Developing a Deep-learning tool to diagnose early stage Alzheimer's Disease using EEG Signals

Bhavana Akilan
Principal Investigator
Laidlaw Leadership and Research Scholar
University of Toronto

Dr V S Shankar Sriram
Research Advisor
SASTRA Deemed University, Thanjavur, Tamil Nadu, India

Dr H Anila Glory
Research Advisor
SASTRA Deemed University, Thanjavur, Tamil Nadu, India

September 1, 2023

Acknowledgement

My research project over the summer as a Laidlaw Leadership and Research Scholar is a culmination of the hardwork and dedication of not just me, but several others who have contributed immensely to my professional and personal growth.

I extend my deepest gratitude to Dr Shankar Sriram for giving me the opportunity to work at his lab for an extended period of time, and overseeing the entire project. Dr Anila Glory, with whom I liaised directly during my research period, was the wind beneath my wings. I thank her for being an excellent teacher and mentor every step of the way. I am also extremely grateful to Surya Girish, a first-year student at SASTRA University who helped me with numerous codes relevant to the project.

The Laidlaw Scholars Program, as well as the International Scholarship Advisors at the University of Toronto, Shraddha Prasad, Yvonne Yang and Tanya Udartseva have been instrumental in the entire process. Without them, this project would not have been possible.

Last but not the least, my heart goes out to my mother, sister and grandmother who have showered me with utmost love and respect and supported me throughout.

Developing a Deep-learning tool to diagnose early stage Alzheimer's Disease using EEG Signals

1. Abstract: Alzheimer's Disease (AD) is an irreversible, untreatable form of dementia that has no standard means of diagnosis, making access to effective treatments a challenge. Early detection and diagnosis of the disease can prevent brain damage and inform necessary biomedical interventions. Out of all available biomarkers of AD, EEG has proven to be the most convenient and effective because of its low cost and high temporal resolution. However, due to the non-linear nature of EEG signals making it prone to error during physician interpretation, this paper aims to explore the avenues in Artificial Intelligence to develop a deep-learning tool to aid in early diagnosis of AD. The dataset used is an open-source EEG dataset developed by Dr Dennis Duke from Florida State University. The signals were subjected to Signal Decomposition, Feature Extraction and Discrimination. The results show a surprising accuracy of 98+/-2% while using classifiers such as Multi-Layer Perceptron and Random Forest. To ensure there was no overfitting, a Recurrent Neural Network was subsequently implemented.

2. Keywords: Alzheimer's Disease, EEG, Artificial Intelligence, Deep-learning, Diagnosis

3. Introduction

Dementia, a prevalent and progressively debilitating condition, has become a significant public health concern worldwide. As the seventh leading cause of death among the elderly, it poses substantial challenges for healthcare systems (1). The global prevalence of dementia is predicted to dramatically increase from 51.6 million at present to an alarming 132 million cases by mid-21st century (2,3). Among these cases, approximately 70% are attributed to Alzheimer's Disease (AD), and 60% are from low-and middle-income countries, representing a significant socioeconomic burden on individuals and society. Despite remarkable advancements in technology and science, the diagnostic process remains challenging due to the complexity of symptoms, lack of a definitive cure, and the influence of negligence and personal biases. Furthermore, upon the incidence of the disease, it continues to progress exponentially with each passing year, thereby priming the need for an effective early diagnostic method.

While definitive diagnosis of AD is usually made through biopsy after the patient's death, recent research shows that biomarkers have aided in early diagnosis (4). At the primary care level, initial testing encompasses assessment of cognitive complaints, clinical inferences, physical exams, blood tests, EEGs, assessment of cognitive abilities and depressive symptoms (5). However, primary healthcare facilities are not equipped to carry out neuropsychological tests, neuroimaging and cerebrospinal fluid analyses, all of which are referred to specialty clinics. Given the complexity of the disease, physician diagnosis is heavily prone to error, whereas deep learning models have shown promising results, making them the prospective gold standard to aid in physician diagnosis (6).

3.1. EEG

EEG signals are a reflection of the superposition of electromagnetic fields generated from cortical neurons' interaction at a macroscopic level, making EEG an important diagnostic tool for dementia diseases, by depicting synaptic dysfunction and loss (7). The low cost (8) and the high temporal resolution of EEG outweigh its relatively low spatial resolution, making it more accessible and effective (9). To avoid physician error discussed above, an automated evaluation of EEG time-series data using present-day ML algorithms can improve the accuracy of diagnosis (10,11,12,13,14,15,16).

3.2. AI and its applications

The applications of Artificial Intelligence (AI) have gained popularity across several fields of study, including healthcare (17). With its ability to process images, learn from inconceivably large amounts of data and perform a variety of operations on complex datasets, AI has revolutionized medical science. In this era of precision medicine, the need to design personalized health regimes and advanced diagnostics for each individual has risen to significant importance. While AI is a forerunner in the list of the greatest technological advancements of the century, very few people understand and appreciate its sheer vastness. There is a need for a shift in perspective from viewing AI as a luxury to viewing it as a necessity.

Machine-learning (ML) based and deep-learning (DL) based models have demonstrated a crucial role in recognising cognitive function impairment with high sensitivity (18,19,20,21). This article aims to address the idea of a deep-learning tool to diagnose Alzheimer’s Disease at an early stage.

4. Literature Review

Article	Salient points
Bi, X., & Wang, H. (2019). Early Alzheimer's disease diagnosis based on EEG spectral images using deep learning. Neural Networks.	• The authors proposed a discriminative version of CssCDBM (DCssCDBM) for EEG spectral image classification. • The effectiveness of a multi-task learning framework for reducing overfitting via EEG spectral image-based Identification and verification tasks was demonstrated.

	• The proposed method showed a better ability for high-level representation extraction and achieved advanced results over several state-of-the-art methods.
Kim, D., & Kim, K. (2018). Detection of Early Stage Alzheimer’s Disease using EEG Relative Power with Deep Neural Network. Annual International Conference of the IEEE Engineering in Medicine and Biology Society.	• A deep neural network (DNN) based classifier using relative power (RP) metrics was proposed to distinguish healthy controls (HC) and mild cognitive impairment (MCI). • The DNN outperformed shallow neural networks in diagnosis results. • The use of DNN enabled the interpretation of results by leveraging well-known RP features as domain knowledge.
Ding, Y., Sohn, J., Kawczynski, M., Trivedi, H., Harnish, R., Jenkins, N., ... & Franc, B. (2019). A Deep Learning Model to Predict a Diagnosis of Alzheimer's Disease by Using 18F-FDG PET of the Brain. Radiology.	• The authors developed a deep learning algorithm to predict the final diagnosis of Alzheimer's disease, mild cognitive impairment, or neither, using fluorodeoxyglucose PET scans. • The algorithm achieved high accuracy and specificity for predicting AD in an independent test set. • The algorithm's saliency map demonstrated attention to known areas of interest in the brain.
Ismail, M., Hofmann, K., & El Ghany, M. E. (2019). Early Diagnoses of Alzheimer's using EEG data and Deep Neural Networks classification. 2019 IEEE Global Conference on Internet of Things (GCIoT).	• A low-cost EEG device was used to collect brain wave signals during a 3-level N-Back working memory test. • Data were transformed into EEG spectral subbands (theta, alpha, and beta) and projected to 2D images. • A convolutional neural network was employed to classify patients into three classes (MCI patients, AD patients, and healthy patients) with high accuracy.
Jo, T., Nho, K., & Saykin, A. (2019). Deep Learning in Alzheimer's Disease: Diagnostic Classification and Prognostic Prediction Using Neuroimaging Data. Frontiers in Aging Neuroscience.	• Deep learning approaches were applied to multimodal neuroimaging data for AD diagnostic classification. • Combining traditional machine learning for classification and stacked auto-encoder (SAE) for feature selection achieved high accuracies for AD classification and predicting MCI to AD conversion. • Deep learning approaches without pre-processing for feature selection (e.g., CNN or RNN) yielded high

	accuracies for AD classification and MCI conversion prediction.
Kam, T.-E., Zhang, H., Shen, D. (2018). A Novel Deep Learning Framework on Brain Functional Networks for Early MCI Diagnosis. MICCAI.	● A novel multiple-BFN-based 3D CNN framework was proposed to automatically and deeply learn complex, high-level, hierarchical diagnostic features from various independent component analysis-derived BFNs. ● The embedded features of different BFNs comprehensively supported each other toward a more accurate early Mild Cognitive Impairment (eMCI) diagnosis in a unified model. ● The proposed framework can be applied to individualized diagnosis of various neurological and psychiatric diseases.
Xia, W., Zhang, R., Zhang, X., & Usman, M. (2023). A novel method for diagnosing Alzheimer's disease using deep pyramid CNN based on EEG signals. Heliyon.	● A novel approach for diagnosing AD using EEG was proposed, employing overlapping sliding windows to augment the EEG data. ● The modified DPCNN was used for classification, achieving an average accuracy rate of 97.10% for AD, MCI, and HC classification.
Pirrone, D., Weitschek, E., Di Paolo, P., De Salvo, S., & De Cola, M. D. (2022). EEG Signal Processing and Supervised Machine Learning to Early Diagnose Alzheimer’s Disease. Applied Sciences.	● A novel method using a finite response filter (FIR) in the double-time domain was proposed to discriminate among AD, MCI, and HC patients. ● The method achieved high accuracy for binary classifications (HC vs. AD, HC vs. MCI, and MCI vs. AD) and good accuracy for three-class classifications (HC vs. AD vs. MCI). ● The proposed method's efficiency may allow future development on embedded devices for low-cost real-time diagnosis.
Deshmukh, A., Karki, M., BhuvanS., R. Gaurav, & HiteshJ. P. (2022). Deep Neural Network Model for Automated Detection of Alzheimer's Disease using	● An automated and accurate algorithm for detecting Alzheimer's disease using EEG signals was proposed. ● The algorithm utilized Butterworth filters, DWT, statistical parameters, data augmentation, and CNN achieving high accuracy. ● A total highest system accuracy of 97.61% was achieved.

EEG Signals. Int. J. Online Biomed. Eng.	
Podgorelec, V. (2012). Analyzing EEG Signals with Machine Learning for Diagnosing Alzheimer's Disease.	● EEG recordings were used to extract features for machine learning algorithms to diagnose Alzheimer's disease. ● The machine learning algorithm accurately diagnosed Alzheimer's disease. ● The results were promising for early and accurate diagnosis of Alzheimer's disease.
Kulkarni, N. (2018). EEG Signal Analysis for Mild Alzheimer's Disease Diagnosis by Means of Spectral- and Complexity-Based Features and Machine Learning Techniques. Proceedings of the 2nd International Conference on Data Engineering and Communication Technology.	● EEG signals were used as a biomarker for Alzheimer's diagnosis. ● Spectral and complexity features of EEG signals differentiated AD patients from healthy individuals. ● Support Vector Machine (SVM) and K-Nearest Neighbor (KNN) classifiers achieved accurate classification for Alzheimer's diagnosis.
Liu, S., Liu, S., Cai, W. (Tom), Pujol, S., Kikinis, R., & Feng, D. (2014). Early diagnosis of Alzheimer's disease with deep learning. IEEE International Symposium on Biomedical Imaging.	● A deep learning architecture aided the diagnosis of AD and its prodromal stage, MCI.
Sun, J., Liu, Y., Wu, H., Jing, P., & Ji, Y. (2022). A novel deep learning approach for diagnosing Alzheimer's disease based on eye-tracking data.	● The authors proposed a novel deep-learning-based model for identifying patients with Alzheimer's Disease (PwAD) and healthy controls (HCs) using eye-movement data. ● The model utilizes a nested autoencoder network to extract eye-movement features from fixation heatmaps and a weight-adaptive network layer for feature fusion.

Frontiers in Human Neuroscience.	• The proposed model achieved an average accuracy of 85% in AD recognition, outperforming machine-learning methods, and other typical deep-learning networks.
Buscema, P. M., Vernieri, F., Massini, G., Scrascia, F., Breda, M., Rossini, P. M., & Grossi, E. (2015). An improved I-FAST system for the diagnosis of Alzheimer's disease from unprocessed electroencephalograms by using robust invariant features. Artificial Intelligence in Medicine.	• The authors developed an artificial adaptive system, I-FAST, for diagnosing AD, MCI, and control subjects based on unprocessed EEG tracks. • An updated system, MS-ROM, was integrated with I-FAST, resulting in improved classification accuracy for EEG data of AD, MCI, and control subjects, achieving an overall accuracy of 98.25%.
Alves, C., Pineda, A. M., Roster, K., Thielemann, C., & Rodrigues, F. (2021). EEG functional connectivity and deep learning for automatic diagnosis of brain disorders: Alzheimer's disease and schizophrenia. arXiv.org.	• The paper presents a method for the automatic diagnosis of mental disorders, including Alzheimer's disease, using the matrix of connections obtained from EEG time series and deep learning. • The approach can classify patients with Alzheimer's disease and schizophrenia with a high level of accuracy, showing promise for the diagnosis of neurological disorders.
Farooq, A., Anwar, S. M., Awais, M., & Alnowami, M. (2017). Artificial intelligence-based smart diagnosis of Alzheimer's disease and mild cognitive impairment. International Smart Cities Conference.	• The authors presented a deep learning-based framework for diagnosing Alzheimer's disease and mild cognitive impairment from structural MRI scans. • The framework achieved high accuracy for the diagnosis of Alzheimer's and mild cognitive impairment, and transfer learning was applied for multiclass classification with an accuracy of 99.7%.
Swarnalatha, R. (2023). A Greedy Optimized Intelligent Framework for Early Detection of	• The paper proposed a novel deep feature for EEG signal analysis and severity specification for Alzheimer's disease diagnosis.

Alzheimer's Disease Using EEG Signal. Computational Intelligence and Neuroscience.	● The proposed scheme achieved the best classification outcome and was implemented in the MATLAB system.
Tzimourta, K. D., Christou, V., Tzallas, A., Giannakeas, N., Astrakas, L., Angelidis, P., Tsalikakis, D., & Tsipouras, M. (2021). Machine Learning Algorithms and Statistical Approaches for Alzheimer's Disease Analysis Based on Resting-State EEG Recordings: A Systematic Review. International Journal of Neural Systems.	● The paper reviews 49 experimental studies published from 2009 until 2020 that applied machine learning algorithms on resting state EEG recordings from AD patients. ● Support Vector Machines (SVMs) were the most commonly used machine learning algorithms for AD detection, while deep learning techniques had not yet been extensively applied on large EEG datasets.
Saratxaga, C. L., Moya, I., Picón, A., Acosta, M., Moreno-Fernandez-de-Leceta, A., Garrote, E., & Bereciartua-Perez, A. (2021). MRI Deep Learning-Based Solution for Alzheimer’s Disease Prediction. Journal of Personalized Medicine.	● The authors proposed a deep learning-based solution for MRI-based Alzheimer’s diagnosis and compared it with previous literature works. ● The proposed method achieved high accuracy for image-based automated diagnosis and disease staging, surpassing state-of-the-art proposals using the OASIS collection.
Hu, C., Ju, R., Shen, Y., Zhou, P., & Li, Q. (2016). Clinical decision support for Alzheimer's disease based on deep learning and brain network. 2016 IEEE International Conference on Communications (ICC).	● Deep learning was employed to diagnose brain diseases and provide clinical decision support. ● An autoencoder network was built to classify the correlation matrix, which is sensitive to Alzheimer's Disease (AD). ● The proposed method for AD prediction achieved a significant improvement in prediction accuracy compared to traditional methods.
Kim, H. T., Kim, B. Y., Park, E. H., Kim, J. W.,	● The authors proposed a combined approach using genetic algorithms (GA) and artificial neural network

Hwang, E. W., Han, S. K., & Cho, S. (2005). Computerized recognition of Alzheimer disease-EEG using genetic algorithms and neural network. Future generation computer systems, 21(7), 1124-1130.	(ANN) for classifying EEG and ERP recordings into two groups automatically. ● The recognition rate of the ANN fed by these input features was 81.9% for an untrained dataset. ● The approach can be extended to develop a reliable classification system using EEG recordings for discriminating between groups.
Drage, R., Escudero, J., Parra, M., Scally, B., Anghinah, R., Araújo, A., Basile, L., & Abásolo, D. (2022). A novel deep learning approach using AlexNet for the classification of electroencephalograms in Alzheimer's Disease and Mild Cognitive Impairment. Annual International Conference of the IEEE Engineering in Medicine and Biology Society.	● The study employed EEG-derived feature images and deep learning techniques for classifying AD patients, MCI subjects, and age-matched healthy control (HC) subjects. ● The CNN architecture AlexNet was modified and used for the three-way classification task, achieving an impressive classification accuracy of 98.13%.
Vialatte, F. B., Cichocki, A., Dreyfus, G., Musha, T., Shishkin, S. L., & Gervais, R. (2005). Early Detection of Alzheimer's Disease by Blind Source Separation, Time Frequency Representation, and Bump Modeling of EEG Signals. ICANN.	● A novel method for early detection of AD using EEG recordings was proposed, involving blind source separation, wavelet transformation, bump modeling, and feature selection. ● The proposed method showed substantially improved performance with 93% correctly classified cases, improved sensitivity, and specificity compared to previous classification results on the same data.
Salehi, A., Baglat, P., & Gupta, G. (2020). Alzheimer's Disease Diagnosis using Deep	● Deep learning techniques, particularly Convolutional Neural Networks (CNNs), are effective for diagnosing Alzheimer's Disease (AD).

Learning Techniques. International Journal of Engineering and Advanced Technology.	● Combining different datasets, such as ADNI and OASIS, can increase the accuracy of AD prediction at earlier stages. ● Deep learning techniques have the potential to improve the accuracy of AD diagnosis and prognosis.
Al-Shoukry, S., Rassem, T. H., & Makbol, N. M. (2020). Alzheimer’s Diseases Detection by Using Deep Learning Algorithms: A Mini-Review. IEEE Access.	● The accurate diagnosis of Alzheimer’s disease (AD) is crucial, especially in the early stages. ● Deep Learning (DL) is a common technique for early AD diagnosis. ● DL can aid researchers in diagnosing AD at its early stages.
Koga, S., Ikeda, A., & Dickson, D. (2021). Deep learning‐based model for diagnosing Alzheimer's disease and tauopathies. Neuropathology and Applied Neurobiology.	● A deep learning-based model was developed to differentiate between tauopathies, including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease (PiD), based on tau-immunostained digital slide images. ● The model achieved an accuracy of 94.2% in distinguishing between the four tauopathies. ● The model accurately identified tauopathies in various digital slide images, even those with low contrast and resolution.
Song, Z., Deng, B., Wang, J., & Yi, G. (2022). An EEG-based systematic explainable detection framework for probing and localizing abnormal patterns in Alzheimer’s disease. Journal of Neural Engineering.	● The proposed framework accurately detects AD patterns from raw EEG recordings without preprocessing. ● Abnormalities in the power of different brain rhythms are present in the frontal lobes of AD patients and spread to central lobes in the alpha and beta rhythms. ● Nonlinear complexity and functional connectivity are weak in AD patterns.
Qiu, S., Joshi, P., Miller, M. I., Xue, C., Zhou, X., Karjadi, C., Chang, G., Joshi, A., Dwyer, B., Zhu, S., Kaku, M., Zhou, Y., Alderazi, Y., Swaminathan,	● The authors developed a deep learning framework for Alzheimer’s disease classification that is highly interpretable and accurately predicts Alzheimer’s disease status.

A., Kedar, S., Saint-Hilaire, M., Auerbach, S., Yuan, J., Sartor, E., Au, R., Kolachalama, V. (2020). Development and validation of an interpretable deep learning framework for Alzheimer's disease classification. Brain: a journal of neurology.	● The model performance was compared to that of neurologists and neuropathological data and found to be comparable. ● The framework generated high-resolution visualizations of Alzheimer's disease risk in humans.
Trambaiolli, L., Lorena, A. C., Fraga, F. J., Kanda, P. A., Anghinah, R., Nitrini, R. (2011). Improving Alzheimer's Disease Diagnosis with Machine Learning Techniques. Clinical EEG and Neuroscience.	● The machine learning technique Support Vector Machine (SVM) was used to search patterns in EEG epochs to differentiate AD patients from controls. ● A quantitative EEG (qEEG) processing method was developed for the automatic differentiation of patients with AD from normal individuals. ● Analysis of EEG epochs resulted in high accuracy and sensitivity, and individual patient analysis achieved even higher accuracy and sensitivity.
Petrosian, A., Prokhorov, D., Schiffer, R. (2000). Early recognition of Alzheimer's disease in EEG using recurrent neural network and wavelet transform. SPIE Optics + Photonics.	● EEG is a quantitative parameter related to Alzheimer's disease, but its limitation is the absence of an identified set of features that discriminates AD EEG abnormalities from those due to confounding conditions. ● Recurrent neural networks (RNNs) combined with wavelet preprocessing can be used to discriminate between EEGs of early onset AD patients and their age-matched control subjects. ● RNNs applied to wavelet-filtered subbands are particularly favorable for detecting AD in EEG.
Vecchio, F., Miraglia, F., Alù, F., Menna, M., Judica, E., Cotelli, M., Rossini, P. (2020). Classification of Alzheimer's Disease with Respect to Physiological Aging with Innovative EEG Biomarkers in a Machine	● EEG connectivity analysis via a combination of source/connectivity biomarkers highly correlates with neuropsychological AD diagnosis. ● A machine-learning classifier (SVM) applied to EEG small-world parameters can accurately classify physiological versus pathological aging from cortical sources' connectivity.

Learning Implementation. Journal of Alzheimer's Disease.	• The approach is a low-cost and non-invasive method with high sensitivity, specificity, and optimal classification accuracy on an individual basis.
Raza, M., Awais, M., Ellahi, W., Aslam, N., Nguyen, H. X., Le, H. M. (2019). Diagnosis and monitoring of Alzheimer's patients using classical and deep learning techniques. Expert Syst. Appl.	• A novel machine learning-based diagnosis and monitoring system for AD-like diseases is proposed. • The AD diagnosis results showed significant improvement compared to existing techniques. • The system achieved above 95% accuracy to classify the activities of daily living.

5. Materials and Methods

The dataset utilized in this study was collaboratively developed by Dr. Dennis Duke and a team of researchers at Florida State University. The data was recorded from the 19 scalp loci of the international 10-20 system, employing a Biologic Systems Brain Atlas III Plus workstation. The dataset is divided into four sets: Sets A and B, which constitute the control group, comprised of 24 healthy elderly individuals with no history of neurological or psychiatric disorders, and Sets C and D, comprising 24 probable Alzheimer's disease (AD) patients diagnosed based on the criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R.

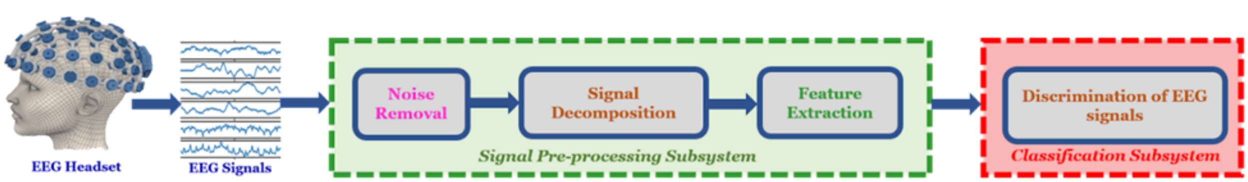


Figure 1. Diagnostic model for AD

5.1. Data Acquisition and Preprocessing

Multi-channel EEG signals were recorded using 19 electrodes (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, O1, and O2) placed according to the international 10-20 system using a Biologic Systems Brain Atlas III Plus workstation. (22) For more details, the reader can refer back to the original study.

The EEG signals in this dataset are accessed through Kaggle. It is observed that for each participant, 19 nodes and 1024 time points are identified, which are then tabulated as columns and rows respectively. No artifact removal techniques were employed since the noise in the dataset improves the robustness, generalizability and learning rate of the DL model (23).

Zhao and He (24) proposed a method to diagnose Alzheimer's Disease using an entropy method to analyze EEG signals. They outlined the basic workflow in two steps: unsupervised training of a deep learning network with the EEG data of Alzheimer's disease patients and healthy people. The second step is to fine-tune the deep learning network with labels of the EEG data.

5.2. Feature Extraction

Feature engineering is the process of building a set of features to represent the input data, in this case, the EEG Dataset (9). The time-series EEG signals contain features in the time and frequency domains (25), dynamic complexity (26) latent in the fluctuations, synchronization between different regions (25). Such features are integral in classifying and distinguishing between healthy controls and stages of dementia (27,28,29,30) as well as other cognitive states presentations (31).

Nonlinear features and Hjorth parameters are utilized due to their ability to detect subtle variations with high sensitivity, enabling accurate detection of rhythms. A total of 22 features were extracted, namely, Mean, Median, Mode, Std Deviation, Kurtosis, Skew, Max, Min, Quartile 1 & 3, Interquartile range, Hjorth parameters, Sample Entropy, Renyi Entropy, Permutation Energy, Shannon Entropy, Energy, Detrended Frequency Analysis, Petrosian Fractal Dimension.

A total of 19 readings were obtained for each feature, implying a total of 228 (=19 x 12) readings for each group A, B, C, D in the dataset and 912 (19x12x4) readings in total. These obtained readings were passed through eight different learning models - Decision Tree, Gaussian Naive Bayes, K-Nearest Neighbor (KNN), Logistic Regression, Multi-Layer Perceptron, Multinomial Naive Bayes, Random Forest, SVM.

Entropy-based features are extracted from each frequency sub-band of the decomposed EEG signal to quantify spectral complexity in time-dependent data effectively. These features play a crucial role in discriminating decomposed EEG signals, contributing to higher accuracy rates in analysis. Features such as sample entropy, Renyi entropy, Permutation entropy, Shannon entropy and energy were extracted from the time-frequency domain.

In this study, both row-wise and column-wise features were extracted from the dataset. The signals underwent wavelet decomposition up to the fifth order, employing a mathematical technique that dissects a signal into various frequency bands or scales called the "Daubechies" wavelets. This process divided the signal into multiple sub-signals or wavelet coefficients, each representing different resolutions. Daubechies wavelet (db10, level 5) was used since (i) it has wide smoothing characteristics, (ii) easy understanding of the nature of the signal, and (iii) changes in the EEG signals are easily observed (32). EEG signals are decomposed using the "db10" wavelet at level 5. Subsequently, entropy features were extracted from these decomposed waves. These entropy features allow capturing various statistical properties of the signal, such as its complexity, regularity, or randomness. Entropy from information theory is an effective way to measure the intrinsic communication of dynamic patterns over time or over channels (33,24). The features prior to and post decomposition were passed into the models again.

5.3. Model Training and Validation

The extracted features were labeled (1 for +ve Dementia, 0 for -ve Dementia) then fed into the classification model one by one with a 70:30 ratio of train-test split (70% of the data was used for training the model while the rest 30% was used for testing the viability of the trained model). After calculating the metrics for the model with the primary testing data it was followed up with a K-fold cross validation. The cross validation performed was done with 10 folds and the metrics were calculated for each fold using the classification_report function. The metrics obtained include precision, recall, f1-score and support for each label (0,1), macro and weighted average. To get a conclusive number to report as the final accuracy, the average of the results for each fold was taken and the final accuracy was calculated as such.

Afterwards, the extracted features were passed through a Recurrent Neural Network to check for overfitting of the models. The neural network was constructed with 10 layers. The recurrent layers LSTM having num_layer = 2 and GRU having num_layer = 1 were used alongside the ReLU activation function for two layers whereas the other layers were Linear with various activation functions such as Leaky ReLU, Sigmoid, Softmax and Tanh. The dataset was split into 64% for training, 16% for validation and the remaining 20% for testing. The data was fed into the model with a batch size of 64 and 100 epochs. Binary Cross Entropy Loss was used to calculate the loss and accuracy for each epoch. Loss was calculated by dividing the running loss by batch size and accuracy was calculated by dividing the number of correct predictions by total number of samples. The optimizer used is Adagrad with a learning rate of 0.001. The graph plots for losses and accuracy of the same are discussed in the results section.

6. Results

Upon extracting features row-wise and column-wise initially, it was observed that the column-wise feature extraction method yielded a better result.

Table 1. Comparison of accuracies for row-wise feature extraction vs column-wise feature extraction

Classifier	Accuracy for Row-wise Features	Accuracy for Column-wise Features
MLP	73.7 +/- 0.7 %	77.0 +/- 7.5 %
KNN	68.2 +/- 0.5 %	73.7 +/- 6.8 %
Decision Tree	82.7 +/- 0.9 %	71.9 +/- 4.6 %

Those features were subsequently passed through eight classifiers: Decision Tree, Gaussian Naive Bayes, K-Nearest Neighbor (KNN), Logistic Regression, Multi-Layer Perceptron (MLP), Multinomial Naive Bayes, Random Forest, SVM. In an attempt to boost efficiency, the signals were further decomposed as elaborated in the Methods section. Features were extracted from the decomposed waves and passed into the classifiers along with the initial set of features. The accuracy in each case was tabulated in Table 2. It is evident that MLP and Random Forest classifiers yield the highest accuracy post training with features extracted column-wise and further decomposition.

Table 2. Comparison of accuracies of classifiers upon feeding features in a row-wise manner vs feeding them after further signal decomposition.

Classifier	Accuracy for column-wise extracted features	Accuracy for column-wise extracted features + decomposed wave features
MLP	77.0 +/- 7.5 %	98.1 +/- 1.5 %
GNB	61.4 +/- 4.8 %	90.3 +/- 2.8 %
Decision Tree	71.9 +/- 4.6 %	92.5 +/- 2.9 %
KNN	73.7 +/- 6.8 %	93.3 +/- 2.9 %
Logistic Regression	72.9 +/- 5.8 %	96.6 +/- 2.1 %
MNB	60.5 +/- 5.7 %	79.6 +/- 5.7 %
SVM	66.5 +/- 4.9 %	93.9 +/- 2.6 %
Random Forest	97.5 +/- 2.4 %	98.0 +/- 2.0 %

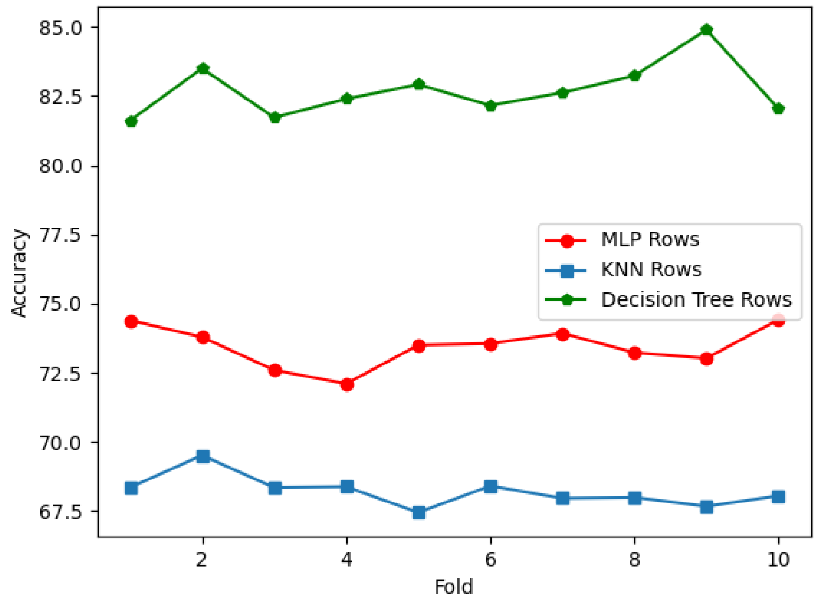


Figure 2.10-fold cross-validation for different models when initial row-wise extracted features are fed.

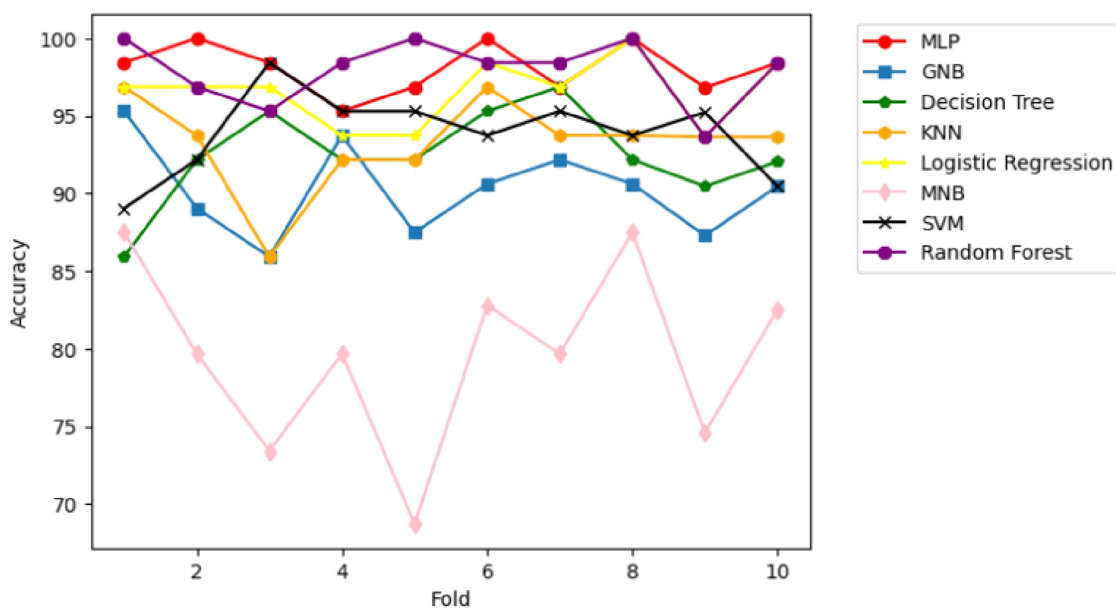


Figure 3.10-fold cross-validation for different models when initial column-wise extracted features are fed.

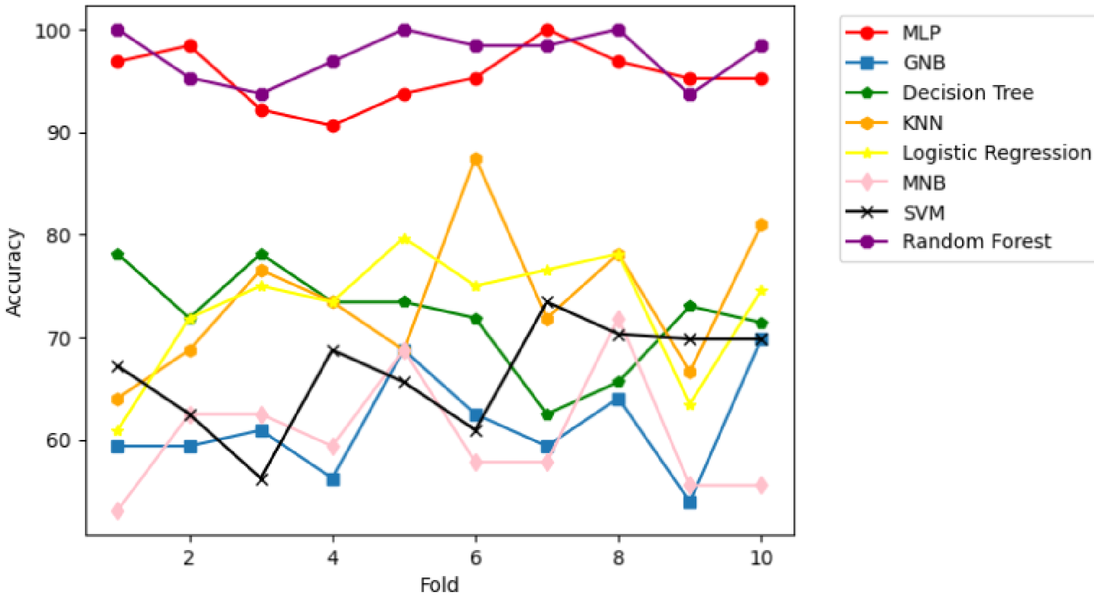
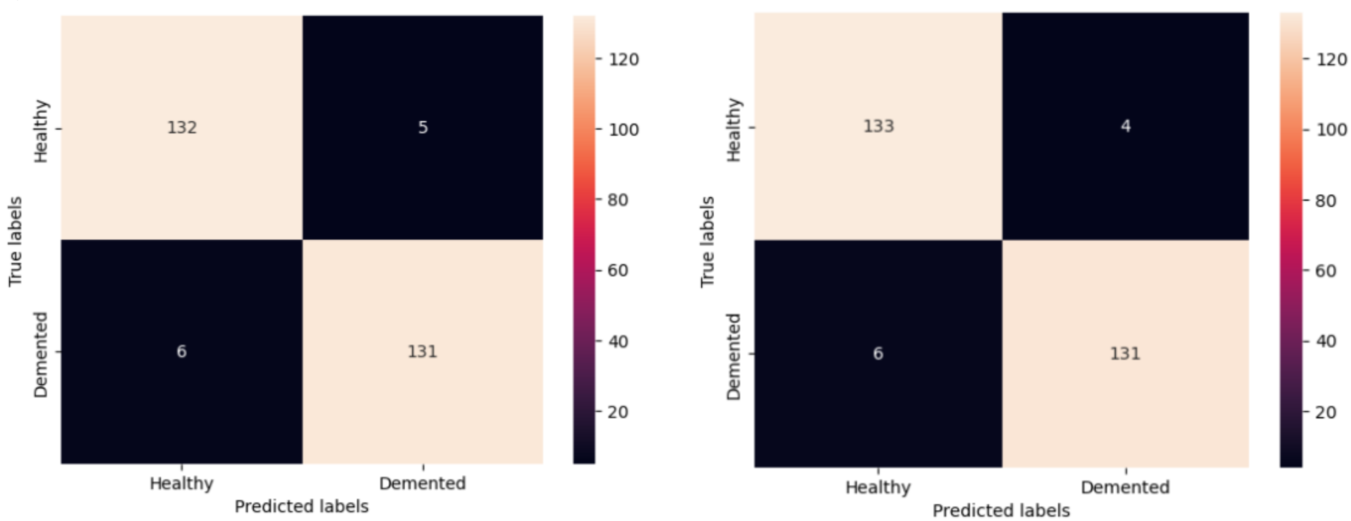


Figure 4.10-fold cross-validation for different models when initial column-wise and subsequently decomposed wavelet extracted features are fed.

a)



b)

Figure 4. Confusion matrices for a) MLP b) Random forest post feature extraction of column-wise and decomposed wavelet features.

Equation 1: Ratio of actual true prediction to the total amount of data gives accuracy.

$$Accuracy = TP + TN\ TP + FP + FN + TN \quad (1)$$

Equation 2: Ratio of actual positive prediction to the total positive forecast gives precision.

$$\text{Precision} = \frac{TP}{TP + FP} \quad (2)$$

Equation 3: Ratio of actual positive prediction to the positively labeled data gives recall.

$$\text{Recall} = \frac{TP}{TP + FN} \quad (3)$$

Equation 4: F1-score indicates the harmonic mean of the two performance parameters precision and recall.

$$F1 - score = \frac{2 * Precision * Recall}{Precision + Recall} \quad (4)$$

Table 3. Comparing the precision, recall and f-score for column-wise extracted features and decomposed wavelet features in MLP and Random Forest Classifiers.

Classifier	***Precision***	***Recall***	***F1-Score***
MLP	0.963235	0.956204	0.959707
Random Forest	0.970370	0.956204	0.963235

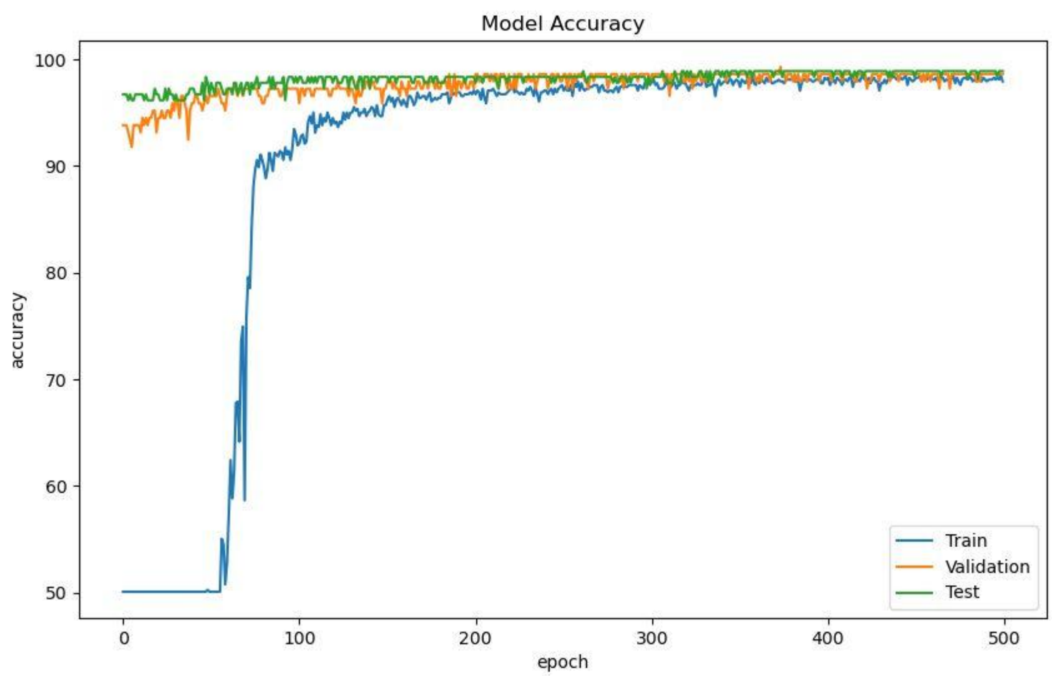


Figure 5. Model Accuracy for RNN

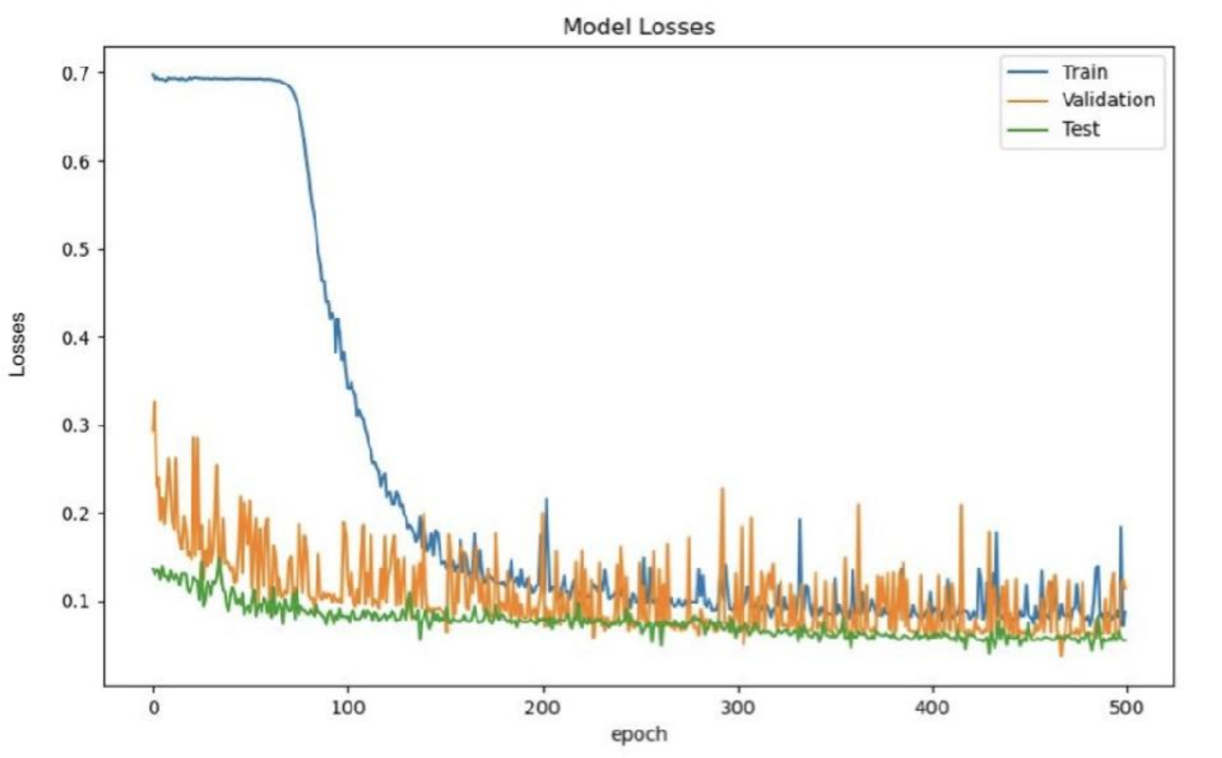


Figure 6. Model Losses for RNN.

7. Discussion

In this paper, several entropy-related features and time-frequency domain features are used as a representative of the EEG signals from the brain to assess whether an individual has Alzheimer's Disease. The EEG signals in question are those obtained from four brain regions such as frontal, parietal, central, and temporal as they act as the seat of predominant changes during early stages of AD (34). The feature selection process in this paper is partly aided by the research conducted on epileptic seizures by Glory et al. (23), with a focus on entropy-related features (35,33) for a more accurate diagnosis of the disease. It was also observed that column-wise feature extraction followed by decomposed wavelet feature extraction yielded the best accuracy during classification. The most effective classification models were found to be the Multi-Layer Perceptron and Random Forest, with commendable accuracies of 98.1+/- 1.5% and 98 +/- 2% respectively.

However, the proposed deep learning tool has a long way to go before being integrated into clinical settings. The tool has to be validated with more datasets, since the one used has a rather small sample size. There should be a way to eliminate possibilities of a misdiagnosis of comorbidities in order to achieve optimum diagnostic accuracy. Additionally, the growing notion that deep-learning models are 'black-box' algorithms, they do not necessarily evaluate underlying diagnostic conditions or indicate which of the input features in reality affect the output predictions (36,37). The model has the scope to be customized to individual needs in order to prepare for the future of precision medicine.

References

1. Dementia (2023) World Health Organization. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia (Accessed: 28 July 2023).
2. S.F. Javaid, C. Giebel, M.A.B. Khan, et al., Epidemiology of Alzheimer's disease and other dementias: rising global burden and forecasted trends, F1000Research 10 (2021) 425–438.
3. T. Dua, K.M. Dua, S. Sivananthan, et al., World health organization's global action plan on the public health response to dementia 2017–2025, Alzheimer's Dementia 13 (2017) 1450–1451.
4. Feldman HH, Woodward M. The staging and assessment of moderate to severe Alzheimer disease. Neurology. 2005; 65. https://doi.org/10.1212/WNL.65.6_suppl_3.S10
5. T. J. Saleem et al., "Deep Learning-Based Diagnosis of Alzheimer's Disease," Journal of Personalized Medicine, vol. 12, no. 5, p. 815, May 2022, doi: https://doi.org/10.3390/jpm12050815.
6. Z. Cao, "A review of artificial intelligence for EEG‐based brain−computer interfaces and applications," Brain Science Advances, vol. 6, no. 3, pp. 162–170, Sep. 2020, doi: https://doi.org/10.26599/bsa.2020.9050017.
7. Hata, M., Watanabe, Y., Tanaka, T., Awata, K., Miyazaki, Y., Fukuma, R., Taomoto, D., Satake, Y., Suehiro, T., Kanemoto, H. and Yoshiyama, K., 2021. Precise Discrimination for Multiple Underlying Pathologies of Dementia Cases Based on Deep-Learning with Electroencephalography.
8. Vecchio, F., Miraglia, F., Alù, F., Menna, M., Judica, E., Cotelli, M. and Rossini, P.M., 2020. Classification of Alzheimer's disease with respect to physiological aging with innovative EEG biomarkers in a machine learning implementation. Journal of Alzheimer's Disease, 75(4), pp.1253-1261.
9. Alves, C.L. et al. (2022) 'EEG functional connectivity and deep learning for automatic diagnosis of brain disorders: Alzheimer's disease and schizophrenia', Journal of Physics: Complexity, 3(2), p. 025001. doi:10.1088/2632-072x/ac5f8d.
10. Trambaiolli L R, Falk T H, Fraga F J, Anghinah R and Lorena A C 2011 EEG spectro-temporal modulation energy: a new feature for automated diagnosis of Alzheimer's disease 2011 Annual Int. Conf. IEEE Engineering in Medicine and Biology Society (Piscataway, NJ: IEEE) 3828–31
11. Falk T H, Fraga F J, Trambaiolli L and Anghinah R 2012 EEG amplitude modulation analysis for semi-automated diagnosis of Alzheimer's disease EURASIP J. Adv. Signal Process. 2012 192

12. Piubelli L, Pollegioni L, Rabattoni V, Mauri M, Cariddi L P, Versino M and Sacchi S 2021 Serum d-serine levels are altered in early phases of Alzheimer's disease: towards a precocious biomarker Transl. Psychiatry 11 77
13. Pineda A M, Ramos F M, Betting L E and Campanharo A S L O 2020 Quantile graphs for EEG-based diagnosis of Alzheimer's disease PLoS One 15 e0231169
14. Oh S L, Vicnesh J, Ciaccio E J, Yuvaraj R and Acharya U R 2019 Deep convolutional neural network model for automated diagnosis of schizophrenia using EEG signals Appl. Sci. 9 2870
15. Ahmadlou M, Adeli H and Adeli A 2011 Fractality and a wavelet-chaos-methodology for EEG-based diagnosis of Alzheimer disease Alzheimer Dis. Assoc. Disord. 25 85
16. Buettner R, Beil D, Scholtz S and Djemai A 2020 Development of a machine learning based algorithm to accurately detect schizophrenia based on one-minute EEG recordings Proc. 53rd Hawaii Int. Conf. System Sciences
17. Arora, B. et al. (2022) ‘Integrating Artificial Intelligence and deep learning for Enhanced Medical Innovation’, 2022 5th International Conference on Contemporary Computing and Informatics (IC3I) [Preprint]. doi:10.1109/ic3i56241.2022.10073054.
18. Fabrizio, C., Termine, A., Caltagirone, C., and Sancesario, G. (2021). Artificial intelligence for Alzheimer's disease: promise or challenge? Diagnostics 11, 1473. doi: 10.3390/diagnostics11081473
19. Miltiadous, A., Tzimourta, K. D., Giannakeas, N., Tsipouras, M. G., Afrantou, T., Ioannidis, P., et al. (2021). Alzheimer's disease and frontotemporal dementia: a robust classification method of eeg signals and a comparison of validation methods. Diagnostics 11, 1437. doi: 10.3390/diagnostics11081437
20. Murdaca, G., Banchero, S., Tonacci, A., Nencioni, A., Monacelli, F., and Gangemi, S. (2021). Vitamin d and folate as predictors of mmse in Alzheimer's disease: a machine learning analysis. Diagnostics 11, 940. doi: 10.3390/diagnostics11060940
21. Rizzo, A., Ermini, S., Zanca, D., Bernabini, D., and Rossi, A. (2022). A machine learning approach for detecting cognitive interference based on eye-tracking data. Front. Hum. Neurosci. 16, 806330. doi: 10.3389/fnhum.2022.806330
22. Pineda, A.M., Ramos, F.M., Betting, L.E. and Campanharo, A.S., 2020. Quantile graphs for EEG-based diagnosis of Alzheimer’s disease. Plos one, 15(6), p.e0231169.
23. Glory, H.A., Vigneswaran, C., Jagtap, S.S., Shruthi, R., Hariharan, G. and Sriram, V.S., 2021. AHW-BGOA-DNN: A novel deep learning model for epileptic seizure detection. Neural Computing and Applications, 33, pp.6065-6093.
24. Zhao, Y. and He, L., 2015. Deep learning in the EEG diagnosis of Alzheimer’s disease. In Computer Vision-ACCV 2014 Workshops: Singapore, Singapore, November 1-2, 2014, Revised Selected Papers, Part I 12 (pp. 340-353). Springer International Publishing.
25. 8. M. X. Cohen, Analyzing neural time series data : theory and practice, Cambridge, Massachusetts:The MIT Press, 2014.

26. 16. R. Ferenets, T. Lipping, A. Anier, V. Jantti, S. Melto and S. Hovilehto, "Comparison of Entropy and Complexity Measures for the Assessment of Depth of Sedation", IEEE Transactions on Biomedical Engineering, vol. 53, no. 6, pp. 1067-1077, 2006.
27. S. Yang, J. M. S. Bornot, K. Wong-Lin and G. Prasad, "M/EEG-Based Bio-Markers to Predict the MCI and Alzheimer's Disease: A Review From the ML Perspective", IEEE Transactions on Biomedical Engineering, vol. 66, no. 10, pp. 2924-2935, 2019.
28. 18. F. C. Morabito, M. Campolo, N. Mammone, M. Versaci, S. Franceschetti, F. Tagliavini, et al., "Deep Learning Representation from Electroencephalography of Early-Stage Creutzfeldt-Jakob Disease and Features for Differentiation from Rapidly Progressive Dementia", International Journal of Neural Systems, vol. 27, no. 02, pp. 1650039, 2017.
29. 19. D. Kim and K. Kim, "Detection of Early Stage Alzheimer's Disease using EEG Relative Power with Deep Neural Network", pp. 352-355, 2018.
30. 20. F. C. Morabito, M. Campolo, C. Ieracitano, J. M. Ebadi, L. Bonanno, A. Bramanti, et al., "Deep convolutional neural networks for classification of mild cognitive impaired and Alzheimer's disease patients from scalp EEG recordings", pp. 1-6.
31. C.-S. Wei, Y.-T. Wang, C.-T. Lin and T.-P. Jung, "Toward Drowsiness Detection Using Non-hair-Bearing EEG-Based Brain-Computer Interfaces", IEEE Transactions on Neural Systems and Rehabilitation Engineering, vol. 26, no. 2, pp. 400-406, 2018.
32. S. Liu, W. Cai, Y. Song et al., "Localized Sparse Code Gradient in Alzheimer's Disease Staging", EMBC 2013, pp. 5398-5401, 2013.
33. Song, Z., Deng, B., Wang, J. and Yi, G., 2022. An EEG-based systematic explainable detection framework for probing and localizing abnormal patterns in Alzheimer's disease. Journal of Neural Engineering, 19(3), p.036007.
34. Kulkarni, N., 2019. EEG Signal Analysis for Mild Alzheimer's Disease Diagnosis by Means of Spectral-and Complexity-Based Features and Machine Learning Techniques. In Proceedings of the 2nd International Conference on Data Engineering and Communication Technology: ICDECT 2017(pp. 395-403). Springer Singapore.
35. Xia, W., Zhang, R., Zhang, X. and Usman, M., 2023. A novel method for diagnosing Alzheimer's disease using deep pyramid CNN based on EEG signals. Heliyon, 9(4).
36. Castelvecchi D. Can we open the black box of AI? Nature 2016; 538: 20–3.
37. Qiu, S., Joshi, P.S., Miller, M.I., Xue, C., Zhou, X., Karjadi, C., Chang, G.H., Joshi, A.S., Dwyer, B., Zhu, S. and Kaku, M., 2020. Development and validation of an interpretable

deep learning framework for Alzheimer’s disease classification. Brain, 143(6), pp.1920-1933.

Appendix

Model	Relevance
Decision Tree:	● Decision trees are simple, interpretable models that divide the data based on features to create a tree-like structure of decisions. ● In EEG analysis, decision trees can be used to identify relevant EEG features and their thresholds to classify patients into Alzheimer's and non-Alzheimer's groups.
Gaussian Naive Bayes:	● Naive Bayes is a probabilistic model based on Bayes' theorem and assumes that the features are conditionally independent given the class label. ● Gaussian Naive Bayes is applicable when the features are continuous and follow a Gaussian (normal) distribution. ● In EEG classification, Gaussian Naive Bayes can be used to estimate the likelihood of a patient belonging to a specific class based on the probability distribution of the EEG features.
KNN	● KNN is a simple, intuitive classification algorithm that assigns a class label to an instance based on the class labels of its k-nearest neighbors in the feature space. ● In EEG analysis, KNN can be used to identify similar EEG patterns in the dataset and classify patients based on the labels of the nearest neighbors.
Logistic Regression	● It is a linear model used for binary classification tasks. ● In EEG-based Alzheimer's diagnosis, logistic regression can be employed to

	model the relationship between EEG features and the probability of a patient belonging to the Alzheimer's or non-Alzheimer's group.
Multinomial Naive Bayes	● Multinomial Naive Bayes is suitable for discrete features, often used for text classification problems. ● In EEG analysis, it can be used when the extracted features are discrete or categorical in nature.
MLP	● MLP is a type of artificial neural network with multiple hidden layers. ● In EEG analysis, MLPs can capture complex patterns in the EEG data, making them apt for diagnosing Alzheimer's using several EEG features.
Random Forest	● Random Forest creates multiple decision trees and combines their predictions. ● In EEG classification, Random Forest can be used for accuracy and robustness of the model by integrating decisions from multiple trees.
SVM	● SVM is a powerful classification algorithm that finds an optimal hyperplane to separate data points into different classes. ● In EEG-based Alzheimer's diagnosis, SVM can be used to find a boundary between Alzheimer's and non-Alzheimer's EEG data in a higher-dimensional feature space.