

Research Paper

fMRI-Based Multi-class DMDC Model Efficiently Decodes the Overlaps between ASD and ADHD



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ABSTRACT

Introduction: Neurodevelopmental disorders comprise a group of neuropsychiatric conditions. Presently, behavior-based diagnostic approaches are utilized in clinical settings, but the overlapping features among these disorders obscure their recognition and management. Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have common characteristics across various levels, from genes to symptoms. Designing a computational framework based on the neuroimaging findings could provide a discriminative tool for ultimate more efficient treatment. Machine learning approaches, specifically classification methods are among the most applied techniques to reach this goal.

Methods: We applied a novel two-level multi-class data maximum dispersion classifier (DMDC) algorithm to classify the functional neuroimaging data (utilizing datasets: ADHD-200 and autism brain imaging data exchange (ABIDE)) into two categories: Neurodevelopmental disorders (ASD and ADHD) or healthy participants, based on calculated functional connectivity values (statistical temporal correlation).

Results: Our model achieved a total accuracy of 62% for healthy controls. Specifically, it demonstrated an accuracy of 51% for healthy subjects, 61% for autism spectrum disorder, and 84% for ADHD. The support vector machine (SVM) model achieved an accuracy of 46% for both the healthy control and ASD groups, while the ADHD group classification accuracy was estimated to be 84%. These two models showed similar classification indices for the ADHD group. However, the discrimination power was higher in the ASD class.

Conclusion: The method employed in this study demonstrated acceptable performance in classifying disorders and healthy conditions compared to the more commonly used SVM method. Notably, functional connections associated with the cerebellum showed discriminative power.

Keywords:

Functional connectivity, data maximum dispersion classifier (DMDC), fMRI, Classification, Autism, Attention deficit hyperactivity disorder (ADHD), High-dimensional low sample size, ADHD-200, Autism brain imaging data exchange (ABIDE)

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Highlights

- Two-level multi-class data maximum dispersion classifier (DMDC) outperforms support vector machine (SVM) in autism spectrum disorder attention-deficit hyperactivity disorder (ASD-ADHD) classification.
- fMRI-based functional connectivity aids ASD-ADHD classification.
- Cerebellum.4.5. l - supramarginal.L is the most discriminative connection.

Plain Language Summary

Neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), can be challenging to diagnose because they share many symptoms. Traditionally, doctors rely on behavioral assessments, but these can be imprecise due to overlapping characteristics. Our study explores a new way to distinguish between these disorders using brain imaging and advanced computer algorithms. We used a method called two-level multi-class DMDC to analyze brain scans from people with ADHD, ASD, and healthy individuals. These scans measure functional connectivity, which shows how different parts of the brain communicate. We aimed to see if our method could better identify which brain patterns correspond to ADHD or ASD compared to a commonly used method called support vector machine (SVM). Our results showed that the two-level multi-class DMDC method performed better than SVM in distinguishing between the disorders. It accurately identified healthy individuals 51% of the time, people with ASD 61% of the time, and those with ADHD 84% of the time. The SVM method was less accurate for healthy individuals and those with ASD but matched the accuracy for ADHD. This study is significant because it suggests that using advanced brain imaging analysis could improve how we diagnose neurodevelopmental disorders. Better diagnosis means more targeted and effective treatments for those affected by ADHD and ASD. For the public, this research highlights the potential of technology to enhance healthcare, leading to better outcomes for individuals and families dealing with these conditions.

1. Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are heterogeneous states with developmental origins and significantly heritable patterns (Thapar & Rutter, 2015). ASD is characterized by age-inappropriate levels of persistent impaired attention and/or hyperactivity and impulsivity, while ADHD encompasses a specific set of disorders characterized by poor social communication/interaction, stereotypical behaviors, and a restricted range of interests (Guha, 2014). These two diagnoses widely affect various dimensions of patients' lives, may persist into adulthood, and often co-occur (Brookman-Frazee et al., 2018); approximately thirteen percent of participants in an epidemiological study on ADHD were diagnosed with ASD simultaneously (Zablotsky et al., 2020). Other reports have also shown that about 13% of individuals with ADHD receive an ASD diagnosis (Jensen & Steinhausen, 2015). Another study indicated that more than one-fifth of individuals diagnosed with ASD also exhibit ADHD-associated traits; impulsion and inattention are often present in ASD. Regarding heritability, family

studies have reported that having relatives with ASD increases the likelihood of receiving an ADHD diagnosis (Ghirardi et al., 2018; Ghirardi et al., 2019; Jokiranta-Olkoniemi et al., 2016; Musser et al., 2014). Although numerous investigations have consistently demonstrated shared genetic components, endophenotypic attributes, and autism-related phenomena in children and adolescents with confirmed ADHD diagnoses and vice versa (Gadow et al., 2006; Simonoff et al., 2008; Yerys et al., 2009), the distinctions in the core psychopathologies of these disorders are well-established (Clark et al., 1999; Grzadzinski et al., 2011; Grzadzinski et al., 2016; Kotte et al., 2013; Kröger et al., 2011; Martin et al., 2014; Mulligan et al., 2009). However, the significant interconnectedness between core behavioral symptoms and certain types of comorbidities (e.g. depression, anxiety, and sleep disturbances) of ADHD and ASD complicates differential diagnosis, prognosis (Grzadzinski et al., 2016), and treatment outcomes; therefore, more clarification of the neuropathophysiological aspects of ADHD, ASD, and ASD+ADHD could be crucial (Craig et al., 2015).

There is limited overlap in neural correlates between individuals with ADHD and those with ASD concerning resting-state connectivity or functional network organizations. Recognizing brain connectivity patterns is a promising approach for the characterization, diagnosis, and prediction of pathologies linked to the abnormal functional or structural organization of the brain. Functional connectivity refers to the temporal correlation of oscillatory activities within the BOLD signal related to distinct nodes of the cerebrum. Recent evidence suggests that connectivity between brain regions significantly contributes to understanding emotional regulation and the hierarchy of cognitive processing. Despite methodological variations, existing research findings (Bethlehem et al., 2017; Di Martino et al., 2013) suggest that ADHD and ASD could be considered large-scale brain connectivity disorders, albeit with insignificant similarities in the specific regions, as confirmed by meta-analyses (Dougherty et al., 2016; Rommelse et al., 2017). The attention-related insufficiencies (sustained attention and attentional shifts) are proposed as frequently observed links between ASD and ADHD. Notably, analyzing functional neuroimaging investigations yields high-dimensional data for a typically small number of subjects, necessitating novel computational approaches.

Classification is a crucial task in statistics and supervised machine learning with numerous applications in various basic and clinical fields (diagnostic and therapeutic), such as image processing. Extensive literature reviews have identified numerous research works on the application of classification methods for discriminating ADHD and Autism based on functional neuroimaging data (Abraham et al., 2017; Itani et al., 2018; Liber et al., 2015; Nielsen et al., 2013). These studies, with varying levels of accuracy, have indicated some specific dimensions of functional neural correlates regarding neurodevelopmental disorders, such as the role of the cerebellum, prefrontal cortices, and temporal lobe contributions to pathogenesis. Some studies have compared both disorders simultaneously but in separate settings without integration (Ghiassian et al., 2016), contrasting ADHD vs Healthy and ASD vs (not ADHD/ASD vs Healthy). The current modeling aims to integrate and compare both disorders with their corresponding healthy states in a unified framework. Specifically, a dataset is represented as an $n \times d$ matrix X , consisting of n data vectors x_i ($i \in \{1, 2, \dots, n\}$) with d features and a class label $y_i \in \{-1, +1\}$. Two sets (classes) of d -dimensional training vectors are the starting point of the two-class discrimination process. The discrimination procedure aims to design a rationale to attribute the labels of -1 or 1 to the vectors of newly added data (the vectors might be “closer to class +1” or “closer to class -1”) (Zou, 2019).

Support vector machine (SVM) is a widely applied method for classifying structural and functional neuro-imaging-derived variables in the clinical setting, as it avoids over-fitting even with a smaller number of samples and delivers high classification accuracy (Bledsoe et al., 2020). It also provides individual classification (patient vs control) according to a boundary that is called a decision boundary (i.e. hyperplane) that separates data into two groups. The linear SVM seeks a hyperplane $\{x:0\}$ that maximizes all data points' smallest margin (Cortes & Vapnik, 1995).

Performance degradation is a recurring challenge in conventional machine learning methods, making it a specific concern in statistics when analyzing high-dimension low-sample size (HDLSS) datasets. When working with HDLSS, and specifically during the data projection onto the normal vector of the separating hyperplane, data piling occurs; which in some HDLSS situations, might influence the SVM performance (Zou, 2019). The data maximum dispersion classifier (DMDC), applicable to general data, especially HDLSS, serves as a novel linear binary classifier. DMDC notably increases data dispersion, thereby inhibiting data pilling. Moreover, it performs well on HDLSS, remains invariant to the intercept term, and involves a straightforward implementation process with minimal computational loads (Shen & Yin, 2020). Another critical aspect is constituting a reasonable interpretation of the ultimate coefficients. The models mentioned earlier and their improved versions could classify the high dimensional observations, but since the standard SVM-based models employ all the variables due to the L2-norm penalty ($\|\beta\|_2$), providing an appropriate description of the findings and making the results more interpretable requires approaching toward L1-norm regularized method. In these sparse methods, some entries of β are set to zero, facilitating interpretation as only a subset of input features is deemed relevant for the final predictive algorithm. In 2003, Zhu et al. developed and introduced the sparse version of the support vector machine (Zhu et al., 2003), proving beneficial for the neuroscience domain. One recent study, Sen et al. (2018) aimed to identify and classify neuroimaging data using structural and functional connectivity characteristics, exploring a series of three learners. Additionally, Ghiassian et al. proposed a classification method based on MRI-derived histograms of oriented gradients (HOG) features and personal information, describing an algorithm capable of efficacious classification for ASD and ADHD. Their framework achieved 69.6% accuracy in classifying ADHD from controls (over a baseline of 55.0%) (Ghiassian et al., 2016).

Since all existing investigations have applied two-class classification techniques (ADHD/ASD vs healthy controls) that are not entirely able to categorize disorders and decode the ambiguities in neural correlates between ADHD and ASD, we aimed to apply a novel multi-class classification model called DMDC (Shen & Yin, 2020), on publicly available functional neuroimaging datasets of these two disorders and their healthy counterparts. Through the current project, primarily, we extended binary DMDC to a multiclass version for discrimination between more than two classes, and then we developed a two-level classification model based on this multiclass DMDC algorithm. This model could help solve the problem of data piling and efficient interpretation of the findings. Then we applied a version of the sparse modified SVM model to find the discriminative functional links between different states (ADHD vs ASD, disordered vs healthy conditions).

2. Materials and Methods

Datasets

The entire methodology is depicted in Figure 1. In this research, we analyzed ADHD-200 and ABIDE (autism brain imaging data exchange) datasets that are publicly accessible at NITRC. The data collection procedures adhered to predefined approval criteria, and to ensure confidentiality, the collecting institutions anonymized all participant data before making them publicly accessible. Both datasets included resting-state fMRI and T1-weighted images. The ADHD-200 dataset comprised 939 subjects (357 with ADHD and 582 healthy controls) from North America, Europe, and China, with diagnoses made based on algorithmic criteria. The Autism brain imaging data exchange (ABIDE I) dataset was another included dataset. Currently, this collection also comprises resting-state fMRI and T1-weighted structural MRI scans from 1112 participants (573 healthy controls (HC) and 539 patients with autism diagnosis), acquired from standard institutions in North America and Europe. Diagnostic characteristics are available on the referenced websites. To ensure consistency in diagnostic criteria, we reviewed the criteria of all imaging sites and excluded collections that had not assessed the presence of comorbid ADHD according to standard procedures. This process resulted in 388 individual data (217 healthy controls, 171 ASD) remaining for analysis. Similarly, we applied this criterion to the ADHD-200 dataset and limited the data to two sites (253 healthy controls and 249 ADHD patients). Subsequently, we combined the two datasets (ADHD-200 and ABIDE I) and randomly partitioned this combination into 332, 119, and 171 in-

dividual data for training procedures respectively for healthy control, ASD, and ADHD groups. For testing partition, 138, 52, and 78 subjects were assigned to the healthy control, ASD, and ADHD groups, respectively. Ultimately, we allocated 30% of the final data for testing and 70% for the training procedure.

Preprocessing

After downloading both datasets, sequential preprocessing steps were performed using FSL software. In order to remove non-brain tissue parts from the structural images, we randomly selected images of three subjects and applied various sets of parameters to identify the most optimized parameters for each data acquisition center. Then MCflirt and rigid body motion correction methods with six specific parameters were performed. In addition, the process of slice-timing correction was performed based on the specific conditions of imaging procedures mentioned in the data acquisition description of each data center. The fMRI data was also motion-corrected, and the voxel intensity was normalized. The band-pass filter was determined to be within the range of 2.8–60 Hz and registered to the MNI-152. Spatial smoothing was performed using full width with half maximum equal to 6 mm. In order to standardize and automate the data preparation process as much as possible, a bash code system was used that was applied to preprocess steps based on the appropriate parameters for each data center.

Feature extraction

The parcellation part was based on the automated anatomical labeling (AAL 116) atlas (the fMRI volumes were segmented into 116 regions through masking the ALL). Functional connectivity metric provides an index of the level of co-activation of brain regions based on the time series of rs-fMRI brain imaging data. From the regional time series (nt time-points \times np regions), time points were variable among different centers, and np was equal to 116. We computed the pairwise inter-regional covariance matrix for each participant. Since the covariance matrix and its inverse are symmetric, the upper triangular elements of these matrices are considered. By adding variables of individual characteristics and the state of communication of the regions, the structures of the datasets were prepared for classification. Also, due to different scattering of fMRI data and individual characteristics (gender, age, and handedness), the values of quantitative variables were standardized by dividing the deviation of each observation from its mean to the standard deviation.

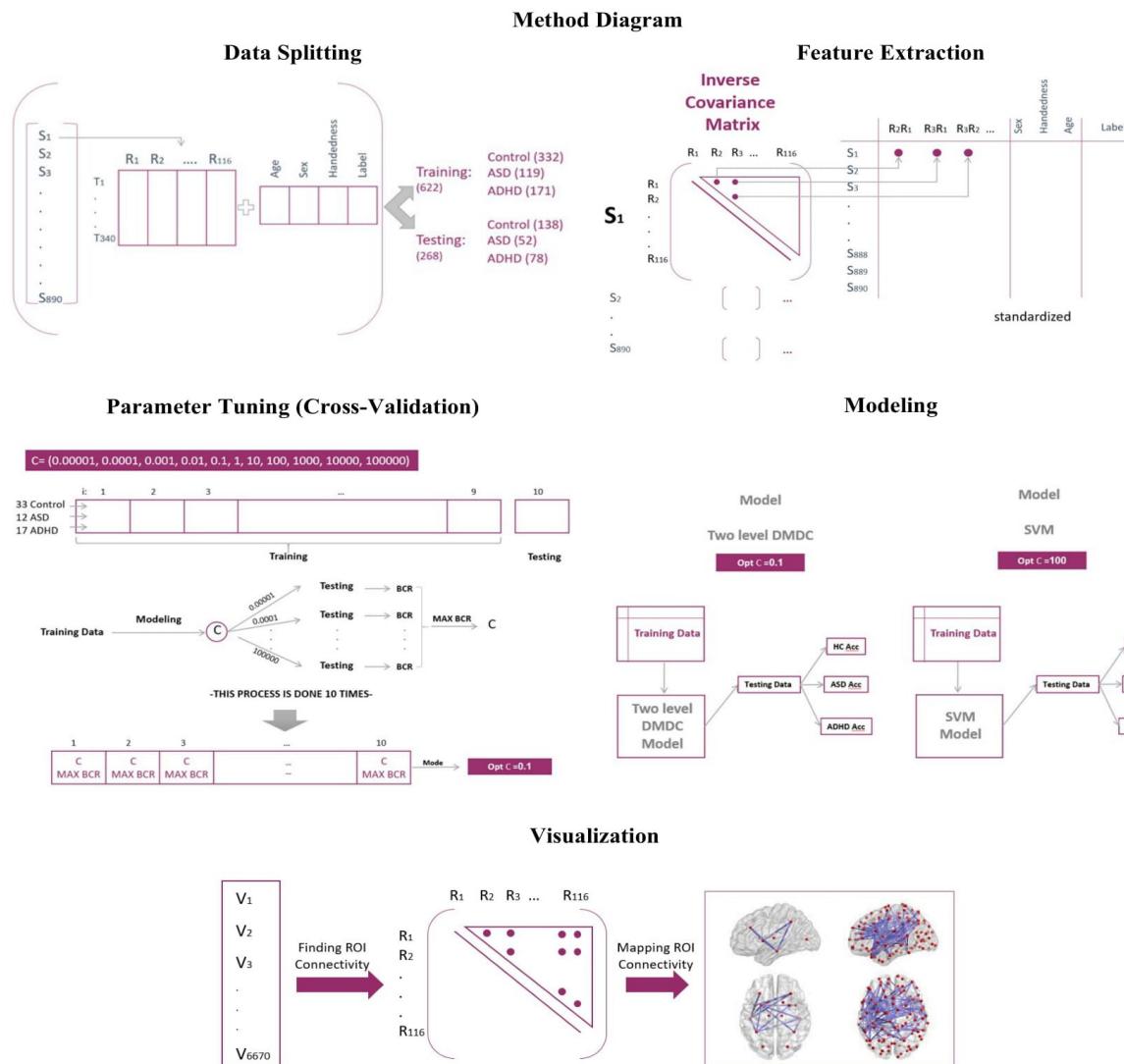


Figure 1. Diagram of the methodology

Note: This process comprises data splitting, feature extraction, parameter tuning, modeling, and visualization, respectively.

Parameter tuning

We used a 10-fold cross-validation design for parameter tuning. The training data were divided into 10 folds, such that each fold approximately encompassed one-tenth of the training data in a random way to discover the optimum parameter across eleven considered parameters. Through every iteration process, 9 folds of the data were considered as training and this modeling was performed with every 11 parameters. Subsequently, the BCR (balanced classification rate: The average accuracy across classes) index was calculated within that single fold of test data. Ultimately, the parameter with the highest value in each test fold would be selected for

the subsequent step. Overall, the mode of the parameter with maximum BCR was obtained and considered as the optimum parameter. This cross-validation process was then performed for either two-level DMDC or SVM models. Furthermore, the current models exhibited acceptable stability during iterations, with insignificant variations in accuracies (below 5%).

Multiclass DMDC

The computational cost of implementing DMDC is low, as it involves solving the convex quadratic programming formulation similar to SVM ([Equation 1](#)):

Table 1. Sex, handedness, and age distribution by groups

Variables	Categories	No. (%)			
		HC	ASD	ADHD	Total
Sex	Female	164(34.9)	21(12.3)	43(17.3)	128(25.6)
	Male	320(65.10)	150(87.7)	206(82.7)	662(74.4)
Handedness	Right	252(53.6)	78(45.6)	123(49.4)	453(50.9)
	Left	109(23.2)	8(4.7)	126(50.6)	243(27.3)
	Ambidextrous	8(1.7)	7(4.1)	0(0.0)	15(1.7)
Age (y)	Unknown	101(21.5)	78(45.6)	0(0.0)	179(20.1)
	Minimum	6.47	7.13	7.24	6.47
	Maximum	30.78	31	17.61	31
	Mean±SD	13.35±4.63	15.57±6.16	11.49±2.47	13.25±4.71

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$$\min_{\beta} \left(\frac{\|\beta\|_2^2}{A^T \beta} + C_0 \sum_{i=1}^n \xi_i \right)$$

1. subject to $y_i(\beta^T x_i + b) \geq 1 - \xi_i, \quad i = 1, 2, \dots, n$

$$\xi_i \geq 0$$

$$A^T \beta > C, \quad C > 1$$

A is the eigenvector related to the largest eigenvalue of $S\beta$ ([Equation 2](#)).

$$2. S_\beta = Q^T Q = \sum_{x \in \text{class}} (x - u_1)(x - u_1)^T + \sum_{x \in \text{class2}} (x - u_2)(x - u_2)^T$$

In this equation, u_j represents the mean of training samples from the j -th class, where $j=1, 2$. The term $A^T \beta$ is utilized to manage the training samples. Following optimization and the formation of $f(x)$, if $f(x)>0$, the new sample would be classified as belonging to $\text{classy}=+1$, otherwise, it would be classified as belonging to $\text{classy}=-1$ ([Shen & Yin, 2020](#)).

As the current output variable (y) encompasses more than two classes and cannot be modeled by binary DMDC, we used a novel methodological framework derived from a one-vs-one strategy. This approach splits the multiclass dataset into one binary classification problem for each pair of classes. By applying our method, any two classes of output variables are defined based on the binary DMDC model; then, we will have

$(k(k-1))/2$ binary classification (k is the number of classes in the target variable space). Consequently, for each observation, there will be an equal number of pre-

dicted classes. To determine the classification for an observation, the class with the highest frequency is considered as the final predicted label, employing a majority voting approach. When multiple classes show the same frequency, the observations are allocated to the class with a maximum absolute value of $f(x)$. Through applying this technique, more precise classifications will be achieved. We also compared the classic SVM and the DMDC models to ensure better accuracy representation.

Moreover, we designed a two-level DMDC model. In the first level, using the training data, a binary DMDC model discriminates between two states (in this case, healthy control and disordered conditions). In the second level, observations that the designed model assigned the disorder label undergo classification using a multiclass DMDC. This process categorizes healthy states (non-accurately assigned), ASD, and ADHD categories. Subsequently, this two-level classification process is applied to the test dataset and yields an ultimate predicted label, which is then compared with the actual diagnostic labels to assess classification performance to evaluate this two-level classification process.

Regarding the applied SVM model, we calculated the non-zero coefficients as the discriminative links and connections.

3. Results

We summarized sex, handedness, and age distribution by groups in [Table 1](#).

Table 2. The metrics of the models in the test dataset

Models	%				No.
	Total Acc	ASD Acc	ADHD Acc	Healthy Control Acc	Non-zero Coefficients
Two-level Multi-class DMDC	62	61	84	51	6670
LASSO SVM	59	46	84	46	6670
SVM	73	87	-	68	13
DMDC		85	-	69	6670
SVM	76	-	84	72	13
DMDC		-	85	73	6670
SVM	98	98	99	-	13
DMDC		98	99	-	6670
SVM	53	61	-	45	26
DMDC		60	83	40	6670

Acc: Accuracy.

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Comparison of two models (DMDC vs SVM)

Applying the DMDC model to the test data resulted in a total accuracy of 62%. The model achieved accuracies of 51%, 61%, and 84% for the control, autism spectrum disorder, and ADHD groups, respectively. In the SVM model, an accuracy of 46% was obtained for the healthy control and autism spectrum disorder groups, while an 84% accuracy was observed for ADHD. As shown in [Table 2](#), these two models exhibit similar performance parameters in the ADHD group; however, the discrimination power is higher in the ASD group.

In the context of healthy versus disordered states, the total accuracy was 53%. Specifically, within the healthy group, the accuracy was 45%, and within the disordered group, it was 61%. Overall, around twenty-six connectivity paths exhibited non-zero coefficients.

The model differentiated between Autism and control fMRI datasets with a total accuracy of 73%. More specifically, within the control group, the accuracy was 68%, and within the autism spectrum disorder group, it was 87%. Overall, around thirteen connectivity paths exhibited non-zero coefficients ([Table 3](#)). In the comparison between ADHD and Control groups, the total accuracy was 76%. Specifically, within the control group, the accuracy was 72%, and within the ADHD group, it was 84%. Overall, approximately thirteen connectivity paths showed non-zero coefficients ([Table 3](#)).

The total accuracy was 98%, with a specific accuracy of 98% within the ASD group and 99% within the ADHD group. Overall, approximately thirteen connectivity paths exhibited non-zero coefficients ([Table 4](#)).

The recognized patterns based on non-zero coefficients are visualized in [Figures 2](#) and [3](#), as functional connectivity maps.

4. Discussion

ASD and ADHD are neurodevelopmental abnormalities that frequently occur together with below-threshold cross-disorder manifestations (the existence of symptoms of the other one despite not receiving the diagnostic label) ([Syed et al., 2017](#)). Since there are ambiguities in diagnosis and subsequent treatment options, in the current study, we used a novel two-level multi-class DMDC algorithm to classify the functional connectivity values for each state of ADHD, ASD, or healthy participants. The obtained values showed that this model might be an efficient extension of the previous support vector machines and could be applied to other disordered states with more than two or even more classes. The total accuracy was 62%, 51% for healthy control subjects, 61% for ASD, and 84% for ADHD. Functional connections of the cerebellum exhibited discriminative features for the two datasets of ADHD-200 and ABIDE.

Table 3. Results of DMDC classification for autism and ADHD vs control and disordered vs healthy controls distinctive connectivity maps

Disordered vs Healthy		Autism vs Healthy		ADHD vs Healthy	
Total Accuracy: 53%		Total Accuracy: 73%		Total Accuracy: 76%	
Connections	Coeff	Connections	Coeff	Connections	Coeff
Insula.l - cerebellum.3. l	-0.5924	Angular.r - cerebellum.7b. r	-0.0238	Cerebellum.6. l - hippocampus.l	0.0144
Frontal.sup. medial.l - amygdala.r	-0.4112	Occipital.sup. l - cerebellum.10. r	-0.6073	Cerebellum.6. l - vermis.1.2	0.0000
Cerebellum.crus2. r - precuneus.l	-0.4070	Cerebellum.8. l - paracentral. lobule. r	-0.3375	Frontal.sup. orb.l - thalamus.r	0.0005
Cerebellum.crus1. l - temporal. inf.r. r	-0.2829	Frontal.med. orb.l - cingulum. ant. l	-0.0733	Frontal.inf. oper.r - occipital. sup. l	0.0005
Vermis.10 - caudate.r	-0.2370	Vermis.9 - Frontal.Sup. Orb.R	-0.0456	Precentral.l - vermis.7	0.0020
Vermis.1.2 - calcarine.r	-0.1517	Cuneus.r - occipital.mid. r	-0.0431	Frontal.sup. orb.l - precuneus.l	0.0039
Cerebellum.9. r - paracentral. lobule. r	-0.1224	Caudate.l - occipital.sup. l	0.0039	Frontal.mid. orb.l - occipital.inf. l	0.1144
Cuneus.r - rectus.l	-0.1043	Insula.r - putamen.r	0.0172	Cerebellum.7b. l - frontal.med. orb.l	0.1163
Heschl.l - insula.l	-0.0827	Insula.l - olfactory.l	0.0813	Cerebellum.crus2. l - calcarine.r	0.2363
Cingulum.ant. l - frontal.med. orb.l	-0.0703	Frontal.inf. tri.l - cingulum.post. r	0.0830	Cuneus.r - occipital.Inf. R	0.2897
Cerebellum.8. l - cerebellum.4.5. r	-0.0648	Parahippocampal.l - frontal.sup. orb.r	0.1400	Frontal.mid. orb.l - olfactory.l	0.3584
Heschl.r - vermis.4.5	-0.0555	Frontal.inf. tri.l - cerebellum.8. r	0.2061	Thalamus.l - hippocampus.r	0.3814
Temporal.inf. l - vermis.6	-0.0186	Cerebellum.7b. l - parahippocampal.l	0.5579	Frontal.sup. l - vermis.1.2	0.4490
Cerebellum.8. l - paracentral. lobule. r	-0.0123				
Cerebellum.4.5. r - temporal.inf. r	-0.0096				
Vermis.7 - parahippocampal.r	0.0276				
Parahippocampal.l - rolandic. oper. r	0.0429				
Cingulum.post. l - cuneus.l	0.0468				
Cerebellum.7b. l - parahippocampal.l	0.0754				
Frontal.med. orb.l - precuneus.l	0.0791				
Supp.motor. area.l - supp.motor. area.r	0.1629				
Cerebellum.7b. l - angular.r	0.2091				
Paracentral.lobule. l - vermis.1.2	0.2165				
Cerebellum.3. r - frontal.mid. orb.r	0.2311				
Insula.l - olfactory.l	0.3779				
Occipital.sup. l - caudate.l	0.4455				
Insula.l - cerebellum.3. l	-0.5924				

Coeff: Coefficients.

Table 4. Results of the DMDC classification for Autism vs ADHD

Connections	Coefficients
Cerebellum.4.5. l - supramarginal.l	-0.3847
Cerebellum.8. r - frontal.inf. oper.r	-0.3375
Frontal.sup. orb.r - paracentral.lobule. l	-0.2329
Cerebellum.10. r - hippocampus.r	-0.0908
Calcarine.l - rolandic.oper. r	-0.0578
Olfactory.l - cerebellum.7b. r	-0.0315
Pallidum.l - supramarginal.r	-0.0096
Cerebellum.10.r - occipital.mid.r	-0.0008
Cerebellum.crus2. l - calcarine.r	0.1372
Cerebellum.7b. l - frontal.med. orb.l	0.2560
Frontal.sup. l - vermis.1.2	0.2620
Frontal.sup. orb.l - precuneus.l	0.2705
Cuneus.r - occipital.inf. r	0.4654
Cerebellum.4.5. l - supramarginal.l	-0.3847

The currently available diagnostic attitudes that exclusively rely on behavioral findings could provide differentiation; however, there has been evidence supporting the insufficiencies. The shared properties of genetic composition and intermediate phenotypes might blur the diagnostic procedures that depend on subjective clinical judgments, particularly for children and young adolescents exhibiting overlapping symptoms that do not neatly align with the combined form of disorders (ADHD+ASD). Furthermore, accurately expressing internally perceived symptoms can be challenging. Incorporating objective parameters derived from diagnostic tools alongside diagnosis and prognosis processes can potentially enhance treatment approaches. Structural and functional magnetic resonance imaging leverage brain tissue attributes to non-invasively map structural and functional characteristics' spatial distribution. Regarding neuromodulation, understanding the precise location of the interventions (either transcranial direct current stimulation or transcranial magnetic stimulation) (Cao et al., 2019; Barreiros et al., 2019) assists in determining the pattern of the stimulation, cognitive changes, and probable side effects. While known functional and structural brain abnormalities exist in ASD and ADHD, they alone cannot fully elucidate the disorders' fundamental aspects. Given the high-dimensional nature of brain con-

nnectivity data, designing a computational framework for precise big data identification is imperative.

Several studies have applied machine learning techniques toward diagnosing neurodevelopmental disorders. Nielsen et al. (2013) obtained 60 % accuracy for classifying ASD and typically developed controls using the ABIDE dataset; Abraham et al. (2017) designed individual FC matrices, achieving 67% classification accuracy. Jin et al. (2015) reached a classification accuracy of 76% using a multi-kernel SVM. Additionally, Libero et al. used multimodal data to perform ASD classification (Libero et al., 2015). More recently, Agastinose Ronicko et al. (2020) examined several classifiers and different input parameters, obtaining 65%-70% accuracy. SVM has also been extensively used in the ADHD classification with different fMRI findings and variables. Dos Santos Siqueira et al. (dos Santos Siqueira et al., 2014) designed a functional brain graph according to the classical temporal correlation between nodes and applied SVM-based classification; the highest achieved accuracy value was 65%. Moreover, Itani et al. (2018) extracted statistical-focused parameters from functional imaging data and demographic information, achieving accuracies of 68.3% and 82.4% for the two applied datasets. Despite numerous investigations for each dataset (ABIDE and ADHD-

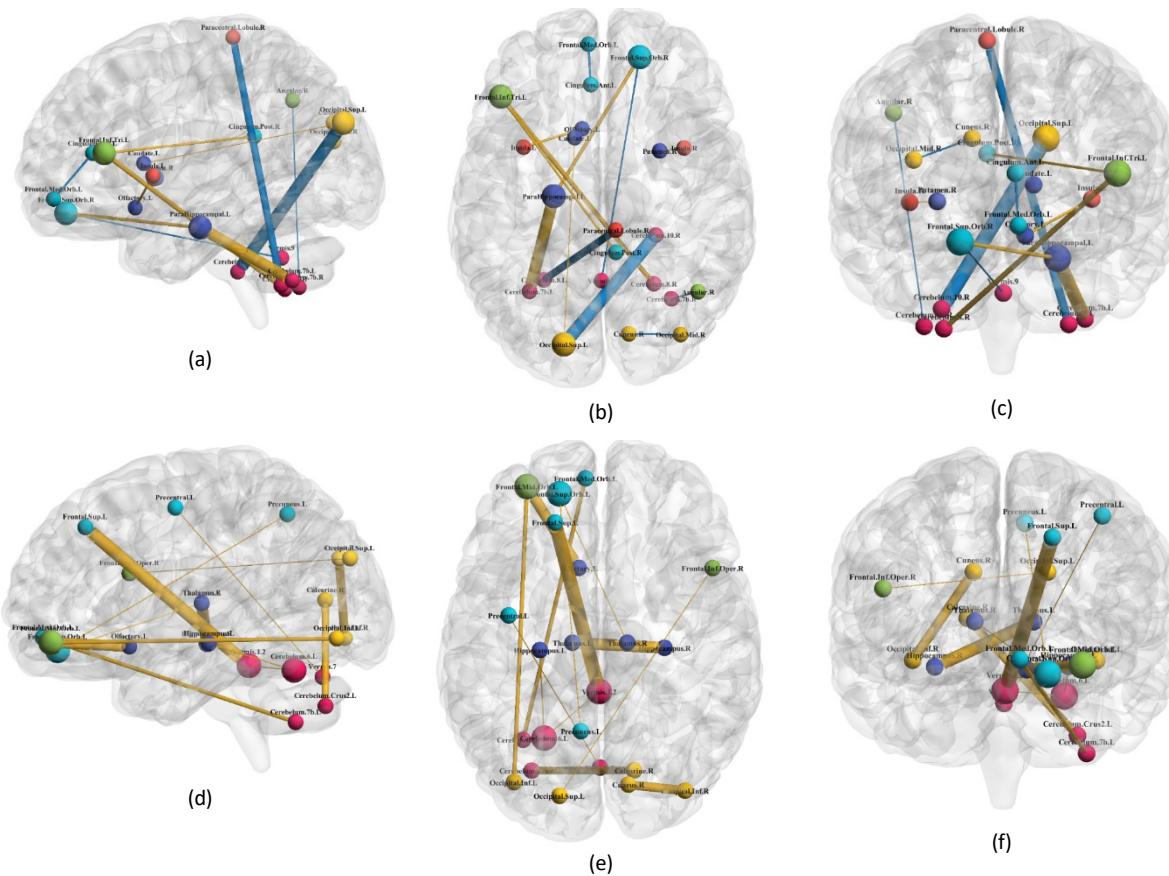


Figure 2. Autism and ADHD vs control: Distinctive connectivity maps

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Notes: (a), (b) and (c) respectively show sagittal, axial, and frontal views of autism vs control distinctive connectivity. Also, (d), (e), and (f) represent sagittal, axial, and frontal views of ADHD vs control distinctive connectivity respectively. The size of the node indicates the number of connections linking the associated node to other nodes (visualized with BrainNetViewer). The size of the node means the number of connections that link the associated node to other nodes (visualized with BrainNet-Viewer). The width of the edge represents the value of the connection weight, where yellow links show positive coefficients and blue links show negative ones.

200), only two studies have combined these datasets in one paper. The following studies have approached the discrimination framework but toward a two-class classification (ADHD vs healthy controls and ASD vs healthy controls). The currently presented model has integrated the classes of ADHD, ASD, and healthy controls to compare the functional neural correlates in a more comprehensive manner (achieving a total accuracy of 62% and 51% for healthy controls, 61% for ASD, and 84% for ADHD). Compared to the DMDC, the SVM model provided accuracies of 46% for the healthy control group, 46% for ASD, and 84% for ADHD. As far as we know, a similar merger work has not been previously conducted; however, two modeling-based assessments have yielded acceptable accuracies for ADHD vs healthy controls and ASD vs healthy controls. Sen et al. in their 2018 investigation used structural texture and functional con-

nnectivity features obtained from anatomical images and functional scans. They achieved an accuracy of 67.3% on the ADHD-200 data and 64.3% on the ABIDE data. Their modeling algorithm identified key components for ADHD, including nodes of the default mode network, peristriate area, lateral and superior occipital gyrus, frontal and occipital lobe, pons, and temporal lobe. Regarding the ABIDE database, they found remarkable discriminative components comprising the visual areas, with relative similarities to some default mode network-associated areas and motor networks (Sen et al., 2018). Similarly, by applying structural imaging parameters and demographic data, Ghiasian et al. (2016) achieved 69.6% accuracy. They provided an accuracy of 65.0% on a holdout set that was better than that of Nielsen et al. (2013). The image features used by their classifiers encompassed the cortical/subcortical and cerebellar re-

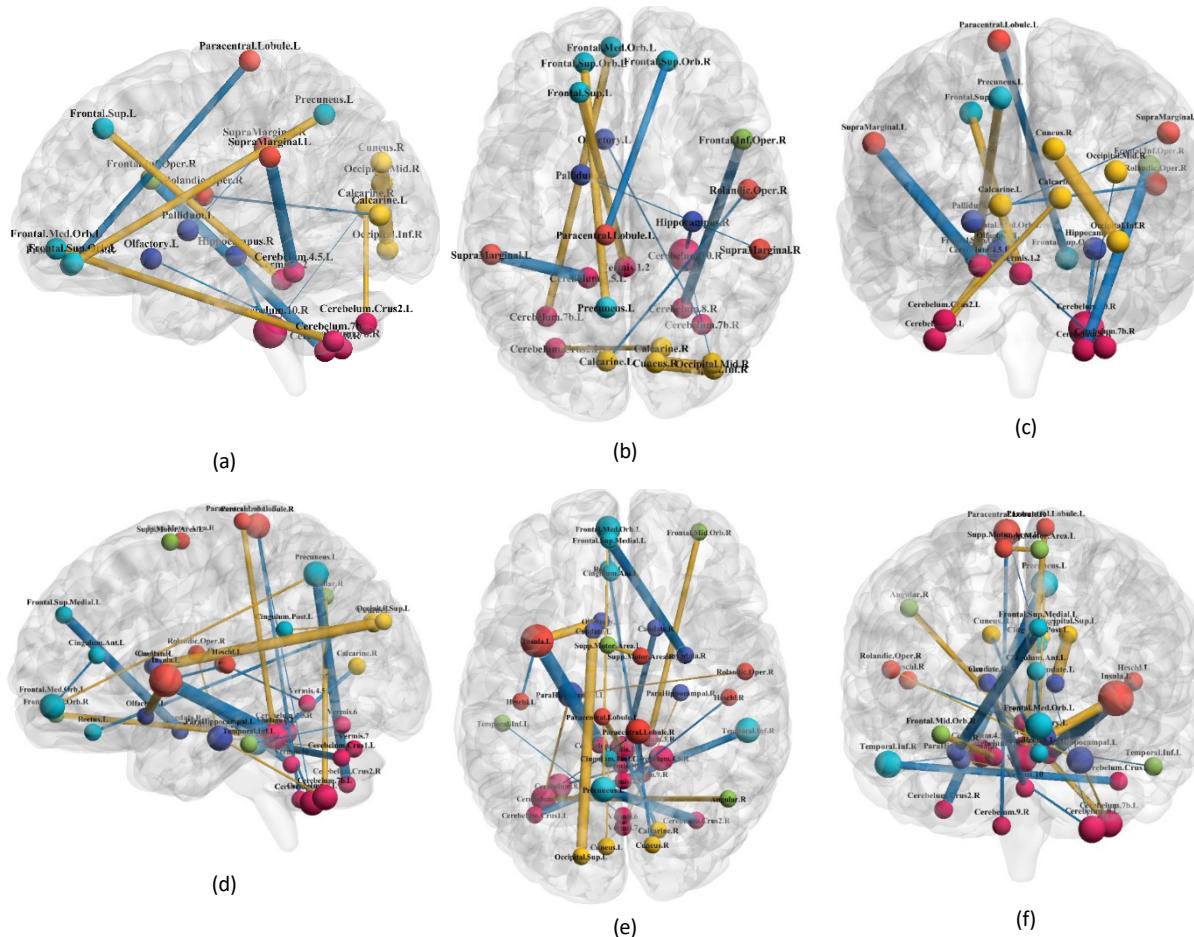


Figure 3. ADHD vs autism and healthy vs disordered states: distinctive connectivity maps

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Notes: (a), (b) and (c) respectively show sagittal, axial, and frontal views of ADHD vs autism distinctive connectivity, respectively. Also (d), (e), and (f) represent sagittal, axial, and frontal views of healthy control vs disordered states distinctive connectivity respectively. The size of the node is proportional to the number of connections linking the corresponding node to others (visualized with BrainNetViewer). The width of the connection is proportional to the absolute value of the corresponding weight. Yellow links show positive coefficients and blue links show negative ones.

gions. The proposed hypothesis was that patients with ADHD show differences in resting-state connections, specifically in the sensorimotor network, default mode network, attention network, striatum, and cerebellum (Cao et al., 2014). Reduced functional connectivity values in the default mode network have been evidenced in subjects with ASD (Minshew & Keller, 2010). Given the relatively shared pathophysiological nature of these two neurodevelopmental disorders, there is a need to model these states together through multiclass classification.

Based on previous findings, there is both contradictory and supportive evidence regarding neurobiological differences between ASD/ADHD and healthy controls. Briefly, decreased functional connectivity (FC) in ASD was investigated by findings obtained from functional imaging data (resting-state and task-based) (Just et al.,

2004; Villalobos et al., 2005; Welchez et al., 2005). These studies have identified decreased connectivity values across nodes of the default mode network (Cherkassky et al., 2006; Di Martino et al., 2014; Kennedy & Courchesne, 2008), social brain (Gotts et al., 2012; von dem Hagen et al., 2013), and attentional networks (Koshino et al., 2005). However, contrary reports have shown either higher or unchanged FC values (Müller et al., 2011), particularly in corticostriatal connections (Di Martino et al., 2011), visual search regions (Keen et al., 2013), and brain network-level metrics (Anderson et al., 2013; Lynch et al., 2013) in individuals with autism spectrum disorder. The interpretation of this contradiction in the current findings becomes even more complicated when we consider the chronological alterations as well. The frontostriatal circuit, which includes areas such as the dorsolateral prefrontal cortex and dor-

sal striatum, plays a crucial role in shaping behavioral components and various cognitive abilities (Rubia et al., 2014). Disruptions in the fronto-cerebellar circuit, involving the cerebellum, are frequently observed in ADHD, particularly in the posterior parts of the vermis (Bledsoe et al., 2009). Also, the attentional circuitry of the brain, mainly comprising prefrontal cortices and the dorsal anterior cingulate, is often disrupted in children with ADHD (Bush, 2010).

As indicated by the present results, different connections with the cerebellum could be considered as discriminative features and connectivities. Regarding healthy controls and all the disordered states (ADHD+ASD), the insular-cerebellum connection has been the most correlated one. Cerebellum connections with the angular area and hippocampus were other distinguishing connections, respectively, for autism vs control and ADHD vs typically developed subjects. The cerebellum is composed of cerebellar lobules and the vermis. The precise functioning framework of these divisions is not identified. However, it is suggested that lobules I-V and VIII may process sensorimotor information, while lobules VI and VII play roles in cognition, and lobules IX and X contribute to visual guidance and vestibular organization, respectively (Stoodley & Schmahmann, 2018). Recognized as a node in the attentional network (Mannarelli et al., 2019), the cerebellum's involvement in neurodevelopmental disorders with attention difficulties is not surprising (Mannarelli et al., 2019; van der Heijden et al., 2021).

A whole-brain, voxel-wise meta-analysis comparing ASD vs healthy control revealed higher activation in the inferior-posterior cerebellum (Hodge et al., 2010). The regions with the most prominent hypoactivation levels were in the default mode network (DMN) and cerebellar crus I. Hodge et al. indicated that the posterior lateral cerebellum was remarkably associated with the frontal parts of the cerebrum, including Broca's area, contributing to the fronto-cortico-cerebellar language network (Hodge et al., 2010). Autistic participants exhibited cerebrocerebellar hypoconnectivity during a finger-tapping task (Mostofsky et al., 2009). However, significant degrees of hyperactivity in cerebellothalamic circuitry were observed in individuals with ASD during a saccade-based task (Takarae et al., 2008).

In 2003, Hill et al. reported that the group with ADHD diagnosis showed area reduction in cerebellar lobules VIII to X and I to V (Hill et al., 2003). Further studies have exhibited a lower volume of the inferior vermis, which was correlated with inattention, hyperactivity,

and impulse control scores. Also, fMRI studies have demonstrated overactivation of the posterior cerebellum coupled with frontal lobe underactivation when performing attention-related tasks (Berquin et al., 1998; Cubillo et al., 2014; Mostofsky et al., 1998; Rubia et al., 2009) and also lower activation in right crus I and left lobule VI during memory processing (Durston, 2003). Moreover, task-negative functional imaging reports showed ADHD-associated disturbances in cerebrocerebellar connectivity (Konrad & Eickhoff, 2010).

We encountered some limitations, there are critical missing data regarding the IQ level; thus, it could not be considered for interpretations. In other words, there were no scores of cognitive states, impeding a complete understanding of neurocognitive conditions, which could be quite crucial. Variations in age distribution are also a significant limitation that could affect the outcomes and interpretations. Longitudinal investigations are recommended to provide a comprehensive assessment, along with age-related considerations. A noticeable limitation of these types of works that also applies to the current research, is the multicenter nature of the acquired data, resulting in differences in imaging facilities and protocols. While this diversity could enhance the generalizability of the results, mild variations in imaging parameters might interfere with the study goals. Accordingly, we attempted to mitigate the influence of these factors through careful preprocessing steps. Moreover, incorporating other categories of neurodevelopmental disorders, such as obsessive-compulsive disorder and some milder forms of intellectual disability might provide a more accurate distinction for these disorders. Additionally, the available diagnosis tools for the subjects of the datasets were not fully explained, so there might be traits of other neurodevelopmental disorders in the "other" category that encompass the structural and functional neural correlates and subsequently affect the classification process and outcomes. Although the aim of this study was to design a supervised classification, performing a parallel clustering method and modeling could reveal more aspects regarding the different categories of disorders and sets of brain connectivities.

5. Conclusion

Neurodevelopmental disorders are a group of neuropsychiatric anomalies that share genetic and endophenotypic correlates. Behavior-based diagnostic approaches are currently used in clinical settings, but the overlapping features among the disorders vague the recognition and management of these disorders. Machine learning approaches based on functional neuroimaging data

could provide a computational setting for discriminating between different states of health and disorder. DMDC showed promising results for classification, with the cerebellum and its attributed connections exhibiting acceptable classifying characteristics.

Ethical Considerations

Compliance with ethical guidelines

In this study, publicly accessible datasets were used. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.PHNS.REC.1402.032).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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