastic Net (EN) based feature selection [6] for extracting discriminant features. EN is an embedded based feature selection algorithm that encourages grouped selection of features and takes advantage of both lasso and ridge regression by combining their penalties in one single solution. Similar to lasso, the L_1 penalty is employed to enable variable selection and continuous shrinkage, and the L_2 penalty is combined to encourage selection of correlated features. If $\boldsymbol{y}$ is the label vector for subjects, $y_i \in (l_1, l_2, \ldots l_n)$, and $\boldsymbol{X} = \{FC_1, FC_2, \ldots FC_n\}$, the cost function to be minimized by Elastic Net is

$$L(\lambda_1, \lambda_2, \beta) = ||\boldsymbol{y} - \boldsymbol{X}\,\boldsymbol{\beta}||^2 + \lambda_1||\,\boldsymbol{\beta}||_1 + \lambda_2||\,\boldsymbol{\beta}||^2 \quad (12)$$

where λ_1 and λ_2 are weights of the terms forming the penalty function and $\boldsymbol{\beta}$ coefficients are estimated by model fitting. By minimizing L in Equation 12, we extract the features that have non-zero coefficients with minimum error during cross validation using a training set. In order to evaluate phenotypic information for classification, we integrate phenotypic information with the selected features to formulate a combined feature set that can be evaluated for classification, as described in the next subsection.

3.4 Classification: The next step in our study is classification where we employ a Support Vector Machines (SVM) classifier to evaluate the discriminative ability of the selected features. SVM is a popular machine learning classifier and has been successfully evaluated in a number of neuroimaging studies (e.g., [2], [15]). It seeks an optimal margin between the two classes (control and ADHD) during training, using labeled training data (1 for control, 2 for ADHD). The learned model is then employed for testing by presenting unseen testing data. The SVM classifier then predicts the label (control or ADHD) for each test subject.

4 Experimentation and results

The proposed framework was evaluated on a dataset provided by the ADHD-200 consortium, and contains four categories of subjects: controls, ADHD-Combined, ADHD-Hyperactive/Impulsive, and ADHD-inattentive. Here we propose a binary classification problem: controls vs. ADHD, by combining all ADHD subtypes in one category, since we want to investigate differences and classification between control and ADHD.

We train the SVM classifier on training data employing selected features and phenotypic information as mentioned above. SMOTE was applied on Peking and KKI datasets to address the data imbalance issue described earlier. The trained SVM classifier was tested with independent test data for each individual site, and results are presented in Table 1, which also provides results with the results of competition teams (reported from NITRC [11]) and highest accuracy achieved by teams in individual imaging sites (data from [5]). It should be noted that parameters of our framework are held constant for all the datasets.

The results show that our framework outperforms the state-of-the-art in three (Peking, KKI and NYU) out of four imaging sites. Our framework performs well in different datasets despite of their diversity. Lower performance on the NI dataset might be due to the fewer number of training subjects and the lack of phenotyping information (unavailable for NI). The order to evaluate the importance of phenotyping information in our framework, we computed the results without integrating the phenotyping information. These results are presented in Table 2, which shows that phenotyping information provides better classification results for Peking and NYU.

For evaluation of our proposed novel methodology to initialize the AP clusters as discussed in Section 3.1, we compared our results with standard AP clustering results presented in Table 3.

Table 1. : Comparison of our results with average results of competition teams [11] and highest accuracy achieved for individual site [5].

Name	Average results of competition teams	Highest accuracy (data by [5])	Accuracy achieved by our methodology
Peking	51.05%	58%	**65%**
KKI	43.18%	81%	**82%**
NYU	32.33%	56%	**61%**
NI	56.95%	--	44%

Table 2. : Results with and without integrating phenotyping information.

Name	With phenotyping	Without phenotyping
Peking	**64.7%**	58.8%
KKI	**81.8%**	**81.8%**
NYU	**61.0%**	24.3%

Table 3 shows that our proposed methodology is able to achieve better accuracy than AP clustering in all imaging sites.

Table 3. Comparison of our proposed methodology with AP results. Results show that our proposed methodology achieves better accuracy than AP clustering.

Name	Proposed Methodology			AP Clustering		
	Specificity	Sensitivity	Accuracy	Specificity	Sensitivity	Accuracy
Peking	**92.59%**	**33.33%**	**64.71%**	81.48%	**33.33%**	58.82%
KKI	75.00%	**100.00%**	**81.82%**	**87.50%**	33.33%	72.73%
NYU	**41.67%**	**68.97%**	**60.98%**	**41.67%**	62.07%	56.10%
NI	**42.86%**	45.45%	**44.00%**	7.14%	**63.64%**	32.00%

5 Conclusions

In this paper we have addressed the problem of identification of discriminant features between control and ADHD subjects for classification based upon fMRI data. Classification of neuroimaging data is considered a difficult task due to the high dimensionality of data. We have proposed a machine learning based framework for this problem and evaluated our method on four training and test datasets provided by NITRC. Our framework introduces a novel method for estimation of functional connectivity between brain regions. The brain is a complex network where a number of brain regions show coherent activity. Therefore, discriminant features might be highly correlated with other. Here, we employed Elastic Net for feature selection that encourages un-

correlated feature selection. In this work, we have evaluated importance of phenotypic information by integrating with selected features. Our results show that Elastic Net based feature selection integrated with phenotypic information may provide an important feature selection strategy. Our selected features and SVM classifier was able to outperform the state-of-the-art in classification accuracy on data from three institutions. In future work we will explore the clinical interpretation of the functional connectivity alterations produced in our framework, particularly in light of the phenotypic information.

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