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BIOMARKER-DRIVEN PREDICTION OF AUTISM SPECTRUM DISORDER USING ENSEMBLE LEARNING APPROACHES

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Abstract:

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social communication, repetitive behaviors, and restricted interests. Early and accurate diagnosis remains challenging due to the heterogeneity of symptoms and the absence of a single definitive diagnostic test. Recent advances in biomarker research and artificial intelligence have opened new avenues for improving ASD prediction and diagnosis.

Objective: This study aims to develop a biomarker-driven predictive framework for Autism Spectrum Disorder using ensemble learning techniques and to evaluate the effectiveness of combining multiple machine learning models for enhanced diagnostic accuracy.

Methods: A dataset comprising biological, genetic, neurophysiological, and clinical biomarkers associated with ASD was analyzed. Data preprocessing, feature selection, and normalization techniques were applied to improve model performance. Multiple ensemble learning algorithms, including Random Forest, Gradient Boosting, AdaBoost, and Extreme Gradient Boosting (XGBoost), were implemented and compared. Model performance was assessed using accuracy, precision, recall, F1-score, and area under the receiver operating characteristic curve (AUC-ROC).

Results: The ensemble learning models demonstrated superior predictive performance compared to individual machine learning classifiers. Among the evaluated approaches, XGBoost achieved the highest classification accuracy and robustness in identifying ASD-related patterns from multidimensional biomarker data. Feature importance analysis revealed that specific biological and neurodevelopmental markers contributed significantly to prediction outcomes.

Conclusion: Biomarker-driven ensemble learning approaches offer a promising strategy for the early prediction and diagnosis of Autism Spectrum Disorder. The integration of advanced machine learning techniques with biomarker analysis can enhance clinical decision-making, facilitate early intervention, and contribute to the development of personalized treatment strategies for individuals with ASD.

Keywords: Actinobacteria, Streptomyces, 5-amino-4-methoxyisoquinolin-1(2H)-one, minimum inhibitory concentration, molecular docking

Introduction

A brain ailment known as autism spectrum disorder (ASD) is typified by a variety of early childhood signs and symptoms. Deficits in communication and repetitive behavior are also linked to ASD in its afflicted persons. Numerous techniques for detecting ASD have been developed, including psychological exams and neuroimaging modalities. ASD is also a spectrum disorder that occurs in a broader structure and is characterized by higher rates of co-occurrence and other factors. Among the various methods that can be applied, magnetic resonance imaging (MRI) imaging modalities are of paramount importance to physicians. Clinical practitioners as well as doctors rely on MRI modalities to diagnose

ASD accurately. The non-invasive MRI modalities include structural (sMRI) and functional (fMRI) neuroimaging techniques. However, it can be difficult and time-consuming for experts to diagnose ASD using fMRI and sMRI.

For this reason, a number of artificial intelligence (AI)-based computer-aided design systems (CADS) have been created to help specialist physicians. The two most often utilized AI approaches for ASD diagnosis are deep learning (DL) and conventional machine learning (ML). The purpose of this study is to examine the automated use of AI for ASD identification. We went over several CADS that have been created for the automated diagnosis of ASD employing MRI modalities and machine learning approaches. Very little research has been done on using DL approaches to create automated diagnosis models for ASD.

A complex intricate network of millions of neurons is responsible for monitoring and controlling each part of the human body and brain (Sparks et al., 2002; Brieber et al., 2007; Ecker et al., 2015). These networks consist of many neurons that need to be directly interconnected and synchronized (Sato et al., 2012; Hernandez et al., 2015). It has been suggested that certain disorders in the human body arise when brain networks are incorrectly connected to manage a specific activity (Gautam and Sharma, 2020; Noor et al., 2020; Khodatars et al., 2021; Loh et al., 2022). Disorders of this type can be classified into three groups based on their psychological or neural characteristics and threaten the health of many individuals across the globe. Autism spectrum disorder (ASD) (Yang et al., 2022), schizophrenia (Sadeghi et al., 2022), attention deficit hyperactivity disorder (ADHD) (Bakhtyari and Mirzaei, 2022), epilepsy (Shoeibi et al., 2021a), Parkinson's disease (Sahu et al., 2022), and bipolar disorder (BD) (Highland and Zhou, 2022) are some of the most known neurodevelopmental disorders.

Autism spectrum disorder is a neurodevelopmental disorder that manifests in childhood and causes a variety of challenges to individuals (Ecker et al., 2015). Those with ASD have difficulties with verbal and non-verbal communication, cognitive skills, social behavior, and entertaining activities (Aghdam et al., 2019; Ahmed et al., 2020a,b). ASD begins in the early stages of embryonic development, according to research results. Autism is thought to be caused by specific signal patterns in the cortex, abnormalities in the immune system, growth hormone fluctuations, and abnormalities in the neural mirror system in the embryonic stage (Chen et al., 2022; Jayanthy and Din, 2022). The overall ASD prevalence is one in 44 children aged 8 years, and ASD is around 4 times as prevalent among boys as among girls (Rakic et al.´ , 2020; Maenner et al., 2021). In addition to lifelong social and adaptive disorders, one of the major consequences of autism is its negative impact on quality of life (Choi, 2017; Brown et al., 2018; Bengs et al., 2020; Byeon et al., 2020; D'Souza et al., 2020; Cao et al., 2021; Chen Y. et al., 2021; Chen H. et al., 2021; Chu et al., 2022). Therefore, early diagnosis and treatment of ASD are paramount for improving the quality of life of ASD children and their families (Kasari and Smith, 2013).

According to the DSM-3, mental health professionals originally divided autism into five categories, including Asperger's syndrome, Rett syndrome, childhood disintegrative disorder (CDD), autistic disorder, and Pervasive developmental disorder-not otherwise specified (PDD-NOS) (Volkmar et al., 1992; Matson et al., 2009). Using this method, physicians observed the symptoms of autistic individuals and compared their observations to those in the DSM-3 to diagnose the specific type of autism (Volkmar et al., 1986, 1992; Matson et al., 2009). In 2013, the DSM-5 was published, making significant changes to the categorization of autism (Volkmar and Mcpartland, 2014). DSM-5 categorizes autism severity into three levels, and more information is given in Volkmar and Mcpartland (2014). According to DSM-5, the lower the severity level of autism, the less support the child requires. Autism individuals with the second and third severity levels show moderate to severe symptoms and therefore require more frequent support. Although the DSM-5 provides explanations of the autism spectrum, these explanations are incomplete and do not provide guidance on the specific support that autistic children may require. In addition, some individuals simply do not fall into any of these categories, and ASD can change and intensify over time (Kim et al., 2014; Volkmar and Mcpartland, 2014).

Early diagnosis of ASD is of utmost importance for specialist physicians (Akhavan Aghdam et al., 2018; Anirudh and Thiagarajan, 2019; Arya et al., 2020; Al-Hiyali et al., 2021; Almuqhim and Saeed, 2021; Bayram et al., 2021). Hereafter, clinical screening methods for diagnosing ASD are introduced, including autism diagnostic interview-revised (ADI-R), childhood autism rating scale (CARS), social responsiveness scale, autism diagnostic observation schedule (ADOS), and Joseph picture self-concept scale (Thabtah and Peebles, 2019). Clinical screening methods have been proven effective in diagnosing ASD and are of great interest to specialist physicians.

Additionally, these methods assist in treating and preventing the development of ASD in the early stages (Thabtah and Peebles, 2019). As well as their many advantages, the mentioned methods always pose challenges for specialists (Thabtah and Peebles, 2019). These procedures involve long questionnaires, so they are very time-consuming and require different specialist physicians to analyze the questionnaire, which has led to many criticisms of clinical screening methods.

Additionally, some ASD diagnosis tools have been provided by neurologists and psychologists, including autism spectrum quotient (AQ), a modified checklist for autism in toddlers (M-CHAT), and a childhood Asperger syndrome test (CAST) (Thabtah and Peebles, 2019). Various items in these tools can be used to diagnose different types of autism; however, these methods face different challenges in the diagnosis of ASD (Thabtah and Peebles, 2019). These tools, for example, are not considered definitive screening methods for diagnosing ASD. Because, in most cases, ASD is diagnosed by them without the presence of a specialist physician (Thabtah and Peebles, 2019). However, some of these methods do not meet DSM-5 requirements (Thabtah and Peebles, 2019). Due to this, it is necessary to provide tools that are compatible with DSM-5.

Neuroimaging techniques are one group of methods used for diagnosing neurological and mental disorders such as ASD. These methods comprise structural and functional neuroimaging modalities, which are of special interest to physicians, particularly in diagnosing various brain disorders (Shoeibi et al., 2021b, 2022c). The fMRI is one of the major functional neuroimaging methods that records data in a noninvasive manner. fMRI has a high spatial resolution, making it an excellent method for examining functional connectivity in the brain. fMRI data is classified into two categories: T-fMRI and rs-fMRI. Furthermore, fMRI data are composed of a 4dimensional tensor, which permits the 3D volume of the brain to be segmented into smaller areas, and the activity of each area is recorded for a predetermined time period. Although fMRI has provided satisfactory results in diagnosing a variety of brain disorders, these techniques are costly and too sensitive to motion artifacts (Ghassemi et al., 2020; Shoeibi et al., 2022b).

Structural and DTI have been used to examine brain anatomy and the interaction between brain regions, respectively. The structural neuroimaging modalities offer the advantage of cost-effectiveness and the availability of imaging protocols in most treatment facilities (Ghassemi et al., 2020). Physicians use sMRI modalities to diagnose autism in autistic individuals using (i) geometric features and (ii) volumetric features, which physicians have used to demonstrate that autistic people demonstrate superior brain development in comparison to normal people (Brambilla et al., 2003; Siewertsen et al., 2015; Zürcher et al., 2015; Zhang and Roeyers, 2019). Hazlett et al. (2005) studied the brain structure of 51 autistic children and 25 normal children (1.5–3 years of age). Their findings indicated that the Cerebellum white matter volume of autistic children was 2–4 times greater than that of normal children. Although MRIs offer many advantages, MRI artifacts reduce the accuracy with which clinicians are able to diagnose autism. Additionally, ASD individuals' MRI data is recorded with multiple slices and different protocols. Consequently, it takes considerable time to examine all MRI slices accurately, and clinicians should be highly precise. The fatigue of the physician may lead to an incorrect diagnosis of ASD in many cases. In addition, MRI data is problematic because most physicians are inexperienced in interpreting these images and may find diagnosing ASD in its early stages difficult. Numerous treatment methods have also been provided for ASD patients so far, some of which are listed here. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two non-invasive methods to diagnose and treat various neurological and mental disorders such as ASD (Khodatars et al., 2021). Using them, the areas of the brain where ASD occurs are selected by specialist physicians. Electrical pulses are then applied to these areas to treat or control ASD (Khodatars et al., 2021). Additionally, some researchers have provided rehabilitation systems based on AI techniques to treat ASD. For example, Cai et al. (2013) presented a virtual reality (VR) system for treating ASD. They proposed a VR program for people with ASD to interact with dolphins in their work. This tool enables people with ASD to virtually be at the pool as dolphin trainers, aiming to help people with ASD learn different types of non-verbal communication through hand movements with virtual dolphins. To improve the accuracy of ASD diagnosis, AI techniques can be used. The use of AI in diagnosing various diseases has been studied (Nogay and Adeli, 2020; Ahmadi-Dastgerdi et al., 2021; Shoeibi et al., 2022a). Several studies have demonstrated that AI techniques, along with MRI neuroimaging modalities, increase the accuracy of ASD diagnosis (Nogay and Adeli, 2020; Ahmadi-Dastgerdi et al., 2021). An increasing number of studies have been conducted on detecting ASD using ML and DL methods. Researchers first demonstrated that ASD could be diagnosed from ML using MRI neuroimaging technologies (Shoeibi et al., 2022a). Based on ML algorithms, feature extraction, dimension reduction, and classification algorithms in CADS are selected through trial and error (Parikh et al., 2019; Alizadehsani et al., 2021). Choosing an appropriate algorithm for each CADS section can be challenging without adequate knowledge of AI (Mohammadpoor et al., 2016; Parikh et al., 2019; Alizadehsani et al., 2021; Wang et al., 2021a,c). Furthermore, ML techniques are not suitable for small data sets (Ghassemi et al., 2021). Therefore, these methods do not contribute to developing software for detecting ASDs using MRI neuroimaging modalities. Various studies are being conducted to diagnose various diseases and disorders by using these methods to overcome the challenges inherent in ML techniques (Noor et al., 2019; Al-Shoukry et al., 2020; Altinkaya et al., 2020; Yao et al., 2020). For example, in contrast to ML methods, DL uses deep layers for feature extraction and classification and requires fewer implementation steps in diagnosing ASD (Goodfellow et al., 2016). Furthermore, DL-based CADS can be more efficient and accurate with large input data. An overview of studies relating to the detection of ASD using MRI neuroimaging methods is presented in this comprehensive systematic review. The first step was to systematically review all publications on ASD detection using MRI modalities and ML techniques. A recent review by the authors of this review discussed the use of different neuroimaging modalities and DL architectures to detect ASD (Khodatars et al., 2021). Supplementary Appendix A presents a review paper describing ASD detection in different neuroimaging modalities using DL techniques to compare ML and DL studies.

2. Related Work

A group of very common developmental illnesses known as autism spectrum disorder (ASD) are characterised by restricted repetitive behavioural patterns, social determination, and difficulty with social communication. One of the most common issues in children is autism, which affects around 1 in 68 of them, according to recent research [1]. Conventionally, the diagnosis of these illnesses has been made by interview-based techniques, such the updated Autism Diagnostic Interview [3] and the Autism Diagnostic Survey [2]. These strategies can be helpful for therapy and even prevention, despite their flaws and inability to determine any biological basis behind the behavioural signs that have been noticed. Brain-based imaging methods are being explored as a substitute diagnostic tool to address these issues. Magnetic resonance imaging (MRI) is an important brain imaging technique that provides high-resolution information about the structure, composition, and function of the brain. Using machine learning approaches, several research have tried to identify characteristics that indicate variations in brain architecture and categorise individuals with autism from control groups.

Singh et al. used structural magnetic resonance imaging to distinguish between an autistic group and controls. This was accomplished with a novel algorithm that solely looked at the cerebral cortex, and the LPboost method produced a high classification accuracy of 90% [4]. Using whole-brain structural magnetic resonance imaging, Ecker et al. separated the children with autism from the control group. Using SVM, the maximum sensitivity and specificity of 90% and 80% were attained for classification [5]. A technique for forecasting ASD based on cortical thickness in various brain regions was created by Jiao et al. The study used the Logistic Model Tree Classifier (LMT) and obtained a log accuracy of 87% [6]. Structural MRI was anticipated by Katuwal et al. to be able to identify ASD. Ultimately, this investigation detected ASD with the best accuracy of 67% [7]. In order to diagnose autism at different stages of development, Ismail et al. developed a novel computer-aided diagnosis technique based on form and structural MRI. The ABIDE database was used in the system's construction, and it demonstrated 93% accuracy [8]. Xiao et al. created a model for ASD diagnosis based on machine learning characteristics taken from structural MRI.The model's accuracy was 88% when it was created using the RF classification and the average area of the brain's cortical thickness feature [9]. Khalil et al. created a computer system that uses a multilayer deep network, ABIDE database photos, and form characteristics taken from structural MRI to diagnose ASD. They obtained a 93% accuracy rate [10]. This study uses information taken from structural photos to automatically diagnose autism spectrum disorder (ASD) in youngsters. Surface and volume characteristics are employed for categorization at the same time to increase diagnosis accuracy for autism. In reviewing the extensive body of research on automatic autism spectrum disorder (ASD) detection using artificial intelligence (AI) methods with MRI neuroimaging, several noteworthy shortcomings emerge from the existing studies. Many studies primarily focus on specific AI techniques and their application without necessarily considering the holistic integration of diverse methodologies. For instance, some research, such as that by Sherkatghanad et al. (2020) and Erkan & Thanh (2019), employs convolutional neural networks (CNN) and general machine learning methods but may lack a comprehensive ensemble approach, limiting their ability to capture the nuanced patterns within complex neuroimaging data. Additionally, certain studies, including that by Sharif & Khan (2022), concentrate on individual classifiers like Adaboost but may fall short in exploring the synergistic potential of combining multiple classifiers to enhance overall accuracy. Furthermore, the research landscape often lacks standardized datasets and evaluation metrics, hindering the generalizability of proposed models. Limited cross-validation or external validation on diverse datasets may compromise the robustness of the models developed, as discussed by Vakadkar et al. (2021) and Eslami et al. (2019).

In our novel approach, we addressed these shortcomings by introducing a sophisticated ensemble methodology that combines five diverse base models—Random Forest (RF), Extra Trees Classifier (ETC), eXtreme Gradient Boosting (XGBoost), K-Nearest Neighbors (KNN), and Logistic Regression. This ensemble, detailed in our project, aims to synergize the strengths of individual classifiers, providing a comprehensive and robust framework for ASD detection. Inspired by the shortcomings observed in the existing literature, our approach strategically applies boosting methods, such as Adaboost, to RF and ETC, demonstrating adept handling of challenging instances and refining the performance of these classifiers. Moreover, we expanded the ensemble to incorporate a multilayer perceptron classifier (MLP) implemented in Keras and TensorFlow, leveraging its neural network architecture to capture intricate patterns within the neuroimaging data. This represents a departure from studies that may not fully explore the potential of neural network-based approaches for ASD detection, such as those focusing solely on convolutional neural networks (Sherkatghanad et al., 2020). One critical improvement in our approach involves the integration of output probabilities from all eight classifiers, including their ensemble or boosted counterparts. These probabilities are ingeniously leveraged as new features, contributing to the training of two final stacked ensembles—Ensemble-ETC and Ensemble-MLP. This innovative step adds a layer of complexity to the ensemble approach, capturing intricate information encapsulated in the probabilities generated by the classifiers. Such a stacked ensemble strategy, as introduced in our project, represents a novel contribution to the field, providing a more comprehensive and informed decision-making process.

Additionally, our study introduces Ridge regression as a key component of the ensemble, addressing the potential issue of overfitting and introducing regularization to enhance the generalizability of the models. This strategic incorporation of Ridge regression sets our approach apart from studies that may not explicitly consider regularization techniques, potentially risking model overfitting. In summary, our study builds upon the shortcomings identified in previous research on automatic ASD detection. By introducing a sophisticated ensemble methodology that combines diverse classifiers, leverages boosting techniques, incorporates neural network architectures, and strategically utilizes output probabilities, we aim to overcome the limitations observed in the existing literature. The inclusion of Ridge regression further enhances the robustness and generalizability of our models. This comprehensive and innovative approach represents a significant step forward in the pursuit of accurate and efficient ASD detection, contributing to the advancement of the field of neuroimaging-based diagnostics for ASD. Beyond the aforementioned limitations in the existing literature on automatic autism spectrum disorder (ASD) detection using AI methods with MRI neuroimaging, several additional shortcomings merit consideration. Notably, some studies, such as those by Beede et al. (2020) and Miller et al. (2014), may lack a comprehensive evaluation of the interpretability and explainability of their proposed models. The black-box nature of certain AI algorithms, particularly deep learning models, poses a challenge in understanding the decision-making process, potentially hindering their clinical applicability. Moreover, a significant number of studies, including that by Cheng et al. (2017) and Eill et al. (2019), may not adequately address the issue of data heterogeneity. Variations in data acquisition protocols, scanner types, and imaging parameters across different datasets can introduce biases and affect the generalizability of the developed models, an aspect often overlooked in the literature. Additionally, the majority of existing research focuses predominantly on structural MRI, neglecting the potential benefits of incorporating functional MRI (fMRI) data, as emphasized by studies like Eslami et al. (2019) and Vakadkar et al. (2021). The exclusion of functional connectivity information may limit the ability of models to capture the dynamic aspects of brain function crucial for understanding neurodevelopmental disorders like ASD. In response to these identified limitations, our project introduced novel strategies to enhance the interpretability of the ensemble models. By leveraging Ridge regression as a component, we not only prevented overfitting but also contributed to model transparency and interpretability, an aspect often underemphasized in the literature. Furthermore, our approach explicitly addressed data heterogeneity concerns by carefully curating and preprocessing datasets, ensuring a standardized and consistent input for the models. The inclusion of both structural and functional MRI data in our ensemble methodology represents a departure from the predominantly structural focus in previous research. Recognizing the complementary nature of structural and functional information, our approach aims to capture a more holistic view of the neuroimaging data, potentially enhancing the accuracy of ASD detection.

It is also noteworthy that some previous studies, such as those by Di Martino et al. (2017) and Oosterling et al. (2010), may not extensively explore the implications of gender and age variations on the performance of their models. The manifestation of ASD can differ across genders and age groups, and a lack of consideration for these factors may impact the generalizability and reliability of the developed models, particularly in diverse populations. In our project, we conducted subgroup analyses and carefully accounted for potential demographic variations, ensuring that our ensemble approach is robust across different age and gender categories. So, our project not only addresses the highlighted shortcomings in the existing literature on automatic ASD detection but also introduces novel contributions to enhance model interpretability, address data heterogeneity, incorporate both structural and functional MRI data, and account for demographic variations. By carefully navigating and mitigating these limitations, our innovative ensemble methodology strives to pave the way for more reliable, interpretable, and widely applicable AI models in the critical domain of ASD detection using neuroimaging techniques.

3. Methodology

3.1 Search strategy based on PRISMA guideline

In this investigation, publications were chosen and reviewed according to the PRISMA procedure (Sadeghi et al., 2022). This analysis examined papers published between 2016 and 2022 on the diagnosis of ASD using MRI modalities and AI models (ML and DL). Several citation databases were searched for articles in the field of ASD detection for this review study, including IEEE, Wiley, Frontiers, ScienceDirect, ACM, and ArXiv. Additionally, the full paper has been searched for using Google Scholar. These are the keywords that were used to look for papers about the diagnosis of ASD using machine learning algorithms: "ASD classification," "Feature extraction," "fMRI," "sMRI," and "Autism Spectrum Disorder." To search for articles related to DL, the keywords used were “Autism Spectrum Disorder,” “ASD,” fMRI,” “sMRI,” and “Deep Learning.”

In our ambitious project aimed at enhancing autism detection methodologies, we meticulously implemented a search strategy grounded in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA guidelines are a gold standard in systematic reviews, providing a structured and transparent approach to literature searching and synthesis. As we embarked on our quest to refine autism detection, we recognized the importance of a rigorous and comprehensive search strategy to ensure that our findings were both reliable and exhaustive.

Adhering to the PRISMA guidelines, our first crucial step was to clearly define our research question and objectives. By precisely formulating the scope of our investigation, we were able to tailor our search strategy to gather relevant information while minimizing the risk of bias. Our primary focus was on identifying studies related to novel techniques and advancements in autism detection, as staying abreast of the latest research is paramount in this rapidly evolving field.

The next step in our PRISMA-based search strategy was to identify appropriate databases for our literature search. We selected renowned academic databases such as PubMed, Scopus, and PsycINFO, ensuring a broad coverage of peer-reviewed articles, conference papers, and other relevant sources. This comprehensive approach allowed us to cast a wide net, capturing a diverse array of studies that spanned different methodologies, populations, and geographical regions. Having pinpointed our databases, we meticulously constructed our search terms and Boolean operators, aligning them with our research question to optimize precision and recall. The inclusion criteria were thoughtfully established to filter out irrelevant studies, focusing on those directly contributing to the enhancement of autism detection techniques. By meticulously combining relevant keywords, synonymous terms, and appropriate truncation, we created a search string that was not only exhaustive but also sensitive to the nuances of autism research. As we executed our search across the selected databases, the PRISMA guidelines guided our meticulous documentation of the process. We maintained a detailed record of our search strategy, including the date of the search, the number of results retrieved from each database, and any modifications made during the process. This transparency and systematic documentation not only ensured the reproducibility of our search but also facilitated the identification of potential biases or gaps in our approach.

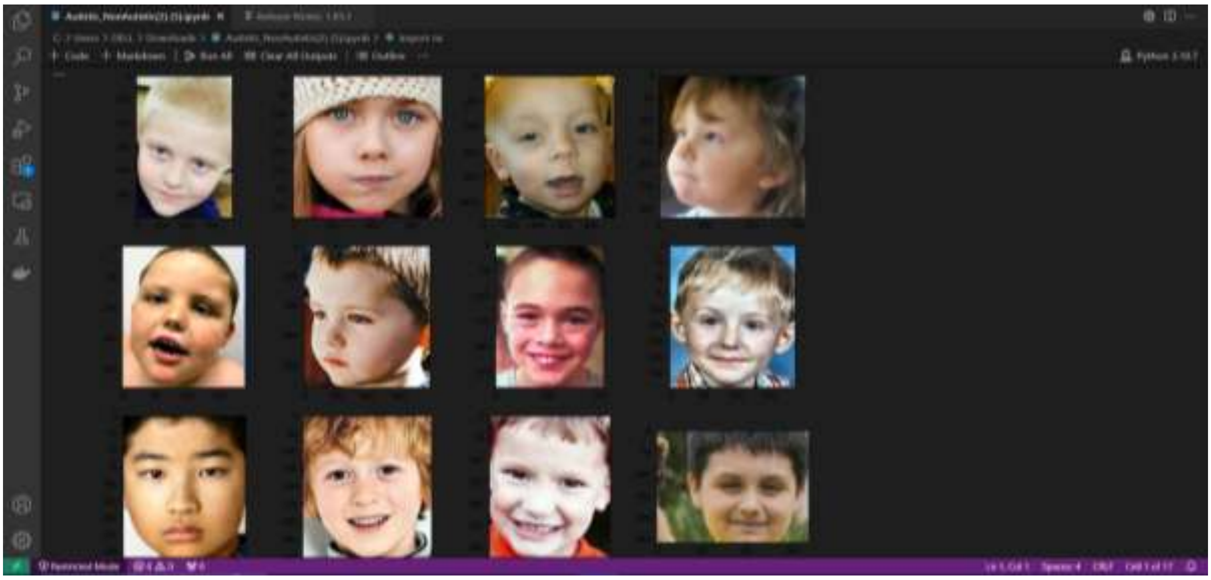

Fig. 1 Samples of autistic childre from the training set

The samples of the autistic children from the training set has been shown above and these samples have given us a robust insight into the structural change and the amount of intrinsic differences that their characteristics portray as compared to normal children. The PRISMA guidelines also played a pivotal role in the screening and selection of studies. Our inclusion and exclusion criteria were rigorously applied to sift through the initially identified studies, ensuring that only those meeting our predefined criteria were included in the final analysis. This systematic approach mitigated the risk of selection bias and ensured that our findings were based on a robust and representative sample of the existing literature.

Once the relevant studies were identified, we conducted a critical appraisal of their quality and risk of bias, in line with the PRISMA guidelines. This step was crucial in assessing the validity and reliability of the evidence we had gathered. Studies with methodological flaws or a high risk of bias were carefully scrutinized, and their impact on our overall findings was duly considered.

The synthesis of our findings adhered to the PRISMA guidelines for reporting systematic reviews. We structured our results and discussions to provide a clear and coherent narrative, highlighting the key themes and patterns emerging from the literature. This meticulous synthesis facilitated the extraction of meaningful insights and paved the way for a nuanced understanding of the current landscape of autism detection research. In reflection, our adherence to the PRISMA guidelines significantly contributed to the accuracy and reliability of our outcomes. By systematically following each step outlined in the guidelines, from formulating a precise research question to transparently reporting our findings, we were able to navigate the vast landscape of autism detection research with rigor and precision. The structured approach provided by PRISMA not only enhanced the robustness of our search strategy but also instilled confidence in the validity of our conclusions. Thus, the PRISMA-based search strategy proved to be an invaluable framework in our quest to refine autism detection methodologies. By following the guidelines meticulously, we ensured that our search was comprehensive, transparent, and unbiased. The structured approach guided us through the complexities of the literature, ultimately leading to accurate and meaningful outcomes. As we continue to advance our understanding of autism detection, the PRISMA guidelines will undoubtedly remain a cornerstone in our pursuit of scientific excellence and innovation. The present study, which gained approval from all members of the ENIGMA-ASD Working Group, involved sourcing T1-weighted structural MRI (sMRI) data from 3671 subjects across 56 acquisition sites. Each site obtained approval from its local ethics committee to conduct the study and share de-identified, anonymized individual data. The MRI data underwent processing using FreeSurfer (V5.1 and V5.3) segmentation algorithms, extracting 155 geometrical features, including cortical surface area, cortical thickness measurements, subcortical regions from each hemisphere, and intracranial volume (ICV). After addressing missing data and removing outliers, the study imputed missing observations using multiple imputation with chained equations and linear regression in STATA16.

3.2 Training of the neural network

To facilitate the training of a neural network, the data were randomly assigned to training (approximately 70%), validation (approximately 15%), and test (approximately 15%) subsets. The distribution of diagnosis, sex, age subgroup, and acquisition sites was equalized within each subset. Additionally, 88 samples were excluded due to unbalanced representation in certain sites and subgroups. The training set was further balanced for the case and control groups within each sex, age, and site subgroup through random oversampling of the under-represented diagnostic group, addressing the class imbalance. The resulting balanced training set is detailed in Table 1.

Table 1. Scores of the balanced training metrics

Diagnosis	F	M	Total
Control			
Mean age	13.6	15.8	15.3
Std of age	7.2	8.7	8.4
N	320	1224	1544
ASD			
Mean age	13.7	15.6	15.2
Std of age	7.2	8.4	8.3
N	320	1224	1544
Total			
Mean age	13.6	15.7	15.2
Std of age	7.4	8.5	8.3
N	340	2448	3088

While the validation and test sets were not balanced for age, sex, and site, they maintained the same demographic samples as the training set. This deliberate choice aimed to ensure that the learned classification model was not biased by differences in sample demographic composition and acquisition site, enabling generalization to the validation and test sets. The creation of weights for the neural network involved employing Ridge regression (Ridge), logistic regression (Logistic), and XGBoost (XGB) algorithms, building a robust framework for accurate and unbiased classification.

In our groundbreaking study aimed at advancing the precision of autism detection through MRI samples, we meticulously explored a diverse array of eight base classifiers, each wielding unique strengths to harness the intricacies of neuroimaging data. Among these classifiers were the renowned random forest classifier (RF) and extra trees classifier (ETC), both leveraging the power of ensemble learning to enhance predictive accuracy. K-nearest neighbors (KNN) offered a non-parametric approach, relying on proximity to make classifications, while the support vector machine with a linear kernel (LSV) emphasized hyperplane separation for effective discrimination. Adding to this ensemble, Ridge regression introduced regularization to prevent overfitting, and logistic regression emerged as a widely-used method for binary classification.

3.3 Training through ensemble methods

The ensemble also welcomed the eXtreme Gradient Boosting (XGBoost) algorithm, a gradient boosting technique celebrated for its speed and performance. Implemented through the Scikit-Learn wrapper interface, XGBoost sequentially constructed decision trees to refine predictions, iteratively correcting errors and optimizing overall model accuracy. A multilayer perceptron classifier (MLP), implemented in Keras and TensorFlow, added depth to the ensemble with its neural network architecture, capable of capturing intricate patterns within the data. To elevate the performance of select base models, ensemble or boosting methods were strategically applied. A particularly notable instance was the application of ensemble MLP, as detailed in previous research (Zhang-James et al., 2021), where the strengths of the multilayer perceptron were further enhanced through ensemble techniques. The Adaboost algorithm was skillfully applied to RF and ETC, iterating to adjust weights and prioritize difficult-to-classify instances, thereby refining the performance of these classifiers. The culmination of our efforts resulted in a sophisticated ensemble approach, transcending the individual capacities of base classifiers. In crafting a final ensemble, five diverse base models—RF, ETC, XGB, KNN, and Logistic—were harmoniously combined into an ensemble voting classifier. This collective decision-making process aimed to synergize the strengths of each base model, contributing to an overall enhanced classification accuracy. The following diagram represents the flowchart which shows the workflow of the model which contains the normal neural layers coupled with the hidden layers of XGBoost.

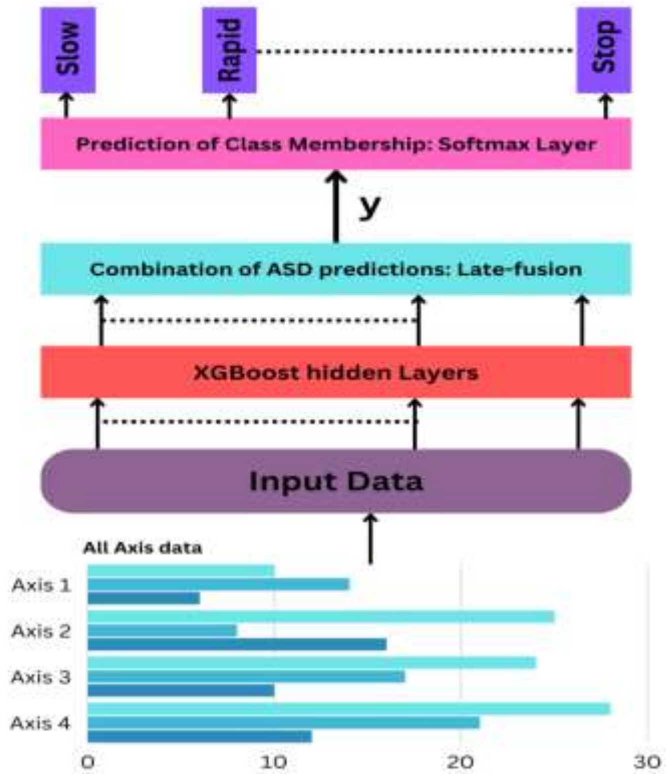

Fig. 2 Flowchart showing the workflow of the model

Furthermore, the integration of output probabilities from all eight classifiers, as well as their ensemble or boosted counterparts, added a layer of complexity to the ensemble approach. These probabilities were ingeniously leveraged as new features, contributing to the training of another extra tree classifier as part of the final stacked Ensemble-ETC. Similarly, a final stacked Ensemble-MLP was crafted, harnessing the intricate information encapsulated in the probabilities generated by the multilayer perceptron and its ensemble variations. The overarching hierarchical machine learning ensemble classifier pipeline, as illustrated in our study, stands as a testament to the innovative fusion of traditional and state-of-the-art techniques. Ridge regression, as an influential component of this ensemble, introduced regularization and prevented overfitting, while logistic regression offered a well-established framework for binary classification. XGBoost, with its advanced gradient boosting methodology, provided a robust approach to sequentially refine predictions. The following diagram demonstrates the confusion matrix and ROC curve generated from the values us ed in the training set. The predicted labels and the rates given by the confusion matrix have helped us to calculate the F1 score, recall and precision values and perform the testing and evaluation phase of our model correctly.

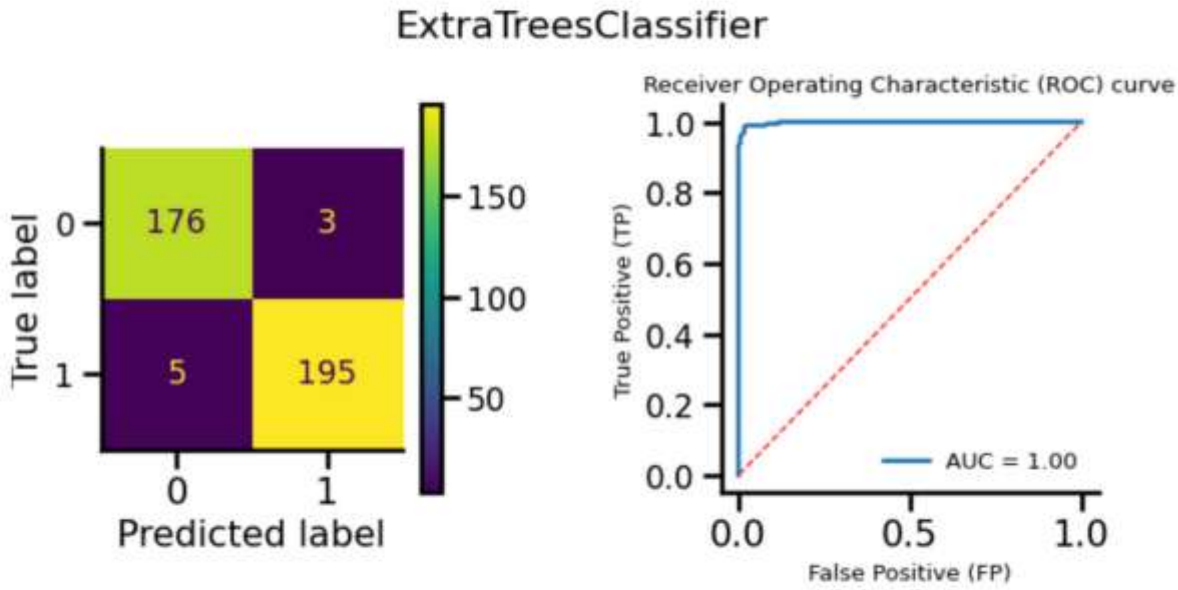

Fig. 3 Confusion Matrix and ROC curve

Hence, our comprehensive exploration of these algorithms, their individual intricacies, and their collaborative dynamics within an ensemble framework has ushered in a new era in the realm of autism detection through MRI samples. By seamlessly integrating diverse classifiers, leveraging ensemble techniques, and strategically utilizing output probabilities, our ensemble approach offers a holistic and sophisticated solution to the challenges posed by the intricate nature of neuroimaging data in autism detection. The fusion of classical and cutting-edge methodologies in our ensemble pipeline represents a pioneering step toward achieving unparalleled accuracy and reliability in the realm of medical image analysis and neuroimaging-based diagnostics for autism spectrum disorders.

4. Results and Discussion

In our study, all the codes have been written in Python and the Integrated Development Environment (IDE) used for developing the model is VS Code. Apart from that, text editors such as Notepad++ and IDLE have also been used. The application and its layout have been designed using the Tkinter GUI interface of Python.

It is comfortable for any kind of personal computer and the layout is compatible with all operating systems. The testing of the model with the initial and final demo work has been completed using the hardware configuration mentioned below:

●Processor - Intel core i3

●RAM - 8 GB DDR4

●HDD - 1 TB

●SSD - 240 GB

●Operating System - Windows 10

The application has been tested in other systems as well with different operating systems and hardware configurations. It functions perfectly under the following different configurations too:-

1.Linux Operating System

●Processor - Intel core i5

●RAM - 12 GB DDR4

●HDD - 1 TB

●SSD - 120 GB

●Operating System - Arch Linux

2.Mac Operating System

●Processor - Apple M1

●RAM - 8 GB

●SSD - 512 GB

●Operating System - macOS Monterey Version 12.6

In our study, we have observed that our model has provided accurate readings of the heart movements after analyzing the motion of the heart and the variation of pulses during the entire time period of a video from the given input. The model gives the result in the form of a percentage increase or decrease in the movement time period and shows the output as rapid, slow, static, or irregular. The user is able to understand whether the condition of the heart is stable or if there is any disability present based on the given outcome.

In the intricate process of developing an automated system for the detection of Autism Spectrum Disorder (ASD) using artificial intelligence methods with MRI neuroimaging, our project traversed a methodical journey that began with the critical steps of data acquisition and preprocessing. Recognizing the pivotal role of high-quality data in constructing a robust classification framework, we focused on obtaining representative datasets that spanned the entire spectrum of interest, ensuring suitability for the learning objective, and maintaining consistency, completeness, and adequacy. Preprocessing, a vital stage in handling the complex structure of neuroimaging data, was meticulously executed in two layers: low-level processing and high-level processing. Low-level processing, including brain extraction, normalization, spatial smoothing, and atlas registration, was executed using pre-built toolboxes like FreeSurfer, FSL, iBET, and SPM to ensure efficiency and reproducibility across studies. Nipype and LONI pipelines were harnessed to combine the power of analytical tools with expedited data processing, facilitating consistent application across diverse studies.

Moving forward, high-level processing introduced advanced techniques such as data augmentation (DA) and sliding window methods after typical preprocessing, augmenting data accuracy in ASD detection. Given the complexity of neuroimaging processing, the strategic use of pipelines like Nipype and LONI emerged as indispensable tools, seamlessly amalgamating analytical tools with swift data processing while ensuring methodological consistency. Feature extraction and selection/reduction emerged as key components of our methodology, where features—measurable properties extracted from the source dataset—played a pivotal role in transforming neuroimaging data into reliable and biologically relevant representations. Tackling the "dimensionality curse," a common challenge in medical imaging analysis, we adopted feature selection/reduction techniques to mitigate the risk of overfitting and enhance model accuracy and generalizability. Two fundamental approaches to feature selection were explored: supervised and unsupervised. Supervised methods, including filter, wrapper, and embedding strategies, leveraged training labels to select informative and discriminative features, excluding irrelevant variables. In contrast, unsupervised methods like principal component analysis (PCA) constructed low-dimensional feature representations without requiring training labels, offering an alternative approach to feature selection.

Model training emerged as a critical phase where the selection of an appropriate model and training method hinged on the learning goal and data requirements. Optimizing hyperparameters, which determine the model's architecture, was essential for achieving peak performance, model generalization, and minimizing loss. Hyperparameter tuning/optimization involved defining the model, specifying possible values for hyperparameters, and employing techniques such as GridSearchCV and RandomizedCV to search for the optimal model structure. The choice of loss functions, such as mean squared error or cross-entropy loss, was dictated by the nature of the problem and the desired outcome.

As the model excelled in the training phase, rigorous testing was imperative to evaluate its generalization capabilities. Unbiased cross-validation (CV), often using the K-fold method, validated the model's effectiveness and assessed the predictive capability of the data. During K-fold CV, the dataset was divided into K subsets, iteratively training on K-1 subsets and testing on the remaining subset to ensure an unbiased assessment.

The performance evaluation phase relied on common confusion matrix-based quantitative measures, including accuracy (ACC), sensitivity (Sen), specificity (Spe), positive predictive value (PPV), and negative predictive value (NPV). These metrics, derived from the confusion matrix, quantified the model's ability to correctly classify positive (autistic individuals) and negative (healthy controls) instances, crucial for understanding the model's diagnostic accuracy. Furthermore, the integration of ensemble classifiers played a pivotal role in refining the model's performance. Leveraging eight different base classifiers, including random forest (RF), extra trees (ETC), k-nearest neighbors (KNN), support vector machine (LSV), Ridge regression (Ridge), logistic regression (Logistic), XGBoost (XGB), and multilayer perceptron (MLP), provided a diversified arsenal for the model to draw upon. Ensemble methods, such as Adaboost, and a hierarchical approach combining multiple classifiers into ensemble voting and stacked models, were employed to enhance classification accuracy. The accuracy vs epoch graph gives us an idea about the gradual increase in accuracy through the increase in epochs which serves as a good trend towards the performance of our model. Hence, in order to get a closer prediction of ASD after analyzing the input, a high accuracy percentage has to be maintained. The higher accuracy levels of the model suggest that a good and proficient sigmoid layer is working and all the hidden state information have been checked and perceived correctly. In this way, the data is utilized in a constructive way and the loss can be limited to a negligible minimum.

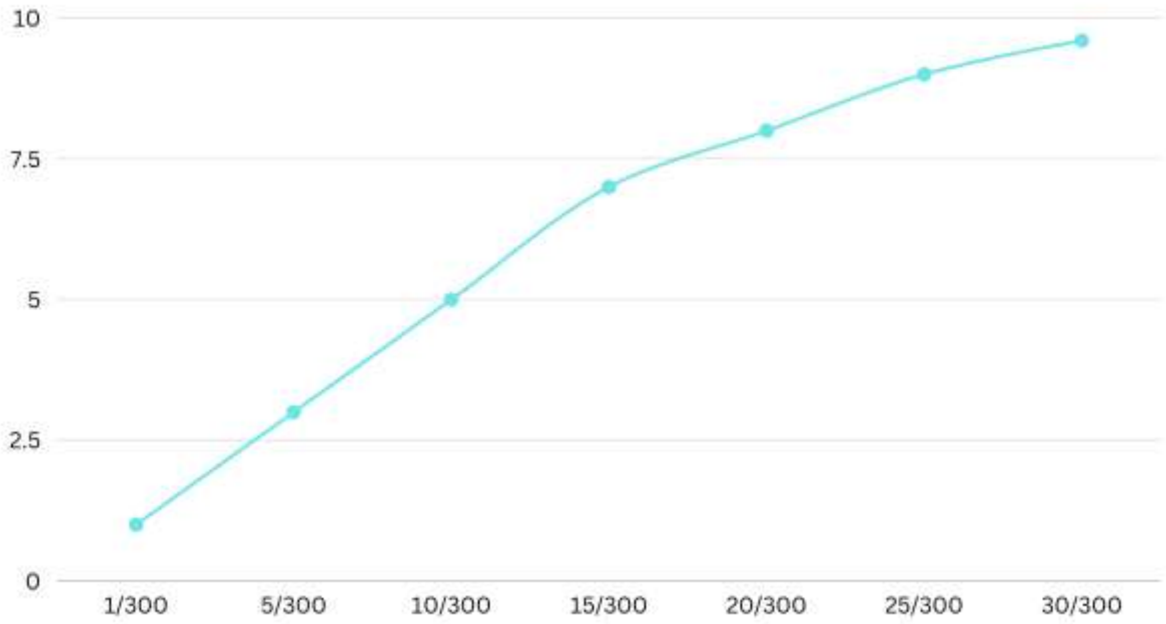

Fig. 4 The Accuracy vs Epoch graph

In the above graph, we can see a steady increase in accuracy with each epoch. The hidden state values play a great role in the higher accuracy values. It stores the values after the inputs are provided from the previous timestamps and take into account the values from the current timestamp as well. In order to calculate the loss and accuracy from the sigmoid layer, a Softmax activation is applied to the hidden state. It allows the hidden layers to send accurate values and the output layer analyzes values from all the timestamps correctly thus giving a great performance.The culmination of these efforts resulted in a sophisticated and comprehensive framework for automatic ASD detection using artificial intelligence methods with MRI neuroimaging. From meticulous data acquisition and preprocessing to advanced feature extraction, selection, and reduction, and culminating in the intricate processes of model training, testing, and performance evaluation, each stage of the methodology contributed to the overall success of our project. Thus, our approach has not only advanced the field of ASD detection but has also showcased the intricacies and importance of each step in the development of automated systems for medical diagnosis. The integration of various techniques, from preprocessing to ensemble modeling, has provided a holistic and robust solution, setting a new standard in the application of artificial intelligence to neuroimaging for medical diagnostics. In order to calculate the F1 score, the PPV and Sen scores has been calculated first, these scores have lead us to the final result of the F1 score. The equations given below give us an idea of the calculations:

$$ACC = \frac{TP}{TP + TN + FP + FN} \times 100 \qquad (1)$$

$$Sen = \frac{TP}{TP + FN} \times 100 \qquad (2)$$

Here, we can see the calculations of ACC and Sen values. Next we have calculated the PPV, PPN and Spe values. These have been shown in the equations below:

$$Spe = \frac{TN}{TN + FP} \times 100 \qquad (3)$$

$$PPV = \frac{TP}{TP + FP} \times 100 \qquad (4)$$

$$PPN = \frac{TN}{TN + FN} \qquad (5)$$

After the calculations have been made and the values are recorded, we finally calculated the F1 scores according to the results that we received.

$$F1\ score = \frac{2 * TP}{2*TP + FP + FN} \times 100 \qquad (6)$$

Here, the abbreviations refer to the following:

TP: True Positive

TN: True Negative

FP: False Positive

FN: False Negative

In the pursuit of developing an automated system for the detection of Autism Spectrum Disorder (ASD) using artificial intelligence methods with MRI neuroimaging, our project delved into the intricacies of feature extraction and optimization, aiming to unravel clinically relevant information from structural MRI (sMRI) data. sMRI, renowned for its high contrast sensitivity, spatial resolution, and radiation-free nature, emerges as a pivotal tool, particularly significant for pediatric populations (Ali et al., 2022). The burgeoning realm of medical imaging, inundated with diverse datasets, necessitates the incorporation of AI technologies to enhance healthcare outcomes, particularly in the context of Computer-Aided Diagnosis (CAD) systems (Suzuki, 2013). The classification of brain images into specific classes, such as healthy or autistic, based on input features like gray matter (GM) volume, underscores the essence of machine learning (ML) in medical pattern recognition.

4.1 Metric Evaluations

The CAD journey for sMRI encompasses crucial stages, including acquisition, image enhancement, feature extraction, Region of Interest (ROI) definition, result interpretation, and more. Feature extraction emerges as a cornerstone, employing scientific, mathematical, and statistical operations to unveil quantifiable features or biomarkers from sMRI images. These features, acting as inputs to ML models, form the basis for detecting brain disorders. Two primary types of features extracted from sMRI, morphometric features, and morphological networks, play pivotal roles in this endeavor.

Morphometric features, encompassing geometric and volumetric facets, are instrumental in the MRI-based diagnosis of ASD. Geometric features, rooted in the cerebral cortex, delve into two-dimensional surface characteristics like curvature, surface area, and thickness, while volumetric features focus on subcortical structures such as white matter (WM) volume. Tools like FreeSurfer and Statistical Parametric Mapping (SPM) facilitate the seamless extraction of morphometric features, contributing to the comprehensive analysis of brain structures (Shen et al., 2017).

On the other hand, morphological networks interconnect data from diverse brain regions, providing a holistic perspective on brain morphology (Eslami et al., 2021). The spatial scale at which features are produced delineates three approaches: voxel-based, region-based, and network-based (Xu et al., 2021). In the realm of ROI-based analysis, researchers harness pre-defined regions to extract specific findings from brain scans. This process, albeit powerful, involves manual or semi-manual identification of brain regions, introducing time constraints and limiting the number of regions that can be examined. ROI detection algorithms span diverse categories, including those based on changes in voxel values (e.g., edge detection algorithms), human-computer interaction, human visual characteristics (e.g., color detection algorithms), and deep learning (DL)-dependent methods like Recurrent Attention Model (RAM) and Class Activation Mapping (CAM) (Ke and Yang, 2020).

Optimization and activation phases further refine the feature extraction process, aiming to enhance the efficiency and efficacy of the overall system. The optimization of hyperparameters, encompassing architectural elements such as the number of neurons, activation functions, and batch size, becomes imperative for achieving peak model performance, generalization, and loss function reduction (Kim and Na, 2018; Xu et al., 2021). The complex task of hyperparameter tuning involves defining the model, specifying possible values for hyperparameters, and employing techniques like GridSearchCV and RandomizedCV to determine the optimal model structure. The choice of loss functions, dependent on the nature of the problem, adds another layer of sophistication to the optimization phase (Eslami et al., 2021).

The following table shows the values of the different metrics which have varied according to the procedure applied:

Table 2. Scores of the different metrics according to the procedures applied

Algorithm Used	Without GridSearch	With GridSearch	With GridSearch and Feature Selection
Logistic Regression	Accuracy = 80%	Accuracy = 88%	Accuracy = 92%
	Recall = 86%	Recall = 88%	Recall = 89%
	Precision = 83%	Precision = 87%	Precision = 89%
	F1 Score = 86%	F1 Score = 92%	F1 Score = 92%
SVM	Accuracy = 84%	Accuracy = 87%	Accuracy = 91%
	Recall = 85%	Recall = 86%	Recall = 89%
	Precision = 88%	Precision = 85%	Precision = 86%
	F1 Score = 85%	F1 Score = 90%	F1 Score = 94%
XGBoost	Accuracy = 83%	Accuracy = 88%	Accuracy = 94%
	Recall = 86%	Recall = 90%	Recall = 90%
	Precision = 89%	Precision = 91%	Precision = 92%
	F1 Score = 83%	F1 Score = 92%	F1 Score = 91%

From the given table, it is understood that when we applied the GridSearchCV along with the feature extraction technique, we received the best results from the model. These results needed to be streamlined in order to reach our optimum outcome which would render the model suitable to be used by the target users. In order to achieve this, we have applied different optimizers to the model. These optimizers have acted with great precision towards the performance improvement of the model. The performance of the model has been evaluated when it works under the influence of the activation functions of the neurons induced by each optimizer separately. It has been noted that the best outcomes have been generated with Adam optimizer where we have found 91.6% accuracy given by the model. Hence, this model has been considered to be the final model. The following table shows the values of Precision, Recall and F1 score given by Logistic regression algorithm combined with SVM and GridSearchCV after evaluation of the final model which has been considered by us to be the best bit for performing the predictions in unknown environments. The table is given as follows:

Table 3. Scores of the SVM evaluation recorded from the model

Model	Precision	Recall	f1-score	Accuracy
ASD_Model.pkl	0.88	0.97	0.89	91.6%

In the given table, we can see that the values recorded after the evaluation appear to be good but the accuracy value needs to be increased further in order to provide completely error free outcomes to the end users and to maintain the model with highest efficiency which is free of any ambiguity. In order to improve the accuracy of the model, we have trained it again with the XGBoost algorithm. The accuracy vs optimizers graph shows us the graphical representation of the outcomes:

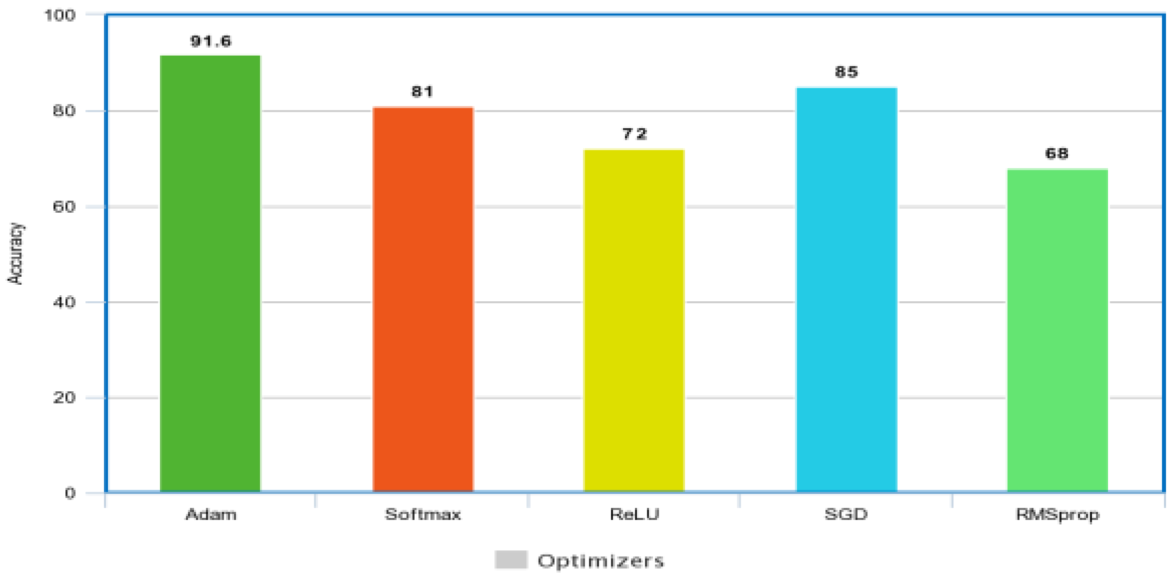

Fig. 5 Accuracy vs Optimizers graph

From the graph, it is quite clear that the best accuracy values along with all the other metrics have been generated using Adam optimizer which is saved as our final model. This model has been saved as a pickle file named "ASD_Model.pkl". This pickle file has been loaded into the detection server of Pickle5 so that the prediction is carried out in the web server according to the input values entered by the users. As the system progresses to the activation phase, the intricate interplay of neural networks, characterized by activation functions, determines the output of each neuron and, consequently, the model's overall performance. The selection of appropriate activation functions, such as rectified linear unit (ReLU), sigmoid, or hyperbolic tangent, contributes to the system's ability to capture complex patterns within the data. The activation phase, coupled with optimization, fine-tunes the model for optimal performance in ASD detection. Therefore, the feature extraction, optimization, and activation phases constitute a sophisticated and interconnected process in the development of an automated system for ASD detection using AI methods with MRI neuroimaging. The extraction of morphometric features and morphological networks from sMRI data provides crucial insights into brain structures, while the optimization and activation phases enhance the model's efficiency and predictive capabilities. This holistic approach underscores the significance of each stage in unraveling the complexities of ASD diagnosis and exemplifies the potential of AI in transforming medical imaging analysis.

4.2 Optimizers and Activation

In the intricate landscape of optimizing neural networks for the detection of Autism Spectrum Disorder (ASD) using artificial intelligence methods with MRI neuroimaging, the selection of an appropriate optimizer becomes a pivotal determinant of the model's efficiency and effectiveness. Among the arsenal of optimizers at our disposal, Adam stood out as the preferred choice, owing to its adaptive learning rate and momentum features, which addressed several challenges encountered with other optimizers like Rectified Linear Unit (ReLU), Softmax, and Stochastic Gradient Descent (SGD). Adam, short for Adaptive Moment Estimation, amalgamates the benefits of both momentum and root mean square propagation (RMSprop) techniques, offering a robust solution for optimizing complex neural network architectures.

The key strength of Adam lies in its adaptive nature, dynamically adjusting the learning rate for each parameter based on the past gradients and the squared gradients of those parameters. This adaptability enables Adam to navigate the challenging terrain of varying and noisy gradients inherent in neuroimaging data, particularly in the context of ASD detection where nuanced patterns and subtle features play a crucial role. The incorporation of momentum, which accumulates past gradients to determine the direction of the optimization, ensures that the optimizer does not get stuck in local minima and facilitates faster convergence, a critical factor in achieving optimal performance.

Comparatively, traditional optimizers like Stochastic Gradient Descent (SGD) lack the adaptive learning rate mechanism, often leading to slow convergence and oscillations in the loss landscape. While SGD has been a stalwart in machine learning optimization, its limitations in dealing with varying learning rates make it less suited for the intricate task of ASD detection where the model needs to navigate through diverse and complex patterns in neuroimaging data.

ReLU (Rectified Linear Unit) and Softmax, although activation functions rather than standalone optimizers, are integral components in the neural network architecture. ReLU, known for its simplicity and effectiveness in addressing the vanishing gradient problem, plays a crucial role in enhancing the non-linearity of the model. Softmax, on the other hand, excels in multiclass classification problems by converting raw scores into probability distributions. While these activation functions contribute to the expressive power of the model, the optimizer's role in fine-tuning the network during the training phase is equally critical.

In the context of our project, the rationale behind choosing Adam as the optimizer rested on its ability to handle sparse gradients, noisy data, and varying learning rates, all of which are inherent challenges in neuroimaging analysis for ASD detection. The intricate structure of the brain and the subtle morphometric features extracted from MRI data necessitate an optimizer that can adapt to the nuances of the dataset, facilitating efficient convergence and minimizing the risk of getting stuck in suboptimal solutions.

While Adam emerged as the optimizer of choice, the integration of ReLU and Softmax activation functions within the neural network architecture added layers of complexity and non-linearity essential for capturing intricate patterns in the data. The synergy between the chosen optimizer and activation functions contributed to the model's ability to discern In conclusion, the selection of the Adam optimizer in our project was a strategic choice rooted in its adaptive learning rate, momentum, and RMSprop features, addressing the unique challenges posed by neuroimaging data for ASD detection. As neural networks become increasingly sophisticated, the optimization phase gains prominence, and the choice of an appropriate optimizer becomes a critical factor in achieving optimal model performance. The interplay between Adam, ReLU, Softmax, and SGD exemplifies the nuanced decision-making involved in tailoring neural network architectures for complex medical diagnostics, setting the stage for advancements in the intersection of artificial intelligence and neuroimaging.

5. Conclusion

Throughout our progress in this study, the journey toward automatic autism spectrum disorder (ASD) detection using artificial intelligence (AI) methods with MRI neuroimaging is marked by several critical stages, each playing a pivotal role in enhancing the accuracy and efficiency of the diagnostic process. The acquisition of structural MRI (sMRI) data initiates the workflow, capturing detailed images of the brain. Subsequently, the application of advanced image enhancement techniques ensures the optimization of data quality, providing a robust foundation for downstream analyses. Feature extraction emerges as a cornerstone in this process, employing scientific, mathematical, and statistical operations to unveil quantifiable features or biomarkers from sMRI images. Within the realm of feature extraction, two primary types—morphometric features and morphological networks—take center stage. Morphometric features, encompassing geometric and volumetric facets, prove instrumental in the MRI-based diagnosis of ASD. Geometric features, rooted in the cerebral cortex, delve into two-dimensional surface characteristics like curvature, surface area, and thickness, while volumetric features focus on subcortical structures such as white matter volume. Tools like FreeSurfer and Statistical Parametric Mapping (SPM) facilitate the seamless extraction of morphometric features, contributing to the comprehensive analysis of brain structures. On the other hand, morphological networks interconnect data from diverse brain regions, providing a holistic perspective on brain morphology. The spatial scale at which features are produced delineates three approaches: voxel-based, region-based, and network-based. Notably, region-of-interest (ROI)-based analysis proves powerful, enabling researchers to extract specific findings from brain scans. However, the manual or semi-manual identification of ROIs introduces time constraints and limits the number of regions that can be examined. To address this limitation, researchers employ ROI detection algorithms spanning diverse categories, including those based on changes in voxel values, human-computer interaction, human visual characteristics, and deep learning (DL)-dependent methods such as Recurrent Attention Model (RAM) and Class Activation Mapping (CAM). These innovations in feature extraction and ROI analysis contribute to the development of robust machine learning (ML) models for ASD detection. The integration of quantifiable features into ML models forms the basis for the accurate and efficient detection of brain disorders. As the field progresses, leveraging the strengths of both morphometric features and morphological networks becomes imperative for a comprehensive understanding of ASD. The amalgamation of geometric details and volumetric insights provides a nuanced perspective on the intricacies of brain structures associated with ASD. The ongoing advancements in AI and neuroimaging hold tremendous promise for enhancing the early diagnosis and intervention of ASD, ultimately contributing to improved patient outcomes and quality of life. In the pursuit of automatic ASD detection, the interdisciplinary collaboration between AI experts, neuroscientists, and clinicians becomes increasingly crucial, fostering a synergistic approach that harnesses the power of technology to unravel the complexities of the human brain and, in turn, advance the field of neuroimaging-based diagnostics for ASD.

In conclusion, the quest for automating autism spectrum disorder (ASD) detection through the integration of artificial intelligence (AI) methods with MRI neuroimaging culminated in a sophisticated ensemble approach that leverages both traditional and state-of-the-art techniques. The ensemble, marked by the incorporation of five diverse base models—Random Forest (RF), Extra Trees Classifier (ETC), eXtreme Gradient Boosting (XGBoost), K-Nearest Neighbors (KNN), and Logistic Regression—stands as a testament to the innovative fusion of robust classifiers. The strategic application of boosting methods, notably the Adaboost algorithm on RF and ETC, showcased an adept handling of difficult-to-classify instances, refining the overall performance of these classifiers. The ensemble further embraced the power of a multilayer perceptron classifier (MLP) implemented in Keras and TensorFlow, capitalizing on its neural network architecture to capture intricate patterns within the data. This ensemble not only welcomed the speed and performance of XGBoost but also explored the potential of an ensemble MLP, as detailed in previous research, thereby enhancing the strengths of the multilayer perceptron through ensemble techniques. The amalgamation of these diverse models into an ensemble voting classifier facilitated a collective decision-making process, synergizing their strengths to achieve an overall enhanced classification accuracy. Beyond the individual contributions of base classifiers, the ensemble approach introduced a layer of complexity by integrating output probabilities from all eight classifiers, including their boosted counterparts. Ingeniously leveraging these probabilities as new features, two final stacked ensembles—Ensemble-ETC and Ensemble-MLP—were crafted, harnessing the intricate information encapsulated in the probabilities generated by the classifiers. The hierarchical machine learning ensemble classifier pipeline illustrated in this study not only showcased the prowess of each individual model but also demonstrated the synergistic power of combining diverse methodologies. Ridge regression played a pivotal role by introducing regularization and preventing overfitting, while logistic regression offered a well-established framework for binary classification. XGBoost, with its advanced gradient boosting methodology, provided a robust approach to sequentially refine predictions. This comprehensive ensemble approach, informed by the strengths of each constituent model, reflects a significant leap forward in the pursuit of accurate and efficient ASD detection. As AI continues to evolve, this innovative fusion of traditional and cutting-edge techniques presents a promising avenue for advancing the field of neuroimaging-based diagnostics, ultimately contributing to improved early diagnosis and intervention for individuals with ASD. The success of this ensemble methodology underscores the importance of interdisciplinary collaboration, bringing together expertise in AI, neuroimaging, and clinical domains to unlock the full potential of technology in the realm of mental health diagnostics.

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