Original Article

Comparison of the performance of machine learning algorithms for the task-switching functional magnetic resonance imaging data for distinguishing attention deficit hyperactivity disorder from bipolar disorder

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Background: Bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD) are two distinct psychiatric disorders characterized by significant overlap in symptoms, making differential diagnosis challenging. Due to the lack of a definitive test for diagnosing and differentiating these disorders, the present study aimed to accurately diagnose and differentiate between patients with BD and ADHD using the support vector machines (SVM) with radial basis function, polynomial, and mixture kernels, as well as ensemble neural networks, to analyze functional magnetic resonance imaging (fMRI) data. **Materials and Methods:** In this study, 49 individuals with BD and 40 individuals with ADHD were analyzed. A protocol based on fMRI imaging and a switching task was proposed for diagnosing ADHD and BD. The graph theory method calculated the graph criteria using the CONN toolbox in 15 areas of the attention circuit. The effective features were then selected using the genetic algorithm (GA), and finally, the performance of the models was evaluated using four criteria: accuracy (ACC), sensitivity (SE), specificity (SP), and area under the curve (AUC). **Results:** 57 effective and important features were selected as input features by GAs with 99.78% ACC. The performance score of the models showed that the SVM with mixture kernels model performed best among the other algorithms (ACC = 92.1%, SE = 92.6%, SP = 97.3%, and AUC = 0.931). **Conclusion:** According to the evaluation criteria values, the best model for diagnosing ADHD from BD has been suggested. This approach can be useful in diagnosis, psychological, and psychiatric interventions.

Key words: Attention deficit hyperactivity disorder, bipolar disorder, functional magnetic resonance imaging, machine learning

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INTRODUCTION

Bipolar disorder (BD) is a mental disorder that affects about 45 million people worldwide; people with BD experience changes in their behavioral states, including emotional peaks (mania or hypomania) and depression.[1] The diagnosis of this disorder is generally consistent worldwide. It is based on diagnostic systems such as the International Classification of Diseases or the Diagnostic and Statistical Manual of Mental Disorders (DSM).[2] Currently, the diagnosis of mood disorders mainly relies on descriptive classification criteria such as DSM-5, which is highly subjective and leads to a decrease in

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the reliability of clinical assessment.[3] Timely and accurate diagnosis of BD and subsequent treatment processes are necessary to prevent the progression and worsening of this disease. However, due to the lack of certain signs in identifying this disorder, bipolar disease may be mistakenly considered by experts as other brain disorders, including attention deficit hyperactivity disorder (ADHD), leading to the adoption of incorrect treatment methods and worsening of the patient's condition.[4]

ADHD is one of the most common neurodevelopmental disorders, usually first diagnosed in childhood and often persisting into adulthood. ADHD is a chronic and debilitating disorder that affects many important aspects of life, including daily activities, social and interpersonal relationships, and academic and occupational performance.[5] This disorder is characterized by symptoms related to inattention, hyperactivity, and impulsivity, as well as cognitive deficits in executive function, reaction time, and alertness, which can vary from mild to severe.[6] In 2020, the worldwide prevalence of adult ADHD with childhood onset was 2.58% (139.84 million individuals), and adult symptomatic ADHD, regardless of childhood onset, was reported to be 6.76% (366.33 million individuals).[7] Considering the high prevalence and lifelong consequences of ADHD, early and accurate diagnosis and effective treatments are much needed.[8]

Although BD and ADHD are two distinct psychiatric disorders, they share many common symptoms, challenging the diagnosis. Neuropsychological studies often report similar neurocognitive deficits in patients with ADHD and BD. Patients with BD have deficits in cognitive flexibility, sustained attention, and verbal working memory, while patients with ADHD show deficits in executive functions, attention, vigilance, working memory, planning, and response inhibition.[9] Since there is no definitive test to diagnose and distinguish between ADHD and BD, researchers and clinicians have been looking for more standardized, objective diagnostic evidence to make the diagnosis of these disorders more scientific and reduce the diagnosis error. For this purpose, the functional magnetic resonance imaging (fMRI) imaging method, which is based on magnetic resonance, has attracted the attention of doctors and researchers due to its safety, high spatial resolution, and ability to evaluate the central areas of the brain.[4]

fMRI can detect abnormalities within the brain that cannot be found with other imaging methods, especially when the changes are minor and there are no significant structural changes.[10] This type of imaging is widely used to identify and determine areas of the brain whose activation levels change in response to specific stimuli and tasks due to changes in blood oxygen levels in the brain.[11] This method can be used to understand human brain mechanisms as well as the diagnosis of brain disorders.[12] Research has shown that fMRI has been used to identify differences in brain activity between people with BD and ADHD,[11,13] distinguishing between BD and ADHD and aiding in clinical diagnosis when other imaging methods cannot diagnose with high accuracy (ACC).[13,14] Although fMRI can be a good candidate as a tool to diagnose and differentiate between BD and ADHD, and patients with BD and ADHD exhibit different functioning of the attention network, the use of a switching task during fMRI can specifically involve the areas related to the attention network in each of these two disorders.

However, because the fMRI imaging recording and analysis protocols for diagnosing these two diseases are not well-defined, identifying biomarkers related to BD and ADHD disorders for more accurate diagnosis is important for treatment. A combination of machine learning techniques with neuroimaging methods can be used. Machine learning models can potentially facilitate the development of more efficient diagnostic methods by utilizing information beyond the practical experience of individual physicians.[15] In the current study, graph theory, a popular tool for quantifying neural relationships and functional and structural differences between diseased and healthy groups, has been used. Using graph theory criteria, researchers can analyze brain connectivity globally, across the entire network, and locally in specific brain areas.[16]

Therefore, this study aims to use combined machine learning methods (support vector machine [SVM], SVM with mixed kernel, and ensemble neural network [ENN]) and advanced analysis of magnetic resonance images (fMRI) using graph theory with a switching task to diagnose and differentiate between patients with BD and ADHD accurately.

MATERIALS AND METHODS

Ethics statements

The Ethics Committee of Kermanshah University of Medical Sciences approved the study (Ethical code: IR.KUMS.REC.1396.448).

Study design

Selection and Description of Participants: In the present study, fMRI brain images of 89 patients, including 49 people with BD and 40 people with ADHD, along with clinical information for participants aged 21–50 years (mean: 33.23; median: 31.0) from https://openneuro.org/, were used. Each participant had completed at least 8 years of formal education, and their native language was Spanish or English. Participants were screened for neurological disease, substance dependence in the past 6 months, history of head injury with loss of consciousness or cognitive consequences, and use of psychoactive drugs.

To better understand, all research steps are shown graphically in Figure 1.

Functional magnetic resonance imaging procedure

Patients underwent an fMRI scan on a 3-Tesla scanner (Siemens Trio). A T1-weighted anatomical scan (MPRAGE) was collected with the following parameters: slice thickness = 1 mm, 176 slices, TR = 1.9s, TE = 2.26 ms, matrix = 256 × 256, and FOV = 250 mm. Diffusion-weighted imaging data were collected with parameters: 64 directions, slice thickness = 2 mm, flip angle = 90°, TR/TE = 9000/93 ms, matrix = 96 × 96, axial slices, and b = 1000 s/mm2. Functional MRI data were collected with a T2*-weighted echoplanar imaging sequence with parameters: 34 slices, slice thickness = 4 mm, TE = 30 ms, TR = 2s, flip angle = 90°, FOV = 192 mm, and matrix = 64 × 64.[17]

Experimental task

In the present study, participants performed task-switching during fMRI, where subjects were shown stimuli that differed in color (red or green) and shape (triangle or circle). They were then asked to respond quickly to the color or shape of the pictures they saw.

Image data preprocessing

Data preprocessing for fMRI analysis was conducted using the functional connectivity toolbox (CONN) in MATLAB (2022b). This involved modifying the field map to reduce image distortion, slice timing correction, realignment to address head motion, coregistration of functional and structural images, segmentation for bias correction, and spatial normalization to Montreal Neurological Institute space. In the smoothing stage, a Gaussian filter with a width of 6 mm was applied to the functional images to remove high-frequency noise.[18]

Brain mapping

Complex network analysis using graph theory is a valuable approach for characterizing functional and anatomical brain connectivity, enabling the quantification of neural differences between healthy and diseased groups.[16] Graphs consist of nodes (brain regions) and edges (connections), typically represented by connectivity matrices that define the network topology.[19]

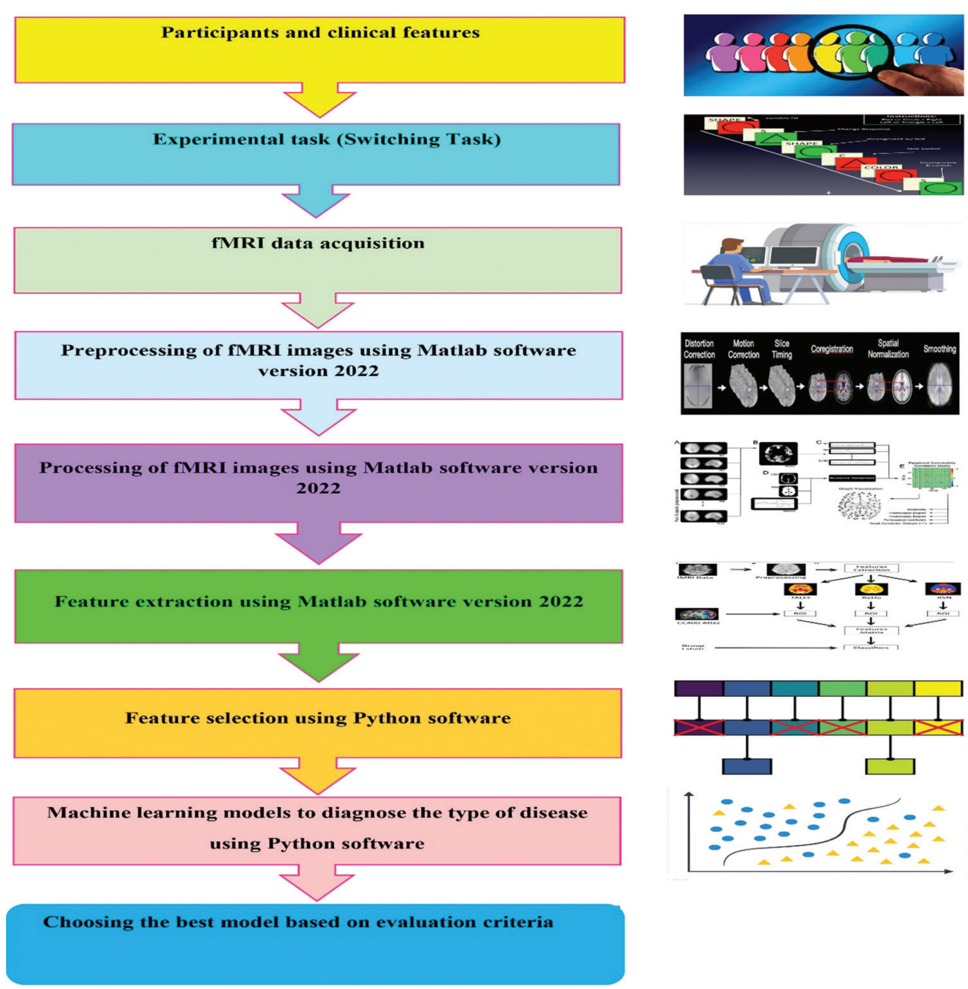


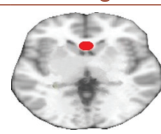
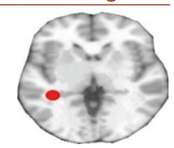
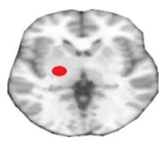
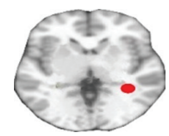
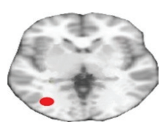
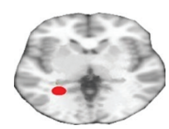
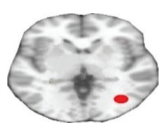
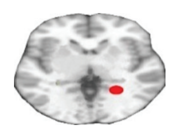
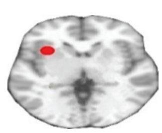
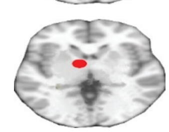
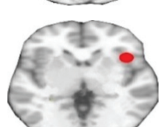
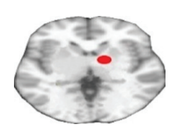
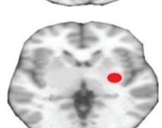
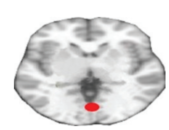
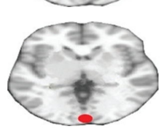
Figure 1: Graphic abstract (steps performed in this study)

In this study, based on previous research, 15 brain regions that play an important role in the attention network in BD and ADHD patients were selected [Table 1].[20] Then, using the CONN toolbox in MATLAB software, graph theory analysis was conducted to calculate the features related to the distribution of neighborhoods and connections in these brain areas. These features can be used as inputs to machine learning models to determine the type of disease.[21]

Feature extraction

After preparing the data (pre-processing) using the graph theory method, the graph criteria of local efficiency (it describes how neighbors in a particular region of the network are related), betweenness centrality (identifying the most influential network nodes), cost (the ratio of edges for the current node), average path length (the average distance of the shortest path between a node and other nodes), clustering coefficient (the proportion of connected nodes in all neighboring nodes), global efficiency (measures the closeness of an individual node to all other nodes in the network), and degree (the number of nodes to which the current node is connected, i.e., the number of its edges) were calculated for each node (15 selected brain regions) using the adjacency matrix.[22] These criteria were calculated for the four task modes: green circle, red circle, green triangle, and red triangle. Along with clinical parameters such as "age" and "gender", these criteria were extracted as input features. Due to the large number of features (420 features), a genetic algorithm (GA) was used to reduce computational complexity and extract the most effective features. The selected features were then used as input for the machine learning models.

Table 1: Coordinates and names of attention network regions

Attention network regions	X	Y	Z	Brain regions	Attention network regions	X	Y	Z	Brain regions
ACC	0	22	35		Left IPS	−39	−43	52	
Left FEF	−27	−9	69		Right IPS	39	−42	54	
Left visual lateral	−37	−79	10		Left SPL	−29	−49	57	
Right visual lateral	38	−72	13		Right SPL	29	−48	59	
Left FO	−40	18	5		Left SMA	−5	−3	56	
Right FO	41	19	5		Right SMA	6	−3	58	
Right FEF	30	−6	64		Medial visual	2	−79	12	
Occipital visual	0	−93	-4						

ACC=Anterior cingulate cortex; Left FEF=Left frontal eye fields; Left FO=Left frontal operculum; Right FO=Right Frontal Operculum; Right FEF=Right Frontal Eye Fields; Left IPS=Left Intraparietal Sulcus; Right IPS=Right Intraparietal Sulcus; Left SPL=Left Superior Parietal Lobule; Right SPL=Right Superior Parietal Lobule; Left SMA=Left Supplementary Motor Area; Right SMA=Right Supplementary Motor Area

Feature selection using genetic algorithm

Feature selection is essential in machine learning to reduce the large number of features, many of which may be noisy, redundant, or irrelevant. By selecting a minimal subset of relevant features, models achieve better generalization, lower computational complexity, and improved classification ACC. Given the high dimensionality of variables in this study, a GA was employed for feature selection. The GA iteratively performs initialization, fitness evaluation, crossover, mutation, and termination steps, cycling through these processes repeatedly until an optimal solution is found.

Statistical analysis

Support vector machine

The SVM method is a powerful machine-learning tool and one of the supervised learning methods used for classification and regression. It is known as a small sample learning method with a strong theoretical base because its temporal and spatial complexities make it unsuitable for large datasets. Consequently,[23] SVM has become very popular for analyzing low sample size data, including neuroimaging and psychiatric data.

Support vector machine with mixture kernels

Kernel function selection is a key challenge in SVM, as it determines the similarity measure between vectors. Common kernels include the radial basis function (RBF), which offers strong local learning but limited generalization, and the polynomial kernel, which provides better generalization with less learning capacity. To address these complementary strengths and weaknesses, a hybrid kernel combining RBF and polynomial functions can be utilized to enhance classification performance.[24]

Ensemble neural network

Artificial neural networks are computational systems used for pattern recognition, classification, and prediction when relationships are nonlinear.[25] ENNs is a collection of a limited number of neural networks (NN), where the networks are trained independently, and then, their predictions are combined. Although each of the NNs in an ENN can provide useful results alone, combining several NNs results in better generalizability. This method is especially useful when insufficient data exists to train each NN.[26]

In this study, due to the low number of available data, the SVM model with two RBF and polynomial kernels, the SVM-MK, which is a combination of RBF and polynomial kernels, and the ENN model were used to diagnose BD and ADHD, because these models can perform properly in studies with a low sample size.

Compare the performance of models

In the present study, a 10-fold validation method was used first to avoid overfitting and increase the model's ACC. After fitting the algorithms, the criteria of ACC, sensitivity (SE), specificity (SP), and the area under the ROC curve (AUC) were used to evaluate the performance of SVM and ENN models.[27]

RESULTS

In the present study, the information of 89 patients, including 49 people with BD and 40 people with ADHD, with an age range of 21–50 years (average age of 33.23 years), has been studied. The BD group included 28 men (57.1%) and 21 women (42.9%) with an average age of 35.29 (±9.02), while the ADHD group included 21 men (52.5) and 19 women (47.5) with an average age of 32.05 (±10.4).

Results of graph theory in the attention network

Table 2 reveals that the regions activated in most criteria for each of the four tasks in ADHD and BD patients were different, and the difference between these criteria can be used to diagnose ADHD and BD. For example, in the green circle task, for the local efficiency criterion, the way neighbors communicate in the superior parietal lobule (Left) and visual lateral (R) regions was different in ADHD and BD patients. Furthermore, for the average path length criterion, the average distance of the shortest path between each region and other regions differed in all regions except the right frontal eye field in ADHD and BD patients. For the clustering coefficient measure, the proportion of connected nodes in all neighboring nodes in the left intraparietal sulcus and visual lateral (R) regions differed in ADHD and BD patients.

Results of feature selection using genetic algorithm

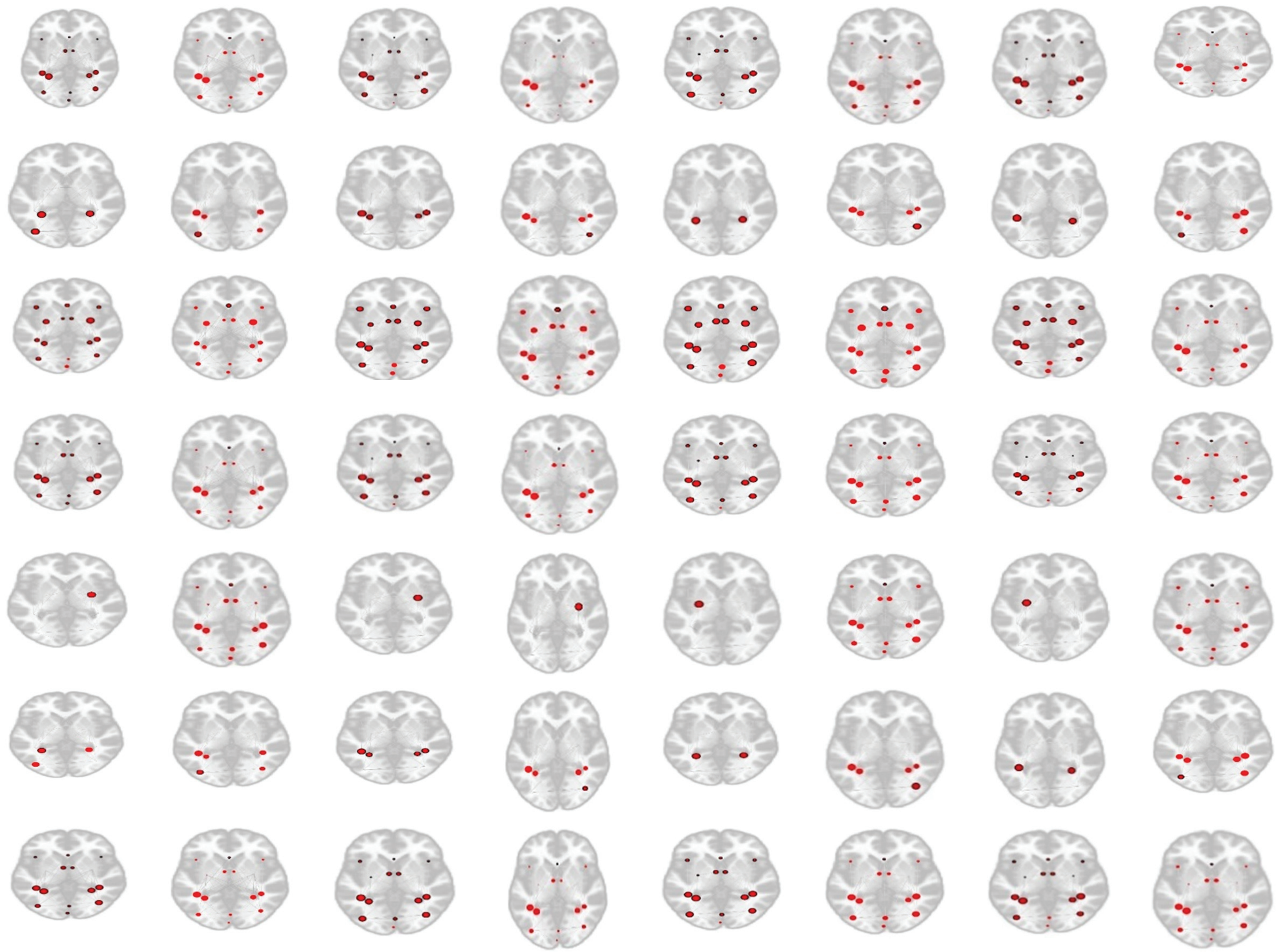
In the present study, due to the large number of features (420 features), a GA was used to reduce computational complexity, improve classification ACC, and select the most effective features. The number of 50 subsets (chromosomes) was considered the initial population, and the fitness index was used to determine the value of each chromosome, which is the ACC value obtained from the classification of the random forest algorithm. The selection of features was calculated using the GA in the third iteration with 99.78% ACC. Finally, 57 effective and important features, including the demographic variables of gender and age, were selected as input features for machine learning models.

Performance of the methods

The results of evaluating the performance of the models used in the present study based on the criteria of ACC, SE, SP, and the area under the ROC curve (AUC) indicated that the SVM-MK model was recognized as the best model

Table 2: Results of graph theory in the attention network for bipolar disorder and attention deficit hyperactivity disorder based on the switching task

Task	Green circle		Red circle		Green triangle		Red triangle	
	ADHD	BD	ADHD	BD	ADHD	BD	ADHD	BD
Global efficiency								
Local efficiency								
Betweenness centrality								
Cost								
Average path length								
Clustering coefficient								
Degree								



Each ROI of the attention network is considered a node and is shown in red circles. The edges between nodes, which show their correlation values, are displayed with gray lines. Graph theory for the attention network was calculated using the CONN toolbox. ADHA: Attention deficit hyperactivity disorder, BD: Bipolar disorder, ROI: Regions of interest, CONN: Connectivity toolbox for diagnosing ADHD from BD (ACC = 92.1%, SE = 92.6%, SP = 97.3% and AUC = 0.931). After the SVM-MK, the ENN model performed best (ACC = 90%, SE = 88.1%, SP = 92.3%, and AUC = 0.912). Considering that a model with higher evaluation criteria has the best performance, the values of ACC, SE, SP, and AUC for polynomial-SVM and RBF-SVM models were ACC = 87.6%, SE = 91%, SP = 85%, and AUC = 0.882 and ACC = 88.2%, SE = 89.7%, SP = 87.5%, and AUC = 0.894, respectively [Table 3]. Figure 2 shows the ROC diagram for each of the models.

DISCUSSION

This study employed a combination of machine learning techniques and advanced analysis of fMRI using graph theory with a switching task to distinguish between BD and ADHD patients.

Machine learning models each have their strengths and limitations in classification tasks, and their ACC can vary depending on the sample size and complexity of the dataset. Due to the limited sample size in this study, we employed RBF-SVM, Poly-SVM, SVM-MK, and ENN models. The SVM-MK model, which combines RBF and polynomial kernels, emerged as the best model for distinguishing ADHD from BD, achieving outstanding evaluation criteria scores (ACC = 98.9%, SE = 1, SP = 97.5%, and AUC = 1).

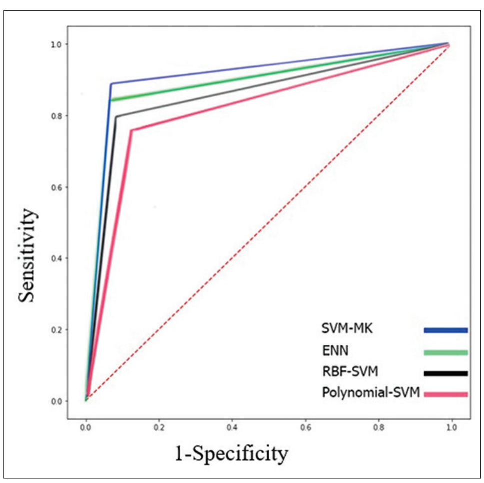


Figure 2: ROC curves of the machine learning models

Table 3: The results of comparing support vector machines kernel types, support vector machines - mixture kernels, and ensemble neural network models

Models	ACC	SE	SP	AUC
RBF -SVM	88.2	89.7	87.5	0.894
Polynomial -SVM	87.6	91	85	0.882
SVM-MK	92.1	92.6	97.3	0.931
ENN	90	88.1	92.3	0.912

MK: Mixture Kernels, SVM: Support vector machines, ENN: Ensemble neural networks, ACC: Accuracy, SE: Sensitivity, SP: Specificity, AUC: Area under the curve

Therefore, this approach can be particularly useful in neurology, psychology, and psychiatry studies with small sample sizes, aiding specialists in accurately diagnosing these conditions.

Previous studies support the superiority of the SVM-MK model. Tian *et al*.'s study on the Berg dataset demonstrated that the SVM-MK model achieved higher classification ACC than the SVM-RBF and SVM-Poly models, with 50.3%, 48.8%, and 46.8%, respectively.[28] Similarly, Song *et al*.'s research comparing SVM-RBF, SVM-Linear, and SVM-MK models across four datasets showed that SVM-MK outperformed other SVM models, exhibiting better learning ability and higher generalization.[29]

In addition, Li *et al*.'s study, which utilized the SVM model for MRI data to diagnose BD, reported a high AUC value of 94.9% for the SVM classifier, indicating excellent performance in classifying BD.[13] Peng *et al*.'s study on diagnosing ADHD using SVM and extreme learning machine (ELM) models on MRI data also found that the SVM model had higher prediction ACC than the ELM model.[30]

In this study, the combined approach of graph theory and SVM techniques demonstrated strong performance in distinguishing between ADHD and BD. Our findings indicate that this combination of methods has significant potential for enhancing diagnostic ACC and understanding the neural mechanisms underlying these two diseases. This suggests that machine learning techniques can be valuable tools in the differential diagnosis of psychiatric disorders.

The graph theory results revealed that the regions activated differed significantly between ADHD and BD patients across most criteria for each task. This difference can assist healthcare professionals in distinguishing between the two disorders. Future research should involve neuroscience experts to investigate the reasons behind these differences, aiming for a comprehensive understanding that could inform therapeutic interventions for ADHD and BD.

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Conflicts of interest

There are no conflicts of interest.

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