Machine Learning Techniques for Alzheimer Detection

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Abstract: *The proper diagnosis of Alzheimer's disease (AD) inthe pre-stage plays a very important role in the treatment of patients. The most important challenges in biomedical researchand clinical practice include the need to develop and apply innovative tools for the effective integration, analysis and understanding of complex biomedical data to identify the testable hypothesis and build perfect models to diagnose and predict various stages of AD. The algorithms must also handle inadequate, noisy, and ambiguous information. Efficient ML/DL approaches become necessary in the health care industry to report these issues. This paper provides a review of some of the important literature on AD and explores how Machine Learning algorithms help scholars for early detection and prediction of AD.*

Keywords: Alzheimer's disease(AD), artificial neuralnetwork, support vector machine(SVM), machine learning(ML), deep learning(DL), deep neural network, Alzheimer's disease Neuroimaging Initiative (ADNI)

I. Introduction

Alzheimer's Disease (AD) characterized by progressive damage of cognitive and memory functions and its early- stage Mild Cognitive Impairment (MCI) is the most widespread neurodegenerative brain disease in elderly persons. [1]

AD is one of the most common forms of dementia in today's world, which is a progressive brain disorder mostly in late life[2]According to the World Alzheimer Report (2019)[3] almost 62% of healthcare providers worldwide think that dementia is part of normal aging,40% of the general public think doctors and nurses ignore people with dementia. According to World Alzheimer Report (2018) [4], around 50 million people were affected by this disease in 2018, which is supposed to triple by 2050. Usually, the symptoms of Alzheimer's are see-able after 60 years of age. However, some forms of AD develop very early (30-50 years) for individuals having gene mutation [5]

In 1910, in the eighth edition of clinical Psychiatry: A Text Book for Students and Physicians, Krapelin discussed a special group of cases with severe call changes that involve too many plaques, the death of about one-third of the outer layer of neural tissue of the cerebrum of the brain, replacing them with the specific burst of colored neurofibrils and represent the most severe form of undernourishment. Krapelin, who offered a description at a time when the clinical definition of AD was unclear [6]

One of the major clinical challenges posed by AD is establishing an approach to ensure its early identification and accurate diagnosis so that it will be possible to treat potentially as well arrest the development of disease before a substantial amount of brain tissue has been permanently injured. Prediction of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) is of key interest in AD research. The accuracy of classification among Control Normal (CN) to AD and Mild Cognitive Impairment to AD stage is needed to be improved for the early detection of disease. In AD patients, the time between a healthy state to Alzheimer spans over several years. First, patients develop MCI, and gradually progress to Alzheimer. However, all MCI patients do not convert to Alzheimer. Current research mainly focuses on the prediction of the conversion of MCI to AD. Changes from one stage o another can be measured using medical imaging and other techniques like blood plasma spectroscopy [5]

Machine learning techniques are found to be very convenient techniques for the diagnosis of Alzheimer in the last few years. The most commonly used classification techniques are support vector machine (SVM), artificial neural network

(ANN), and deep learning. Feature extraction is an important step in both SVM and ANN, However, deep learning incorporates the feature extraction step in the learning model itself. For large datasets, especially for image data deep learning is found to be useful. Some researchers also used ensemble methods to improve the classification accuracy for Alzheimer [5]

1.2 Machine Learning

Machine Learning is a method of data analytics that automates model building, as it relates to the building of models. [7] Nithya et al.[8] in 2017 focus on the part of machine learning in prediction as well as how to apply machine learning to the data.

1. Machine Learning's Role in Predictions: Machine learning is provided with effective algorithms, applications and frameworks to attain more predictive accuracy and value to data sets
2. Steps to apply machine learning to data

As shown in Fig 1.1.1 Machine learning task can be broken into the below steps.

1. Collecting data
2. Data Exploration and preparation
3. Training a model on data
4. Evaluating model performance
5. Model performance Improvement

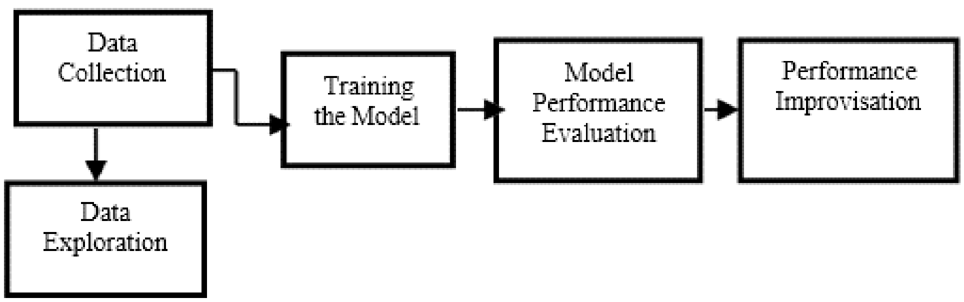

Figure: Machine Learning Process

After these steps have been accomplished, if the model appears to be performing acceptably, it can be deployed for its intended task.

1.3 Applications of ML in Healthcare

The Machine learning algorithms used in distinguishing complicated patterns within prosperous and vast data. This facility is especially well-suited for clinical use, particularly those people who rely on advanced genomics and proteomics measurements. It is frequently utilized in numerous illness diagnoses and detection. Machine learning algorithms will be used for higher decisions regarding treatment action for patients by suggesting the implementation of the useful healthcare system in medical applications [9]

1.4. Different Techniques used by ML

A. Support Vector Machine

A collection of training samples is given each sample is divided into different categories. Support vector machine (SVM) is mainly used for classification and regression problems [10]

B. Naive Bayes Classification

Statistical classifiers are the example for Bayesian classifiers. Based on the given class label Naive Bayes identify the class membership probabilities. It performs one scanning of data and hence classification is easy.

C. Decision Tree

Decision Tree (DT) is a generally used technique for classification containing an internal node and one leaf node with a class label. The nodes at the top of the decision tree (DT) are called root nodes.

D. K-nearest-Neighbor

K-nearest neighbor is the most used approach for the classification of samples. Distance measures will be calculated from the N number of training samples using this technique. KNN can be used for classification, regression, and search.

E. Fuzzy Logic

Fuzzy Logic which is evolved from Fuzzy set theory. These values lie in between 0 and 1. It is a very popular method that is used in engineering applications [10]

F. CART

The classification and Regression Tree technique is called the CART. In classification and regression trees the target variable is represented as categorical and continuous. These variables are used to guess values in the tree.

G. Random Forests

In random forests, instead of training a single tree, a group of trees is trained. Each tree is trained on a subset of the training set, chosen randomly along with a replacement using an arbitrarily chosen subset of M input variables (features).

II. Machine Learning Techniques

This section discusses the various techniques used for the prediction of diseases using machine learning techniques Rohan Bhardwaj et al. [11] in 2017 discussed the machine learning initiatives in the healthcare sector. Machine learning provides solution for both reducing the rising cost of healthcare and helping establish a better patient-doctor relationship. Machine learning and big data solutions can be used for health-related uses, some include helping doctors to determine more personalized prescriptions and treatments for patients.

The main cause of dementia in Western countries is considered Alzheimer's disease (AD). It is characterized by memory loss and impairment of at least one cognitive function. The most common early indication is difficulty in remembering recent events. Probable diagnosis is based on the history of the sickness and cognitive testing with medical imaging and blood tests to rule out other possible causes. The symptoms at the beginning are often mistaken for normal aging. Brain tissues need to be examined for a definite diagnosis. To decrease the risk of AD Mental and physical exercise and avoiding obesity is necessary; evidence to support these recommendations is weak. There are no medications or supplements that have been shown to decrease risk.

R. Chaves et al.[12]in 2010 introduced a competent classification method for early diagnosis of Alzheimer's disease. Using association rule mining, they found the associations between attributes of the pre-processed data sets. The proposed method was based on the tridimensional activated brain regions of interest (ROIs). For this purpose, a SPECT dataset of 97 instances was used out of which 43 were normal controls and the remaining 54 were AD patients. The authors made comparisons with other techniques like VAF, PCA-SVM, and GMM-SVM, and results revealed a classification accuracy of 95.87% (100% sensitivity, 92.86 specificity) with a claim of reducing the computational cost. These results show a negligible difference in the accuracies with better efficiency in terms of computational time. The author claims it to be an "Effective" approach rather than an efficient diagnosis of AD. Differentiating the early stage of the disease in AD patients using clinical conventions remained a diagnostic task.

Chaves, R., J. Górriz, et al.[13] in 2011 Distinguishing the early stage of the disease in AD patients using clinical conventions remained a diagnostic challenge. R. Chaves et al. (2011), later on, continued with his work by finding the associations among attributes while characterizing the perfusion patterns in SPECT images of normal subjects. A complete image database was evaluated to reproduce the knowledge of medical experts. The pathologically unproven dataset from ADNI of 97 participants was used of which 41 were labeled as healthy controls and 56 were labeled as AD patients by expert physicians. Comparing with other techniques like PCA-SVM, GMM-SVM, output revealed the classification accuracy of 94.87% with 91.07% sensitivity and 100% specificity. The results were based on pathologically unproven data with no discussion about missing values while class imbalance was minimized as possible For prior diagnosis and to follow treatment results L. R. Trambaiolli et. al. in 2011[14] suggested a new approach, SVM technique is used to search patterns in EEG epochs to differentiate AD patients from controls. Quantitative EEG (qEEG) processing method for automatic differentiation of patients with AD from normal individuals is developed, as a complement to the diagnosis of possible dementia. SVM is used to develop a model which will extract and classify the digital EEG signals dataset patterns from probands previously diagnosed as controls or AD patients. This technique is known for processing high-dimensional data as EEG signals. Several different combinations of features extracted from the EEG exams were considered as input for the SVMs. The classification per patient had the best results when authors used as inputs for SVMs only the frequencies of the peaks of the spectrum obtained by bipolar recording. Therefore, the authors suggest that the use of bipolar peaks is a good tool providing a set of characteristics from EEG signals for SVMs in the classification of patients with AD.

R. Chaves et al. [15] in 2012 the pathological unverified data sets of AD made it applicable to different imaging technologies as well to diagnose other neurodegenerative diseases. To address this, R. Chaves et al.introduced a mining technique using association rule mining defined over discriminant regions using pre-processed SPECT and PET imaging modalities. Datasets consist of 97 participants, 42 were labeled as healthy controls and 55 were labeled as AD patients by expert physicians. The proposed method was compared with other techniques like PCA-SVM, VAF-SVM and the results of this paper proved them with the accuracy of 92.78% with 87.5% sensitivity & 100% specificity for SPECT and 91.33% accuracy with 82.67% sensitivity & 100% specificity for PET. With no discussion about the missing values, the class imbalance has been reduced. The authors have introduced a method for analyzing Alzheimer's. disease by incorporating more detailed PET, for instance, FDG-PET and PiB-PET. The data set comprised of 103 participants where 19 were control (CTRL), 19 were AD patients and 65 were with Mild cognitive impairment (MCI). The authors came with good results for PiB PET having classification accuracy of 97.37% and in combination with FDG, it achieved the classification accuracy of 94.74% while FDG PET alone received 92.11% accuracy. The proposed method worked with a very small- sized pathologically unproven data set with a class imbalance problem which produces uncertainty in the acquired accuracies. Ramı´rez et al. (2013) [16] contributed towards the early diagnosis of AD by evolving a CAD model for improving the early detection of AD. This model was based on picking the parameters of the image and classification using a support vector machine. A research was conducted to determine the Region of interest (ROIs) and most discriminant metrics of the image. The main objective of this study was to decrease the dimensionality of the input space and diagnose the AD with higher accuracy with the aid of the radial basis function (RBF) SVM. The technique accomplished a sensitivity of 93.10%, an accuracy of 90.38%, and a specificity of 86.96%. However, it's tough to classify the images into quite two classes during a single setting using an SVM classifier.

Sidra Minhas et al.(2015)[17] implemented a machine learning framework for the prediction of AD in MCI patients using longitudinal data from ADNI. Five different techniques are implemented for the computation of missing feature values of neuropsychological predictors of AD. Appropriate selection of significant neuropsychological biomarkers, effective replacement of missing feature readings, and a strong summary measure for the longitudinal data helps retain substantial differences between MCIp and MCIs. This work presents an improved accuracy of 71.16% in the prediction of pre-clinical AD.

Aunsia Khan et al. in 2015[18] Proposed a new method consists of four steps 1. Pre-processing 2. Attribute selection 3. Classification and 4. Class Threshold. To avoid class imbalance, data is over-sampled using the machine learning synthetic minority oversampling technique (SMOTE). The input data type is converted from numeric into nominal/numeric to nominal values so that the algorithms which use said data type as input can be implemented. Attribute selection involves searching through all possible combinations of attributes in the data to find which subset of attributes works best for prediction and classification. It is helpful in dimensionality reduction and omitting improper attributes. For classification tasks, it can lead to increased accuracy or to reduced computational costs. The third step is based on classification using AR mining with minimum support and minimum confidence. Classification is done using 10-fold cross-validation. The training set is used for classification to identify the specific parameters. The association rules results in unique associations among the attributes which are exploited in next step. To classify the instances into two classes such as Control and AD certain threshold is used over the resultant rules. The proposed method deals with pathologically proven data and overcomes the class imbalance and overtraining issues. The proposed model is based on single modality to overcome the increased cost of computing and combining different modalities. Authors believe that pathologically proven data may increase the accuracy and validity, while a balanced class will help the classifiers to give accurate results. This model is can help to improve the prediction performance by physicians and cover the limitations pointed out in the previous research.

As per A.B. Rabeh et al.[19] Proposed a method to detect Alzheimer's disease in the early stage. Segmentation is used to extract three sections of the brain Frontal, Sagittal and Axial. Classification is based on Support Vector Machine (SVM) and decision tree. The proposed solution yields a 90.66% accuracy by combining the classification of three sections in the early diagnosis of AD.

Ortiz et al. [20] presented a method for diagnosing early AD and AD by the fusion of structural and functional imaging data based on the deep learning technique mainly DBN. The sections of the brain are defined based on automated anatomical labeling (AAL). The grey matter (GM) images from each section of the brain are separated into three-dimensional patches based on the areas that were described by AAL and these patches aid the training of the DBN. Two structures based on deep learning and four distinct schemes of voting were implemented. The resulting method is evaluated using the ADNI database. The architecture provided an accuracy of 90% for NC/AD and 84% for MCI/AD classification. Tejeswinee K et al.[21] in 2017 used three feature selection methodologies for the selection of optimal feature sets. Information Gain (IG), Gain Ratio (GR), and Correlation Feature Subset Selection (CFS) were deployed individually to the complete dataset. The optimized feature subset was obtained as a result. This subset was fed to each of the six classification algorithms in the classification phase. The algorithms investigated were SVM, Random Forest, Decision Tree, Naïve Bayes, Adaboost, and Nearest Neighbor (K-NN). When the SVM classifier was enforced, the accuracy increased from 93.7% to 97.3% under CFS feature selection. Information Gain technique when applied along with the SVM classifier showed a raise in accuracy from 86.5% to 87.4%. Random Forest classifier employed over Gain Ratio method increased the accuracy from 85.6% to 88.3%. The number of features in the feature subset reduced from 54, 42, and 50 to 49, 37, and 36 for CFS, IG, and GR techniques respectively. This investigation aimed to examine the performance of the classification algorithms such as SVM, Random Forest, Decision Tree, Naïve Bayes, Adaboost and K-NN on the generated dataset. It was evident from the study that prior to feature selection when weighed against the other classification techniques. Random forest and K-NN classifiers predicted the diagnostic classes with high accuracy (~82%) . SVM gave the best accuracy (~94%) with CFS subset evaluation. In the Gain Ratio method, Random Forest showed impressive results (~85%). It was followed by SVM and Decision tree classifiers. From the study, it is observed that selecting the optimal features by CFS followed by DFS implementation, creating a hybrid feature selection technique improves the classification accuracy and aids in early disease diagnosis. For designing appropriate drugs towards providing relief to affected subjects these results can be utilized N. G. Maity et al. in[22] discussed ML tools for solving problems and discovering relationships in data. In this case study authors built a Bayesian model for diagnosing AD. Once the model is created by computing conditional probabilities using historical data, given a new patient's current condition, and test results it can infer the probability of a diagnosis of the disease. Five cognitive test results were selected in this analysis. Some of the test scores and age were grouped into a fewer number of enumerated values. From the historical data, three categories of diagnosis were used: Alzheimer's, Mild Cognitive Impairment (MCI), and Normal. Author ran the test on 100 batches of 50 observations each, computing the correct diagnoses made by each batch. The Bayesian model was able to make correct predictions nearly 80% of the time. The beauty of this simple model is that as more data on patient's historical clinical data is collected over time, it can be easily updated to provide more reliable analysis.

The OASIS dataset contains two types of data: Cross- sectional MRI data and Longitudinal MRI data of non- demented and demented older adults. The author applied J48, Naïve Bayes, Random Forest, and Multilayer Perceptron classification techniques using the WEKA tool. CFSSubsetEval is used to apply the Attribute Selection technique as per the author J48 is showing the best classification accuracy of 99.52% and on applying attribute selection, the Random Forest algorithm is performing 75.96%, the least of all in the case of Oasis Cross-sectional data. In the Oasis Longitudinal data J48 is outperforming in both the cases among all the classifiers showing 99.20% and 98.66% on applying attribute selection

[23]. Firouzeh Razavi et al. in [24] a two-stage method was presented for an intelligent diagnosis of Alzheimer's disease. Scattered filtering, an uncontrolled two-layer neural network applied to directly learn features from raw data. To Categorize health statuses based on the learned features SoftMax regression was applied. The suggested method was validated by the data sets of Alzheimer's Brain Images. The results showed that the method achieved very good diagnostic accuracy and was better than the existing methods for brain image data sets. The method suggested by Author reduces the need for human work and makes it easy to intelligently diagnose for big data processing because the learning features are adaptive.

Lee Kuok Leong et al.[25] published a study based on the comparison and evaluation of different ML techniques with preprocessing and Boruta algorithm in the prognosis and prediction of AD. In a proposed method in the column of SES and MMSE the missing values were cleansed by column deletion. The investigational results validate that a combination of pre-processing and experimental results with Boruta features selection is a reliable technique for early prediction of AD. Among all proposed algorithms, Random Forest Grid Search Cross-Validation(RF GSCV) with Boruta algorithm is the best classifier outperformed with the accuracy of 94.39%. Even for the small dataset RF model has better feature propagation and provides better classification results. Developed GUI prediction tool provides the prediction on the rank of dementia based on the available patient data which includes demographics, clinical and MRI derived anatomic volume features able to cover the limitations pointed out from the earlier researches

Rashmi Kumari et al.[26] presents a ML model that effectively diagnosed AD, cMCI, ncMCI and CN which are being detected during pre-stages by itself. MRI image dataset is collected from the open access database of OASIS-3. Gaussian filter is applied to remove any of the unwanted noise during image preprocessing. Image segmentation is done using Otsu thresholding algorithm and Prewitt edge detection technique is applied for detecting the edges. The images clustering is performed with the help of fuzzy clustering technique and then features are extracted by GLCM feature extraction technique. At last, dataset is classified using convolutional neural networks (CNN). The classifier categorized the images with an accuracy and sensitivity of 90.25% & 85.53% respectively. J. Neelaveni et al.(2020)[27] uses machine learning algorithms to predict Alzheimer disease using psychological parameters like MMSE score, age, number of visits, and education of the patients. The model predicts the disease in the patient using Support Vector Machine with accuracy 85% and Decision Tree with accuracy 83% as well separates between the cognitive impairment.

SVM-based, automated diagnostic models for neuropsychiatric disorders tend to use hand-crafted features due to their inability to mine adaptive features. DL models allow a system to use raw data as input, thereby allowing them to automatically determine highly discriminative features in the given training data set. This end-to-end learning design idea is the fundamental basis of DL. [28]

III. Neural Network and Deep Learning Concept

Deep Learning is a multi-layered supervised machine learning method that uses the models of deep neural networks and neurons that is the basic computational unit in a neural network and capable of learning complex structures of data to achieve a high degree of abstraction. Generally, deep neural network is comprised of three layers, each layer consists of nodes the first layer is the input layer, the middle is the hidden layer and the last layer used for learning and analyzing the data is called output layer, the more hidden layer in neural network is the more accurate detection of patterns. There are two types of models. One is called a feed forward network and another is called a Recurrent network. DL uses labeled datasets to automatically create such a classifier for AD prediction for image classification. A general view of a neural network is represented in figure 3.1, multiple signals are taken as inputs in which they are combined in linear form then by using weights and it passes those input signals by non-linear operations to generate the output signal.

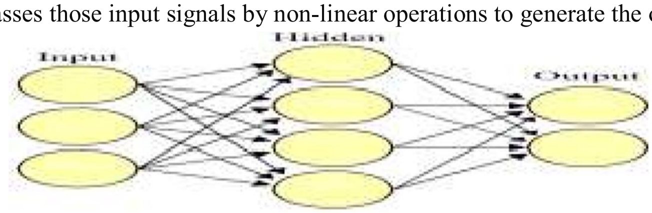

Figure 3.1: General view of neural network architecture [29]

DL is a flexible approach, in which the same model can have the combination of different architecture and manipulating a range of hyper parameters [29]. DL generally have more than two levels of abstraction and representation to help understand sound, text, and image data[6] It can be classified into two sections generative and discriminative architecture as shown in figure 3.2 Generative architecture can be partitioned into the four sections of Recurrent Neural Network (RNN), Deep Auto- Encoder (DAE), Deep Boltzmann Machine (DBM) and Deep Belief Networks (DBN) whereas discriminative architecture can be divided into Convolutional Neural Network (CNN) and RNN.

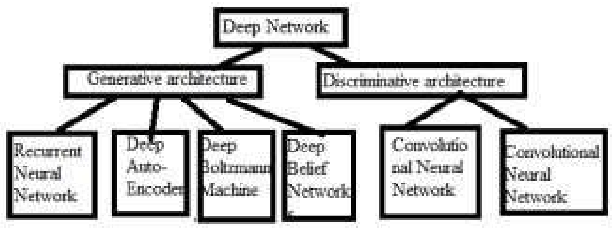

Figure 3.2: Generative architecture of Deep Network

The application of deep learning to early detection and automatic classification of Alzheimer's disease (AD) has recently gained appreciable attention, as rapid progress in neuroimaging techniques has generated large-scale multimodal neuroimaging data.[30]

3.1 Deep Learning Techniques Used

Suk et al.[1] Propose a deep learning-based feature representation with a stacked auto-encoder. The author believes that there exist latent complicated patterns, e.g., non-linear relations, inherent in the low-level features. Combining latent information with the original low-level features helps build a robust model for AD/MCI classification with high diagnostic accuracy. Experiments conducted using the ADNI dataset showing that the proposed method is 95.9%, 85.0% and 75.8% accurate for AD, MCI and MCI-converter diagnosis respectively.

[2] Proposed a novel method for the early diagnosis of AD and MCI based on deep learning which contains stacked autoencoder and softmax output layer. AD diagnosis is carried out as a multi-class classification task with minimal prior knowledge dependency in the model optimization to reserve the synergy between data modalities. It also performs dimensionality reduction and data fusion at the same time. A performance gain was achieved in both binary and four-class classifications. The proposed method classifies the patients into AD, MCI, and NC category with an 47.42 % accuracy.

The combination of a traditional machine learning algorithm for classification and stacked auto-encoder (SAE) for feature selection gives accuracies of up to 98.8% for AD classification and 83.7% for prediction of conversion from mild cognitive impairment (MCI) to AD. Deep learning techniques such as convolutional neural network (CNN) or recurrent neural network (RNN) without pre-processing for feature selection have yielded accuracies of up to 96.0% for AD classification and 84.2% uses neuroimaging data for MCI conversion prediction. The classification performance will be improved when multimodal neuroimaging and fluid biomarkers were combined. [30]

Represents a study by using a volumetric convolutional neural network (CNN) model for four binary classification tasks (AD vs. normal control (NC), progressive mild cognitive impairment (pMCI) vs. NC, stable mild cognitive impairment (sMCI) vs. NC and pMCI vs. sMCI) based on magnetic resonance imaging (MRI) and visualizes its outcomes in terms of the decision of the CNNs without any human intervention. In the proposed technique convolutional auto-encoder (CAE) based unsupervised learning for the AD vs. NC classification task and supervised transfer learning is applied to solve the pMCI vs. sMCI classification task. To detect the most important biomarkers related to AD and pMCI a gradient-based visualization method that approximates the spatial influence of the CNN model's decision was applied. For validation of results, ADNI database is used and the results verified that the proposed approach achieved the accuracies of 86.60% and 73.95% for the AD and pMCI classification tasks respectively. [28]

Garam Lee et al.[31]applied deep learning technique, a multimodal recurrent neural network for prediction of conversion from MCI to AD . Multiple Gated Recurrent Units (GRUs) are applied to use longitudinal multi-domain data and all subjects with each modality data. Better prediction accuracy of MCI to AD conversion is achieved with the help of longitudinal multi-modal data.

Jong Bin Bae et. al. Developed a convolutional neural network (CNN) based AD classification algorithm using magnetic resonance imaging (MRI) scans from AD patients and age/gender-matched cognitively normal controls from two populations that differ in ethnicity and education level. These populations come from the Seoul National University Bundang Hospital (SNUBH) and ADNI. CNN's on five subsets using coronal slices of T1-weighted images trained for each population that cover the medial temporal lobe. Models are evaluated on validation subsets from both the same population, models achieved average areas under the curves of 0.91–.94 for within data set validation and 0.88–.89 for between data set validation. The mean processing time per person was 23–24 s.

According to recent research, deep learning is promising for the analysis of brain MRI and can overcome the issues associated with the earlier state-of-the-art machine learning algorithms. Brain MRI analysis using computer-aided techniques has been difficult because of its complex structure, irregular appearance, imperfect image acquisition, non-standardized MR scales, imaging protocol variations, and presence of pathology. Hence, more generic methods using deep learning are preferable to manage these vulnerabilities [33]

IV. Conclusion

In this work major machine learning techniques, as well as deep learning techniques are analyzed. This helps researchers working with any of these techniques on Alzheimer. As per this survey SVM based models have been used widely for detection and prediction of Alzheimer showing its robustness. When the task requires long sequences of input to be processed training an RNN is difficult whereas GRU works well for each modality of data to process multiple time points of the input. The classification performance will be improved when multimodal neuroimaging and fluid biomarkers were combined. Multimodal CNN, multi-class classification, binary classification based on deep neural network models achieved better accuracy. Deep learning and ensemble methods give favorable result when applied on highly complex data.

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