

Data Mining for ADHD & ASD prediction based on resting-state fMRI signals: A literature review ^{*}

Sarah Itani^{1,2}, Fabian Lecron², and Philippe Fortemps²

¹ Fund for Scientific Research - FNRS (F.R.S.-FNRS), Brussels, Belgium

² University of Mons, Department of computer engineering and management, Mons, Belgium

{sarah.itani, fabian.lecron, philippe.fortemps}@umons.ac.be

Abstract. Despite ongoing research advances in the medical field, mental disorders remain subject to the absence of a common etiology. The current diagnosis of the syndromes is based on descriptive criteria whose interpretation is often specific to the clinician. Biomarker research is thus of paramount importance to move forward towards a more objective psychiatric diagnosis. In children, a leap in the knowledge of Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) would allow to diagnose these highly prevalent disorders better and earlier. There is great hope that computational approaches may tackle this question, notably through the capabilities provided by modern Data Mining (DM). Diagnosis predictors are sought among features extracted from brain data such as resting-state functional Magnetic Resonance Imaging (rs-fMRI) signals. This paper aims to provide a comprehensive synthesis of the recent literature about DM for diagnosis prediction based on rs-fMRI signals extracted from the open and freely available ADHD-200 and ABIDE collections, related respectively to ADHD and ASD. We also present some perspectives for the development of diagnosis aid models with greater applicability and efficiency.

Keywords: Children mental disorders · Resting-state functional magnetic resonance imaging · Data Mining

1 Introduction

A thriving culture of data sharing in the neuroimaging community

For some years now, the culture of data sharing has been encouraged by the neuroimaging community to multiply research efforts for a better understanding of mental disorders. The 1000 Functional Connectomes Project (1000 FCP) and the International Neuroimaging Data Sharing Initiative (INDI) were pioneers in this regard [28].

Among neuroimaging technologies, resting-state functional Magnetic Resonance Imaging (rs-fMRI) is appreciated for its practicality [22]. In particular, the

^{*} Copyright ©2019 for this paper by its authors. Use permitted under Creative Commons License Attribution 4.0 International (CC BY 4.0).

task-free nature of rs-fMRI acquisitions facilitates the pooling of data from different imaging sites worldwide, and thus the constitution of large datasets. Blood-Oxygen Level Dependent (BOLD) signals are derived from rs-fMRI images. These signals are related to the changes in blood oxygenation due to the neuronal activity measured in each voxel [27]. The extraction and preprocessing of BOLD timecourses is a process far from being trivial and straightforward. Preprocessed data have been generously made available for some INDI datasets to open up the opportunity for non-medical experts of contributing their expertise.

The ADHD-200 and ABIDE datasets as successful outcomes

Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are neurodevelopmental disorders which start at early age, and whose symptoms are still seen through adulthood. Though research has evidenced neurobiological and genetic origins for such disorders, there is no scientific consensus on a common etiology. Accelerating research on these disorders was the source of motivation for the release of the ADHD-200 and ABIDE collections.

The ADHD-200 collection [3, 29] was proposed on the occasion of an international contest. The ADHD-200 competition challenged researchers to propose a diagnosis aid model able to predict ADHD with the best prediction accuracy [29]. The ADHD-200 collection includes neuroimaging data on altogether 947 Typically Developing (TD) and ADHD subjects, with separate training and test sets. There are three ADHD subtypes: Inattentive (ADHD-I), Hyperactive-Impulsive (ADHD-HI) and a Combination of both types (ADHD-C). The data collection results from the contribution of eight imaging sites: Peking University (PU), Kennedy Krieger Institute (KKI), NeuroImage (NI), New-York University Child Study Center (NYU), Oregon Health & Sciences University (OHSU), University of Pittsburgh (Pitt.U), Washington University in St. Louis (WU) and Brown University³.

The Autism Brain Imaging Data Exchange (ABIDE) [8, 11] initiative has compiled a large set of brain data related to TD and ASD subjects. This dataset was not intended specifically for a competition. Two compilations were proposed by the ABIDE initiative: the ABIDE-I and ABIDE-II datasets, which were released respectively in 2012 and 2016, by 17 and 19 contributing sites, on 1112 and 1119 subjects [10, 11]. The ABIDE-I dataset has been the most studied up to now. The ABIDE-I collection is attractive since it proposes preprocessed data unlike the ABIDE-II dataset.

A strong involvement by the data mining community

Over the last ten years, the availability of open and freely available datasets such as the ADHD-200 and ABIDE collections has attracted interest from the community of Data Mining (DM) [3], which gives a new impetus to the neuroscience research. In the present paper, we propose a general overview on the DM works

³ The data from this site are usually discarded as diagnosis labels are not provided.

Table 1: Atlas specifications [31]

Atlas	# ROIs
Automated Anatomical Labeling, including cerebellum (AAL116)	116
Automated Anatomical Labeling, excluding cerebellum (AAL90)	90
Eickhoff-Zilles (EZ)	116
Harvard-Oxford (HO)	110
Talaraich and Tournoux (TT)	110
Craddock 200 (CC200)	200
Craddock 400 (CC400)	400
Dosenbach 160	160

which tackled ADHD and ASD diagnosis prediction based on the rs-fMRI signals extracted from the ADHD-200 and ABIDE datasets.

The remainder of the paper is organized as follows. First, we present the modalities for brain exploration (see Sec. 2) and the methods proposed to handle data heterogeneity (see Sec. 3). We also elaborate on the personal and brain features that are usually used as diagnosis predictors (see Sec. 4). These first sections will thus allow the reader to understand the data, the related preprocessing steps, and the features that are usually considered to perform diagnosis prediction. Then, we expose our literature review (see Sec. 5). Finally, the paper concludes with a discussion on the state of the art and some future perspectives (see Sec. 6).

2 Brain exploration

Basically, the modalities for brain exploration relate to two distinct aspects.

- **Node definition:** the representation of the brain into nodes may be either voxel-based or region-based. Many region-based parcellations (*atlases*) exist (see Table 1); they may significantly reduce the amount of data.
- **Analysis level:** this aspect relies on three parameters.
 - *Nature of features:* element-wise features (e.g., BOLD signals) relate to each brain node (voxel/region), while network-based features relate to the interactions existing between the brain nodes.
 - *Scale of investigation:* the brain may be studied in its entirety, but it is also possible to focus on specific regions or sub-networks.
 - *Frequency band:* frequency oscillations in the band $[0.01, 0.1]$ Hz are thought to be related to the neuronal activity [42]. Interestingly, the amplitude of these slow oscillations may also be studied on some narrower standardized frequency bands: SLOW-5 ($[0.01, 0.027]$ Hz), SLOW-4 ($[0.027, 0.073]$ Hz), SLOW-3 ($[0.073, 0.198]$ Hz), and SLOW-2 ($[0.198, 0.25]$ Hz) [17].

3 Heterogeneous data processing

Multi-site medical data are subject to many sources of disparities [19, 20]. The experimental conditions differ from a site to another, e.g., the subject may be asked to open or close his/her eyes during the exam. The cultural and social contexts in which these data are collected may also constitute significant factors of disparity. Likewise, the diversity of ages should be handled properly: the human brain neither works nor is structured in the same way in a lifetime [25]. Many approaches were considered to deal with such sources of heterogeneity.

- **Merging all the training data regardless of the disparities**, hoping that the training process will reach a suitable level of generalization, e.g., see [41].
- **Merging all the training data with the internal handling of the disparities**. There are basically two ways to achieve this.
 - *Applying some adjustments to homogenize the data at best*. This may be done by adding a nominal training variable which identifies the sites in which the data were collected. Intensity normalization techniques may also be applied on BOLD signals to address between-subject variations e.g., see [2, 5, 12, 13, 36].
 - *Merging all the data within a single training set, and integrating the assessment of robustness to the training process*. Two Cross-Validation (CV) strategies were proposed to deal with multi-site datasets. Intra-site CV [1] consists of randomly splitting the initial training set into training and test subsets in which each site is represented in proportion to its weight in the original training set. Inter-site CV [1, 18] aims to test the performances of a classifier against each site subset alternately.
- **Constituting the most possible homogeneous subsets based on inclusion criteria** e.g., site, age, IQ. In this case, the prediction targets specific subjects' profiles, e.g., see [6, 7, 9, 14, 16, 22, 23, 26, 32, 33, 38–40].

4 Features

4.1 Phenotype

Phenotypic features are among the simplest data found to describe a patient. These data relate to information such as **age**, **gender**, **Intellectual Quotient (IQ)**, and **handedness**. Phenotypic features may also include **scores** related to screening tests which are usually used for behavioral assessment and diagnosis. Another important feature is the **diagnosis label** related to each subject. In the remainder, we denote indifferently as Typically Developing (TD), Typical Control (TC) or NeuroTypical (NT), the subjects who are disorder-free. In other cases, the subjects are affected either by ADHD or by ASD.

4.2 Frequency

The fMRI signals present a frequency content which is worth summarizing as features. In this respect, it is common to consider the **Discrete Fourier Transform**

(DFT), computed through the popular Fast Fourier Transform (FFT) algorithm. Several features are extracted from a brain signal in the frequency domain.

- The **amplitudes of the FFT coefficients** and the estimation of the **power spectrum** are among the most common features.
- The **Amplitude of Low Frequency Fluctuations** (ALFF) [42] corresponds to the averaged square root amplitudes of the FFT power spectrum on a given frequency range (typically between 0.01 and 0.1 Hz).
- The **fractional Amplitude of Low Frequency Fluctuations** (fALFF) [45] corresponds to the ALFF of a signal divided by the ALFF computed over the whole frequency range (typically between 0 and 0.25 Hz).

4.3 Connectivity

Functional Connectivity (FC) is a basic measure of interactions between brain nodes: it has proved to provide discriminative biomarkers for the identification of ADHD and ASD.

Correlation is mostly considered to compute FC. In this respect, the Pearson Correlation Coefficient (PCC) measures pairwise correlations related to the activity of the brain nodes [4]. In general, correlation-based FC results in a dense brain network [32]. This may penalize the performance of classifiers trained on such measures. Dimensionality reduction techniques or thresholding may alleviate this issue. At a local scale, **Regional Homogeneity** (ReHo) [43] measures the functional connectivity between a node and its spatially closest neighbors. The ReHo is computed as the Kendall's coefficient of concordance [24].

Clustering techniques constitute an interesting alternative to address the detection of functionally coordinated brain nodes, which provides a comprehensive and simplified view of the brain network. The resulting connectivity matrix informs about whether a pair of nodes are connected (value: 1) or not (value: 0). The K -means technique was successfully used to this end [44]. The number of cluster centroids K is a parameter of the method. Iteratively, each brain node is assigned to the closest centroid based on the similarity of their timeseries. After an iteration, the centroids are computed as the mean of each cluster. The same process is applied until convergence. The main drawback of such a technique is the necessity to define the number of cluster centroids beforehand. Such an issue was recently addressed in [32].

Representation learning was lately considered to compute FC, exploiting the potentialities of deep learning methods such as the Convolutional Neural Network. FCNet, proposed in [33], implements such an idea: it computes FC without the need to resort to distance-based measures. FCNet is advocated as a method which takes into consideration the inherent characteristics of the time-series to compute a pairwise measure of similarity directly from the raw data.

4.4 Complex network measures

Networks computed from fMRI data are weighted and undirected. In such networks (or graphs), two adjacent nodes are connected by an edge. The adjacency

Table 2: Complex network measures, with definitions found in [7, 9, 34]

MEASURE	DEFINITION
Basic concepts	
Degree (or strength)	Number of connections incident on a node. Measure of centrality.
Shortest Path Length (SPL)	Shortest distance between a pair of nodes
Integration	
Characteristic Path Length (CPL)	Average path length (in number of edges); influenced by long paths.
Global efficiency	Inverse of CPL; influenced by short paths.
Segregation	
Clustering coefficient	Fraction of triangles in the neighborhood of a node.
Local efficiency	Global efficiency computed on the neighborhood of a given node.
Centrality	
Betweenness centrality	Fraction of the shortest paths that include a node.
Participation coefficient	Degree to which a node eases intermodular connection.
Resilience	
Average neighbor degree	Average degree measured over the neighbors of a given node.
Assortativity coefficient	Correlation between connected nodes.

matrix A indicates the pairwise connections existing between the nodes of the graph. This matrix is derived from the FC matrix by a filtering operation, e.g., thresholding or binarization [15]. Table 2 presents some main complex network measures; the reader can obtain more information in [34]. The characteristics are defined in the case of a binary network; the definitions are easily adapted to weighted networks. These features are related to different aspects of brain functionality described below.

- **Integration** is related to the ease with which information is communicated between the nodes of the network. Integration measures are defined around the concept of path length.
- **Segregation** is related to the existence of identifiable subnetworks, called clusters or modules, within the network. Segregation measures are defined around the concept of number of triangles.
- **Centrality** is related to how a node interacts with the others, how it favors integration, and how it contributes to the network resilience. The degree is a basic and common measure of centrality.
- **Resilience** is related to the impact of an adjustment brought to the network. The assortativity coefficient is an important measure of resilience. In assortative networks, nodes are likely to be connected to nodes with a similar degree. This involves that removing a high-degree node from the network will have a small impact on the network connectivity [30].

4.5 Timeseries

The rs-fMRI signals may be either directly processed by a classification algorithm specifically intended for timeseries (e.g., Long-Short Term Memory (LSTM) [12]) or reduced prior to classification.

5 Related work

Tables 3 and 4 give a global picture of research works which tackled diagnosis prediction through DM on rs-fMRI signals extracted from the ADHD-200 and ABIDE datasets. We comment on them below.

5.1 ADHD-200 collection

At the end of the ADHD-200 contest, it was shown that phenotype (PHEN) outperforms neuroimaging features for diagnosis with a prediction accuracy of 63.7% achieved by a Logistic Regression (LR) [5]. The solution was judged as out of scope since the competition was precisely intended to promote the use of neuroimaging data for diagnosis prediction. For its part, the official winning team proposed a classification system built on phenotypic features and biomarkers derived from functional and structural brain data [13]. This system comprised four classifiers whose predictions were combined through a vote. With a test accuracy of 61%, this sophisticated system barely achieved the performance yielded from the only use of phenotypic data. In the second place of the official ranking, the work of [7] achieved site-specific diagnosis predictions in two steps. First, the predictions of SVMs learned on different types of features were combined by a majority vote to classify ADHD and TD subjects. The ADHD subtype was then predicted as the most prevalent one in each training set site. Such a strategy lead to an overall accuracy of 59% on the test set. A few time after the competition, Sidhu et al. [36] performed a kernel Principal Component Analysis (kPCA) on the amplitude of the FFT coefficients derived from the rs-fMRI signals. The resulting factors were used in combination with phenotypic features to learn a LR which achieved a final test accuracy of 68.6%.

Since then, a considerable number of research works have tackled ADHD prediction. In Table 3, we indicate for each work whether the issue was addressed as a 2-class (TC vs ADHD), a 3-class (TC vs ADHD-I vs ADHD-C) or a 4-class (TC vs ADHD-I vs ADHD-C vs ADHD-HI) problem. Due to the low proportion of ADHD-HI cases in the dataset, the subtype prediction generally concerns the inattentive and combined patterns of ADHD. Site-specific classification has been envisaged in the works which are marked by an asterisk (see column *Problem*).

A general observation on the state of the art is the common use of FC (by correlation, noted as ρ , clustering, learning, or ReHo) and network measures as training features. The work of [39] stood out from this common practice, and introduced the interesting concept of *Functional Volume* (FV), which is not directly derived from the rs-fMRI signals. As a counter-part of anatomical volume, the FV of a given brain region represents the percentage of voxels which were functionally active over time. In [35], measures of fALFF and ReHo were combined to a spatial map determined by applying Independent Component Analysis (ICA) to the BOLD signals. The work of [19, 21] uses the variance of the BOLD signals as predictors and selects the most discriminative ones through a Correlation-based Feature Selection (CFS) approach.

Table 3: Summary of DM studies based on rs-fMRI signals from the ADHD-200 collection

Year	Authors	Training features	Data reduction algorithm	Classifier	Results (accuracy)	Problem
2019	[21]	PHEN + Variance (AAL116)	CFS	DT	Test - NYU : 73.2%	2-class*
2018	[19]	PHEN + Variance (AAL116)	CFS	DT	Test - NYU : 58.0%, PU : 66.7%	3-class*
2018	[14]	FC (ρ , 190 regions)	-	KNN	Test - KKI : 81%, NYU : 53%, OHSU : 64%	4-class*
2018	[32]	PHEN + FC (clustering - AAL90)	EN on FC	SVM	Test - KKI : 81.8%, NYU : 60.9%, PU : 64.7%	2-class*
2017	[33]	PHEN + FC (learning - AAL90)	-	CNN	Test - NI : 64%, NYU : 63.4%, PU : 68.6%	2-class*
2017	[39]	PHEN + FV or fALFF (CC400)	SVM-RFE	SVM	10-fold CV on NYU site : <ul style="list-style-type: none"> • 68.6 \pm 1.7% [PHEN + FV] • 67.7 \pm 1.5% [PHEN + fALFF] 	2-class
2016	[41]	FC (ρ - CC200)	TMMc	KNN	Repeated holdout : 79.7 \pm 9.4%	3-class
2014	[2]	PHEN + Func. data (incl. network measures) + Struct. data	NMF	DT	LOOCV : 66.8%	2-class
2014	[9]	Network measures (CC200 - voxel-based)	MDS	SVM	Test - KKI : 54.6%, NI : 100%, OHSU : 61.76%, PU : 72.5%	2-class*
2012	[26]	FC (ρ , ReHo - voxel-based)	PCA	LDA	2-fold CV on NYU site : 80.08 \pm 3.8%	2-class*
2012	[35]	fALFF, ReHo, DMN-ICA map	-	LR	Test : 67%	2-class
2012	[36]	PHEN + FFT - voxel-based	PCA	LR	Test : 68.6%	3-class
2012	[37]	Network measures - voxel-based	BoW	SVM	LOOCV on KKI site : 65%	2-class*
<i>ADHD-200 competition</i>						
2012	[5]	PHEN	-	LR	Test : 63.7%	3-class
2012	[13]	PHEN + Func. & Struct. data	Four different strategies Voting structure	LR	61% on the whole sites (sensitivity: 21%)	3-class
2012	[7]	PHEN + Struct. data + Power spectrum, FC (ρ , ReHo), network measures - voxel- based, several atlases	SVM-RFE	SVM Voting	Test - KKI : 73%, NI : 68%, NYU : 37%, OHSU : 76%, PU : 57% (overall accuracy: 59%)	3-class*

Features are computed, processed and eventually combined in a myriad of ways. A diversity of pipelines for feature engineering are thus found in the literature. As regards data reduction, it is usually performed with algorithms such as PCA, Elastic Net (EN), SVM with Recursive Feature Elimination (SVM-RFE) and Multi-Dimensional Scaling (MDS). Besides these traditional algorithms, other original approaches were considered to process the rs-fMRI signals. In the same spirit as MDS and LDA, the Transductive Maximum Margin Classification (TMMC), proposed in [41], aims to project the data in a space characterized by a maximized discriminability, while preserving proximity relations between the instances in the projection space. The Bag-of-Words (BoW) approach, used in [37], achieves the transformation of timeseries into histograms which group the brain nodes depending on their spatial localization and degree. In [2], a kind of profile-based classification framework was achieved through a Non-negative Matrix Factorization (NMF) decomposition. In this case, each subject is represented by a vector concatenating exhaustive information (phenotypic features, functional and structural features). The NMF allows to raise sparse reference vectors in such a way that any instance may be written as a positive linear combination of these basis elements. The weights were used to train a Decision Tree (DT).

5.2 ABIDE-I preprocessed collection

Unlike the ADHD-200 collection, the ABIDE-I dataset is concerned by an increased diversity in the processing pipelines proposed by the investigators. This is in part due to the absence of a common definition for training and test sets. Moreover, the gender gap (14% of females vs 37% in the ADHD-200 dataset) and age variability (7-64 years old vs 7-22 in the ADHD-200 dataset) in the dataset often induced the definition of inclusion criteria on the basis of such factors. Consequently, many options were considered to constitute homogenous datasets. The inclusion criteria are presented in Table 4 (if applicable), with further details concerning the preliminary processing of the data. We also indicate the number (#) of subjects in the resulting training datasets.

As in the case of ADHD prediction, FC coefficients constitute a persistent choice for ASD prediction. They have been used to train models such as SVM [6, 18, 22, 38], Random Forests (RF) [18] and Neural Network-based (NN-based) ones [16, 18, 40]. The work of [12] stands out from this classical procedure. Indeed, the authors tackled directly the rs-fMRI signals; the latter were normalized (mean percentage change), resampled at intervals of 2 s and randomly cropped to cover 90 observations. These operations allowed to increase the training set size to 11000 samples. The signals were then input into a LSTM. The combination of the resulting coefficients with the phenotypic features was shown to be efficient for diagnosis prediction through a fully connected neural network.

In [38], the FC coefficients were processed through a Spatial Filtering Method (SFM) which was proposed as a supervised technique for dimensionality reduction. In the same spirit as LDA, SFM has the capability to project data in a space where discriminability is maximized. But SFM differs from LDA in the way in which such a goal is achieved, i.e., through the simultaneous diagonalization of

Table 4: Summary of DM studies based on rs-fMRI signals from the ABIDE-I preprocessed collection

Year	Authors	Inclusion criteria / Preliminaries	# Subjects	Training features	Data reduction algorithm	Classifier	Results (accuracy)
2019	[23]	Subjects with 0 timeseries excluded, dataset split into 5 age-ranges	<ul style="list-style-type: none"> • 05-10 years : 109 • 10-15 years : 342 • 15-20 years : 190 • 20-30 years : 137 • 30-65 years : 51 	Network measures (AAL116)	SFF	SVM	10-fold CV: <ul style="list-style-type: none"> • 05-10 y : 86% • 10-15 y : 69% • 15-20 y : 78% • 20-30 y : 80% • 30-65 y : 95%
2018	[12]	rs-fMRI signals, normalized (mean % change), resampled (2s), randomly cropped (90 time points)	529 ASD - 571 TC, † at 11000 samples (cropping)	PHEN + rs-fMRI signals (CC-200)	-	NN-based (LSTM)	10-fold CV: 70.1%
2018	[18]	-	505 ASD - 530 TC	FC (ρ - CG200)	-	SVM, RF, NN-based	10-fold CV SVM: 65%, RF: 63%, NN-based : 70%
2017	[16]	UM site (sample 1)	55 ASD - 55 TC	FC (ρ - AAL116)	NN-based	SVM	5-fold CV: 86.36 %
2017	[38]	Dataset split into 4 categories: $\sigma^2 < 18$ y, $\sigma^2 \geq 18$ y, $\rho < 18$ y, $\rho \geq 18$ y.	<ul style="list-style-type: none"> • σ^2: 443 ASD - 435 TC • ρ: 62 ASD - 95 TC 	FC (ρ - AAL90)	SFM	SVM	Repeated holdout: <ul style="list-style-type: none"> • $\sigma^2 < 18$ y : 78.6 \pm 5.0% • $\sigma^2 \geq 18$ y : 85.4 \pm 6.8% • $\rho < 18$ y : 86.7 \pm 10.3% • $\rho \geq 18$ y : 95.0 \pm 15.4%
2016	[6]	Age: between 12 and 18, sites with <30 subjects and low quality data excluded	112 ASD - 128 TC	FC (ρ - Dosenbach, slow 4-5)	F-score	SVM	LOOCV: 79.17%
2016	[22]	σ^2 , age < 40, IQ > 80, low quality data excluded, balancing data per site	77 ASD - 77 TC	FC (ρ - CG200)	SVM-RFE	SVM	10-fold CV: 63%
2015	[40]	σ^2 , data randomly split in training and test sets (ratio: 75% vs 25%)	<18 years: 137 ASD - 143 TC ≥ 18 years: 292 ASD - 306 TC	FC (ReHo - AAL116)	χ^2 statistical score	NN-based	Test <18 y : 68.9%, ≥ 18 y : 79.4%

the mean FC matrices computed across the ASD and TC subjects. Other reduction algorithms, considered in [6] and [40], were used to perform a ranking-based feature selection on the FC coefficients based on indicators such as the F-score and the χ^2 statistical score respectively.

Lately, network measures of integration, segregation and centrality were considered for diagnosis prediction; their reduction was achieved through the Sequential Forward Floating (SFF) algorithm [23]. Starting with an empty feature subset, the iterative algorithm performs, at each step, the selection of a feature judged as meaningful in the sense of a given criterion. In this case, the feature which yielded the best classification accuracy in combination with those of the feature subset was held as relevant.

6 Discussion & Conclusion

Tables 3 and 4 report predictive accuracies achieved on the ADHD-200 and ABIDE-I preprocessed collections. These results are related to the performances achieved on a test set or with regards to a CV procedure. It is here important to raise the interest of a common data segmentation into training and test sets. This allows to facilitate the comparison of literature data, to perceive the related contributions, and thus to accelerate research progress. The ABIDE-I dataset was not released in the context of a competition, which probably explains the non-existent segmentation into well-defined training and test data. Consequently, CV approaches have been extensively favored to assess classification performance. Beyond inter-site variability, demographic disparities have also multiplied the strategies for data segmentation. With such a diversity of modalities for the definition of a training set, it is quite difficult to perceive the advances made on the ABIDE-I dataset.

For sure, the availability of large and free datasets gives an extraordinary impetus for research, and such an effort of data sharing can only be applauded. This definitely promotes the development of diagnosis aid models and the identification of explanatory biomarkers. With the availability of preprocessed data, the issue has been made accessible to a broader community, including data miners. As discussed in [20], the DM community definitely needs to be made aware of the clinicians' requirements towards diagnosis aid. For more applicability and efficiency, data miners should integrate these specifics to their methodologies. Of course, that raises the complex question of how to achieve this in practice, but this remains to a very large extent within the competence of the data miners. Nevertheless, to make their task easier, efforts are still expected from the neuroimaging community. The harmonization of the protocols for data collection would no doubt improve the reliability and the quality of the research conducted on these data. The neuroimaging community should also deal with the segmentation of the data into common homogeneous subsets, i.e., sets of subjects that may be reasonably studied simultaneously in view of their demographics.

Then, brain features are mostly drawn from the notion of connectivity in possible combination with complex network measures. Though these features

seem to show a certain efficiency as predictors, it would be worth assessing the functioning of an individual node, regardless its interactions with others. ALFF, fALFF and FV are examples of such features; they have been little considered so far. Moreover, the role of phenotypic features in the predictive mechanisms is a question of paramount importance. The research works which were interested in it expressed an observation beyond dispute. Phenotypic data improve systematically the predictive performances acquired based on the only use of neuroimaging data [12, 33, 36]. This is understandable to a certain extent since the etiology of a neuropathology may be influenced by factors such as the age, gender or IQ. Using the results of screening tests, as was the case in [2], is by contrast questionable. Indeed, these tests are used by clinicians to make a diagnosis. Yet the resulting diagnosis labels are used by the supervised training process. Therefore, the results of screening tests may lead to bias and to limit the contribution of neuroimaging features in the prediction of a diagnosis.

There is an uncomfortable, but practically unavoidable aspect of supervised learning in this context: the process relies on diagnosis labels deduced from the traditional diagnostic procedures [22]. Yet these diagnostic labels are prone to errors and result from subjective assessment techniques. This adds noise to the analyzed datasets. The use of unsupervised techniques may alleviate this drawback, without strong guarantees of success though. Indeed, recall that in the current state of the neuroscientific knowledge, we ignore the biomarkers (i.e., potential predictors) that may be of use to predict a neuropathology. In orienting a model into the prediction of a diagnosis label, a supervised learning task enables the emergence of discriminative predictors more explicitly.

In terms of classifiers, there has been a strong preference for SVMs, and more recently for NN-based models with the advent of deep learning. Though they have proved to be efficient, the interpretation of these models is not straightforward. Further research efforts deserve to be invested in this regard. Decision trees could be prone to such a research. Of course, they are hardly suitable to model complex relations but they could be studied as part of ensemble strategies such as a set of decision trees learned on different types of features. This would reinforce the predictive performances achieved with such models.

In conclusion, through this paper, we aimed to provide a summary of the features, predictive models and modalities which are usually considered to achieve predict ADHD or ASD based on rs-fMRI signals. A considerable number of research works have addressed this challenge. The results achieved so far are promising but there is still room for significant improvement to ensure a certain level of clinical validity.

Acknowledgments

This work is supported by the Belgian Fund for Scientific Research (F.R.S.-FNRS).

Bibliography

- [1] Abraham, A., et al.: Deriving reproducible biomarkers from multi-site resting-state data: An Autism-based example. *NeuroImage* **147**, 736–745 (2017)
- [2] Anderson, A., et al.: Non-negative matrix factorization of multimodal MRI, fMRI and phenotypic data reveals differential changes in default mode subnetworks in ADHD. *NeuroImage* **102**, 207–219 (2014)
- [3] Bellec, P., et al.: The Neuro Bureau ADHD-200 Preprocessed Repository. *NeuroImage* **144**, 275–286 (2017)
- [4] Benesty, J., Chen, J., Huang, Y., Cohen, I.: Pearson correlation coefficient. In: *Noise reduction in speech processing*, pp. 1–4. Springer (2009)
- [5] Brown, M., et al.: ADHD-200 Global Competition: Diagnosing ADHD using personal characteristic data can outperform resting state fMRI measurements. *Frontiers in Systems Neuroscience* **6**, 69 (2012)
- [6] Chen, H., et al.: Multivariate classification of autism spectrum disorder using frequency-specific resting-state functional connectivity – A multi-center study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **64**, 1–9 (2016)
- [7] Colby, J., Rudie, J., Brown, J., Douglas, P.K., Cohen, M., Shehzad, Z.: Insights into multimodal imaging classification of ADHD. *Frontiers in Systems Neuroscience* **6**, 59 (2012)
- [8] Craddock, C., et al.: The Neuro Bureau Preprocessing Initiative: Open sharing of preprocessed neuroimaging data and derivatives. *Frontiers in Neuroinformatics* **7** (2013)
- [9] Dey, S., Rao, A., Shah, M.: Attributed graph distance measure for automatic detection of attention deficit hyperactive disordered subjects. *Frontiers in neural circuits* **8**, 64 (2014)
- [10] Di Martino, A., Oconnor, D., Chen, B., et al.: Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. *Scientific data* **4**, 170010 (2017)
- [11] Di Martino, A., Yan, C.G., Li, Q., et al.: The autism brain imaging data exchange: Towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular psychiatry* **19**(6), 659–667 (2014)
- [12] Dvornek, N., Ventola, P., Duncan, J.: Combining phenotypic and resting-state fMRI data for autism classification with recurrent neural networks. In: *2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*. pp. 725–728. IEEE (2018)
- [13] Eloyan, A., et al.: Automated diagnoses of attention deficit hyperactive disorder using magnetic resonance imaging. *Frontiers in Systems Neuroscience* **6**, 61 (2012)
- [14] Eslami, T., Saeed, F.: Similarity based classification of adhd using singular value decomposition. In: *Proceedings of the 15th ACM International Conference on Computing Frontiers*. pp. 19–25. ACM (2018)

- [15] Fornito, A., Zalesky, A., Bullmore, E.: Connectivity matrices and brain graphs. *Fundamentals of brain network analysis* pp. 89–113 (2016)
- [16] Guo, X., Dominick, K., Minai, A., Li, H., Erickson, C., Lu, L.: Diagnosing autism spectrum disorder from brain resting-state functional connectivity patterns using a deep neural network with a novel feature selection method. *Frontiers in neuroscience* **11**, 460 (2017)
- [17] Han, Y., et al.: Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnesic mild cognitive impairment: A resting-state fMRI study. *Neuroimage* **55**(1), 287–295 (2011)
- [18] Heinsfeld, A., Franco, A., Craddock, R., Buchweitz, A., Meneguzzi, F.: Identification of autism spectrum disorder using deep learning and the ABIDE dataset. *NeuroImage: Clinical* **17**, 16–23 (2018)
- [19] Itani, S., Lecron, F., Fortemps, P.: A multi-level classification framework for multi-site medical data: Application to the ADHD-200 collection. *Expert Systems with Applications* **91**, 36–45 (2018)
- [20] Itani, S., Lecron, F., Fortemps, P.: Specifics of medical data mining for diagnosis aid: A survey. *Expert Systems with Applications* **119**, 300–314 (2019)
- [21] Itani, S., Rossignol, M., Lecron, F., Fortemps, P.: Towards interpretable machine learning models for diagnosis aid: A case study on attention deficit/hyperactivity disorder. *PLOS ONE* **14**(4), e0215720 (2019). <https://doi.org/10.1371/journal.pone.0215720>, <http://dx.plos.org/10.1371/journal.pone.0215720>
- [22] Kassraian-Fard, P., Matthis, C., Balsters, J., , Maathuis, M., Wenderoth, N.: Promises, pitfalls, and basic guidelines for applying machine learning classifiers to psychiatric imaging data, with autism as an example. *Frontiers in psychiatry* **7**, 177 (2016)
- [23] Kazeminejad, A., Sotero, R.: Topological properties of resting-state fMRI functional networks improves machine learning-based autism classification. *Frontiers in neuroscience* **12**, 1018 (2018)
- [24] Kendall, M.: Rank correlation method. london: Griffin, 1970. Google Scholar (1970)
- [25] Lenroot, R., Giedd, J.: Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews* **30**, 718–729 (2006)
- [26] Liang, S.F., et al.: Differentiation between resting-state fMRI data from ADHD and normal subjects: based on functional connectivity and machine learning. In: 2012 International conference on Fuzzy Theory and Its Applications (iFUZZY2012). pp. 294–298. IEEE (2012)
- [27] Logothetis, N., Wandell, B.: Interpreting the BOLD signal. *Annual Review of Physiology* **66**, 735–769 (2004)
- [28] Mennes, M., Biswal, B., Castellanos, F., Milham, M.: Making data sharing work: The FCP/INDI experience. *NeuroImage* **82**, 683–691 (2013)
- [29] Milham, M., et al.: The ADHD-200 consortium: A model to advance the translational potential of neuroimaging in clinical neuroscience. *Frontiers in Systems Neuroscience* **6**, 62 (2012)

- [30] Newman, M.: Modularity and community structure in networks. *Proceedings of the national academy of sciences* **103**(23), 8577–8582 (2006)
- [31] Preprocessed Connectomes Project: ABIDE Preprocessed. <https://bit.ly/2Z1xKk4> (2014), [Online; accessed 03-11-2018]
- [32] Riaz, A., Asad, M., Alonso, E., Slabaugh, G.: Fusion of fMRI and non-imaging data for ADHD classification. *Computerized Medical Imaging and Graphics* **65**, 115–128 (2018)
- [33] Riaz, A., et al.: FCNet: a convolutional neural network for calculating functional connectivity from functional MRI. In: *International Workshop on Connectomics in Neuroimaging*. pp. 70–78. Springer (2017)
- [34] Rubinov, M., Sporns, O.: Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage* **52**(3), 1059–1069 (2010)
- [35] Sato, J., Hoexter, M., Fujita, A., Rohde, L.: Evaluation of pattern recognition and feature extraction methods in ADHD prediction. *Frontiers in systems neuroscience* **6**, 68 (2012)
- [36] Sidhu, G., Asgarian, N., Greiner, R., Brown, M.: Kernel Principal Component Analysis for dimensionality reduction in fMRI-based diagnosis of ADHD. *Frontiers in Systems Neuroscience* **6**, 74 (2012)
- [37] Solmaz, B., Dey, S., Rao, A., Shah, M.: ADHD classification using bag of words approach on network features. In: *Medical Imaging 2012: Image Processing*. vol. 8314, p. 83144T. International Society for Optics and Photonics (2012)
- [38] Subbaraju, V., Suresh, M., Sundaram, S., Narasimhan, S.: Identifying differences in brain activities and an accurate detection of autism spectrum disorder using resting state functional-magnetic resonance imaging: A spatial filtering approach. *Medical image analysis* **35**, 375–389 (2017)
- [39] Tan, L., Guo, X., Ren, S., et al.: A computational model for the automatic diagnosis of attention deficit hyperactivity disorder based on functional brain volume. *Frontiers in computational neuroscience* **11**, 75 (2017)
- [40] Vigneshwaran, S., Mahanand, B., Suresh, S., Sundararajan, N.: Using regional homogeneity from functional mri for diagnosis of asd among males. In: *2015 International Joint Conference on Neural Networks (IJCNN)*. pp. 1–8. IEEE (2015)
- [41] Wang, L., Li, D., He, T., et al.: Transductive maximum margin classification of ADHD using resting state fMRI. In: *International workshop on machine learning in medical imaging*. pp. 221–228. Springer (2016)
- [42] Yu-Feng, Z., Yong, H., Chao-Zhe, Z., et al.: Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain and Development* **29**(2), 83–91 (2007)
- [43] Zang, Y., Jiang, T., Lu, Y., et al.: Regional homogeneity approach to fMRI data analysis. *Neuroimage* **22**(1), 394–400 (2004)
- [44] Zhang, J., Cheng, W., Wang, Z., et al.: Pattern classification of large-scale functional brain networks: identification of informative neuroimaging markers for epilepsy. *PloS one* **7**(5), e36733 (2012)
- [45] Zou, Q.H., Zhu, C.Z., Yang, Y., et al.: An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *Journal of neuroscience methods* **172**(1), 137–141 (2008)