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Exploring the methods on early detection of Alzheimer's disease

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Abstract*:** ***Alzheimer's disease (AD) is a disorder which is said to be irreversible and affects the behavior and cognitive processes which will eventually affect the memory. This disease beget difficulty in performing the daily task of a patient. It is one of the most common form of dementia affecting people above the age 65 and the risk increases with age. The treatments currently available can only mitigate AD progression but there is no treatment to stop this progression. To bring down the progression of AD early detection becomes necessary. Researchers have found that many machine learning (ML) methods have been useful in detection of AD. Machine learning is a part of artificial intelligence involving probabilistic and optimization techniques such as neural networks that prepares pc's to gain a model from complex datasets. This paper Scrutinizes the developments taken in the field of ML for the possibly early diagnosis of AD. It discusses about various approaches used in recent times for the detection of AD at an early stage. Through this research we found several classification methods such as Recurrent neural networks(RNN), Convolution neural networks(CNN), many more binary and multiclass classifiers along with various methods of preprocessing steps involved in the detection of AD. This paper also throws light on the datasets being used and how these preprocessing steps and different classifiers attribute to increase of accuracy in prediction of AD. Finally, coming to the objective of this paper is to analyze and evaluate these different techniques of ML contributing for the detection AD as early as possible and also to help the researchers to get maximum information and comparison of techniques in one go.

Keywords* : *Magnetic Resonance Imaging(MRI), Preprocessing, Feature extraction, Classification, Alzheimer's Disease(AD), Machine Learning(ML), Mild Cognitive Impairment (MCI), Alzheimer's Disease Neuroimaging Initiative (ADNI), National Alzheimer's Coordinating Center(NACC).

I. INTRODUCTION

Alzheimer's disease(AD) is a neuro-degenerative disease also called as dementia. It is a condition where functioning of the neurons in the brain stops and even loses the connection with the other neurons of the brain and eventually die. From studies it is revealed that it occurs to in the people of age 65 or in early 40's to 60's. The symptoms of AD include memory loss, difficulty in speaking, degradation in thinking ability and judgment, change in personality and behavior. The actual causes of AD are unknown, but research shows that it is due to problems with brain proteins that do not function usually, interrupts the functionality of brain cells (neurons) and make way for a series of events toxic to the patient. The main proteins that causes AD are Beta amyloid and Hyper phosphorylated tau. It might also be caused due to genes that are linked to AD. In 2017 research, an approximate of 5.4 million were found to live with AD and according to studies of NACC in America. It was found that AD to be leading causes for death in the United states[4]. To the patient who has been detected to have AD, it is observed that over a long period of time, condition will progressively deteriorate. It has been estimated that if any treatment or prevention method is not discovered, the treatments of people with AD and other dementia's would approximately cost about 1 trillion by end of 2050 in United states[13]. There are lot of approaches which have been found to focus on early prediction at individualized level which varies with respect to patients and changes over time. Therefore, by understanding the way in which AD progress on each individual patient for duration of certain time period is the key to the enable early prediction of AD and to provide health care services accordingly in an effective manner.

Predicting it at an early stage becomes very prominent for the following reasons:

- If predicted at early stage then access to different treatment options become easier.
- Provides an opportunity to participate in clinical trials.
- The support programs and related resources can be accessed.
- Cost of treatment can be reduced.

II. RELATED WORKS

The following papers were studied as a part of the survey on detection of AD at early stages. In paper [22] MCI patients were diagnosed who had 2 to 5years of carry out time and it has observed that the effects on performance in prediction of volumetric MRI measures at baseline is considered to be involved in AD, includes the entorhinal cortex and hippocampal volumes. Prediction has been valuated based on the sensitivity, specificity and Area Under the ROC curve (AUC) in the considered data set of 248 MCI patients for about period of 5years. The comparison studies of performance that includes measure of sensitivity in the MCI stage which converted before 2years.

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The ones converted after time of 2years implies that the stable MCI of about 23 at 2years had progressed in the next 3years. The study also shows that the MRI volumetric measures are efficient in prediction of conversion from MCI to AD, the better specificity and accuracy was found as follow up time increased.

The combination of entorhinal cortex volumes and hippocampal region has resulted higher accuracy for 5year follow up timeline (AUC=73 at 2years vs AUC=84 at 5years), as well as for specificity (56 vs. 71). Totally, their performance of proposed classifier model was in accordance and comparable with that of other ML classifier models for the same follow up times.

In paper [1], it foretells how MCI is converted to probable AD, they have approached using a deep learning method and multimodal RNN (Recurrent Neural Networks). A combined framework has been developed that includes not only longitudinal cerebrospinal fluid (CSF) but also includes cross-sectional neuroimaging and the biomarkers obtained from the ADNI database. The given framework has combined longitudinal multi-domain data. The obtained outcome of their prototype for MCI transforming to AD gave up to accuracy of 75 when single modality of data was used and when the longitudinal multi-modal data was considered, about 81 accuracy (AUC=0.86) was achieved for the performance of the prediction model. This appeal has potential to find people at risk of getting AD and such individuals can get most benefit from a clinical trial. The authors of the paper[5] have investigated how to prognosticate AD growth for a patient from their next clinical visit using clinical data. Data taken by NACC is used for examination. Their approach of Long short term RNN reckon on an upgraded “many-to-one” RNN network to brace the shift of time lapses. consequently, this method could very well be dealt with patient's different visits at irregular time gaps. From the obtained upshot, it shows the suggested model was able to predict patient's AD progressions on their following visits with total accuracy by 99, by outranging the traditional methods. Thus the prognosis problem of the AD progression can be solved by Recurrent Neural Networks effectively by considering the temporal lobe region and the patients periodic or historic visits. In the paper [3], Longitudinal 3D MRI scans which were T1 weighted were acquired from a ADNI database which comprises of totally 403 subjects, which includes 79 normal, 50 preclinical AD (PreAD), and 274 MCI. Amyloid CSF (< 192 pg/ml) are best measures to establish diagnostic categories. If amyloid is found negative then, the individuals were defined as cognitively unimpaired normals and PreAD otherwise. If amyloid positive, then it is defined as MCI/AD group. SPM12 has been used to perform longitudinal morphometric analysis which helps in finding Jacobian determinant maps. In order to foresee how much of abnormal amyloid levels is present in cognitively unimpaired individuals an Machine Learning classifier called longitudinal voxel-based classifier was used on the Jacobian determinant maps. By using receiver operating characteristic curve analysis the performance of the classifier is evaluated. The false positive rate vs true positive rate i.e., Area Under the Curve(AUC) of 0.87 is achieved by the longitudinal voxel-based classifier.

In the paper[2], the relation between pathophysiological changes and MRI scans of patients with AD is taken as main point of research. The amyloid and tau factor distribution indicates propagation of the Alzheimer's disease and it follows a unique sequence which be used to track brain pattern changes from MRI scans. In the population which is progressing from MCI to AD, Entorhinal cortex and Hippocampal(HC) atrophy contains few predictive value that manually defined HC volume which alone was found to predicted the conversion to AD from MCI (60 accuracy), and the prediction accuracy increased with the addition of the clinical data to 78.8. The other major predictor of conversion from MCI to AD was found to be the medial temporal lobe. An overall predictive accuracy got was found to be relatively low as per results from the paper. The prediction in progression was also found from the whole brain MRI and the ventricle volume. The non-focal changes can also be observed from structural MRI(sMRI) which can be indicators of early signs of AD. By using ML approaches can be used on changes in the temporal lobe which has the predictive value for the development of AD. Classification been done using sMRI data[18]. For this purpose, different dimensionality reduction techniques and different ML approaches were used. Some biomarker data is observed and collected before diagnosis of AD, while few other data is considered to be basic indicators of Alzheimer's disease. Dimensional reduction of the dataset is done and Tree based classifying methods including random forests and SVM have resulted in promising classification accuracies. To the standardized ADNI MRI dataset some major ML algorithms such as decision tree and rule-based ones, and also neural networks were applied. Classifying algorithms like Random forests, SVM, and recently evolved deep neural networks have shown good performance in classifying Alzheimer's patient data. In the future the model can be developed for no or little dimensionality reduction. The Random forest approach to predict AD[4], shows that there are some missing or irregularly sampled data from the time-dependent data being collected for the study of Alzheimer's disease. For this reason, the pre-processing step can't be applied directly since the time series methods assumes regular sampling. Random forest classifier has been applied on the data points to evaluate the dependencies between pairs of data at different time separations. The input data consists of demographic, genetic data and also a vector of time series history. They have used the TADPOLE grand challenge data for testing. Above cited paper has concentrated on prediction diagnosis of normalized ventricles volume. The area under the curve (AUC) was found to be 0.82 and classification accuracy of 0.73 were obtained in the paper when compared with a SVM classifier which gave an accuracy of AUC=0.62 for the diagnosis. The paper [20] analyses different machine learning strategies for early diagnosis of AD. The datasets can be accessed from two databases namely ADNI and OASIS database for the study of classifiers. The OASIS dataset which includes 416 subjects between 18 and 96 years of age were considered for the study. ML strategies are categorized as supervised and unsupervised techniques. In many of the Alzheimer’s research linear regression curves are used for early diagnosis and for predicting progression of AD and K-means clustering in unsupervised type. The classification of MRI images using ML algorithm involved several steps involving pre-processing followed by image segmentation. Later feature extraction and selection is done to select necessary features.

The performance is analyzed based on classifier sensitivity, specificity and accuracy in prediction of AD. Based on the results obtained it was concluded that the accuracy of SVM was 97.6 and was found to give best performance compared to other classifiers.

Deep Learning for Prognostic Prediction has been used in the paper[21], CNN and RNN which are deep learning approaches has been evaluated. The performance of classification is computed using back-propagation procedure. Using which the error is calculated as a difference between the network output and expected output. The error is computed repeatedly with different weights. The weights are continuously monitored and updated till the error/differential value becomes zero. Performance comparison was also done for different neuroimaging techniques which showed that prediction of progression to AD was better done when PET data was considered instead of MRI scans. The performance comparison was also done for deep learning algorithms indicating that hybrid approaches yielded better results. 3D CNN model using the data with PET scans showed better performance in prediction of Alzheimer's disease. The hybrid approaches showed accuracy's ranging upto 98.8 while the deep learning approaches showed accuracy's of up to 96.0 and 84.2 for AD classification and prediction algorithms respectively. For the study of AD extending 2D CNN to 3D CNN was found to be important since it deals with multimodal neuroimages and gives better performance.

Multistage classifiers[19] gives a better performance in terms of classification and prediction compared to individual performance of prediction classifiers like naïve bayes, KNN and SVM. The proposed model has two folds of work. One model to distinguish between MCI and AD. The other model develops a multistage CAD system and to study the performance. The biomarkers are also made use for the detection. Based on the biomarker selected, the multistage classifier is modeled using combination of KNN, naïve bayes and SVM classifiers for AD detection. In the design of the multistage classifier, the first stage included the classification of the image input whether it belongs to AD/MCI or CN using Gaussian naïve bayes classifier. The second stage consisted of SVN and KNN classifier which classified the input MRI data based on the results of the first stage of classification. It has been found that the thickness features represented stages of disease better than that of volume features. It was also found that the features selected using PSO actually showed improvement in the performance for detection of MCI/AD. The AD detection performance was also increased by the thickness features. The better performance was observed because of combining the biomarker data along with the sMRI and concludes that, to build a multistage classifier, the most important step would be selection of the first stage classifier.

III. RESULTS

Result comparison of different research papers is shown in Table-1 where all the methods used in different paper on early detection of Alzheimer's disease is discussed. We can see that paper "Predictive Modeling of the Progression of Alzheimer's Disease with Recurrent Neural Networks" has given the best result with accuracy of 99.06% using long short-term memory RNN.

In paper "Multistage classifier-based approach for Alzheimer's disease prediction and retrieval" has conferred that a multiclass classifier which includes SVM, KNN, PSO and Naive Bayes classifier has worked well in the early detection of Alzheimer's with accuracy of 96.3%. These results show that the early detection of Alzheimer with high accuracy is achievable.

IV. CONCLUSION

In recent reports by Alzheimer's Association, sharp increase has been witnessed in Alzheimer's prevalence, deaths and the costs of care. Machine Learning is one of the ways in which the data can be successfully analyzed, patterns can be detected and appropriate actions can be taken. In this paper, many Machine Learning algorithms were selected and reviewed. Accuracy and efficiency of different algorithms were discussed. Different algorithms have used appropriate datasets for analysis. The sensitivity provided by these algorithms seemed to have helped in the successful classification of the data[6]. Many ongoing researches is concentrating on the enhancement of the Machine Learning algorithms, how to add more data to the system, also concentrating on the enhancement of the segmentation tool and how to assess the classification result. It is observed that cognitive assessment shows highest accuracy and multi-modal approach has high accuracy when the demographic data is used[1]. 3D MRI scans considered without dimensionality reduction is observed to have highest accuracy but found to be economically unreliable[10]. Random forest classifier showed better accuracy compared to SVM classifier and can be used over time-varying data. Amyloid beta and tau species were considered as major biomarkers that contribute for prediction of Alzheimer's[4]. Summarizing all these observations and discussions it can be concluded that using combination of brain imaging data, genetic information and demographic data, neuropsychological test results, cerebrospinal fluid biomarkers like amyloid beta and tau species as input to the efficient classifiers like random forest classifiers, can result in very high predictive accuracy.

Table- I: Results Comparison of Various research papers on early detection of Alzheimer's Disease

Name of the author	Dataset	Method used	Subjects considered	Modality	Classifier	Accuracy	Area Under the Curve(AUC)
Garam Lee, et.al, 2019[1]	ADNI	Integrative approach for MCI and AD prediction using Deep learning approach.	CN – 415 sMCI – 558 pMCI – 301 AD – 338	Longitudinal CSF, Cross section neuroimaging biomarkers, cognitive performance biomarkers	Multimodal recurrent neural network	Single modal data - 75% Multimodal data – 81%	Single modal data – 0.83 Multimodal data – 0.86
Tingyan Wang, et.al, 2018 [5]	NACC	LSTM RNN is different from traditional RNN that allows temporal information to get passed periodically.	5432 patients with possibility of AD from Aug 2009 to May 2017	Demographic data, CDR scale, GDS and MMSE	Long short term memory(LSTM) RNN	99.06%	-
P J Moore, et.al, 2019 [4]	TADPOLE grand challenge based on ADNI	Classification and prediction based on relationship between pair of data points at different time separation .	LB1 – 1627 LB2 – 110	Structural MRI	Random forest	73%	0.82
Moscoso, et.al, 2019 [22]	ADNI 1	Prediction beyond the short term i.e., from 2 years to 5 years.	NC – 124 AD – 124 sMCI – 134 pMCI – 89	MRI	Logistic regression	-	73% at 2 year 84% at 5 year
K R Kruthika, et.al, 2018[19]	ADNI	Multiclass classification technique	AD – 178 MCI – 160 NC - 137	MRI	Naïve bayes, SVM, KNN	SVM+KNN = 81.6% NB+SVM+KNN = 90.47% NB+SVM+KNN+PSO = 96.31%	-
Paula M. petrone, et.al, 2019	ADNI	Longitudinal morphometric analysis	NC – 79 PreAD – 50 MCI – 274	Longitudinal 3D MRI	Longitudinal voxel based classifier	-	0.87

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