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Review on Early Detection of Alzheimer's Disease using Neuroimaging Techniques

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Abstract: ***Alzheimer's disease (AD) is the most common form of dementia. AD begins slowly, where it first involves a part of the brain that controls thought, memory, and language. Names and incidents are things that initial stage AD patients have a hard time remembering. Early detection of AD is very crucial for further aid and treatment. This paper presents a review and analysis of the different methods employed to detect AD or mild cognitive impairment (MCI). Machine learning, neuroimaging, and deep learning neural networks are few of the techniques which are compared and analysed based on their performance and accuracy. Each model is critically analysed and provided with limitations, advantages, and best application.***

Keywords: Alzheimer's Disease; Machine Learning; SVM; Neuroimaging Techniques; MRI; SPECT; PET

I. INTRODUCTION

Alzheimer's disease is the most common form of dementia which causes degeneration of brain cells. It is characterized by a progressive decline in cognitive function. Alzheimer's disease is caused by the formation of abnormal deposits of protein in the brain. These are called tangles and plaques and they are made up of two key proteins which are tau and amyloid previously present in healthy brains, but in Alzheimer's disease, they function abnormally. plaques are formed outside the cell and tangles are formed inside it due to amyloid and tau. This damages the nerve cells causing them to die and leads to the shrinking of the brain. The hippocampus is the first area of the brain to be affected and plays a vital role to form memories. Due to this Alzheimer's patients have trouble making memories, and struggle to remember the tasks they performed and usually repeat themselves in conversations. There are 50 million new cases of people suffering from dementia every year, Where Alzheimer's disease is the best understood and most common. According to the WHO, treating and caring for people with dementia costs more than US$ 604 billion per year.

Early detection of Alzheimer's is important as it would first allow the recruitment of individuals in clinical trials and testing, which suggest some change in lifestyle and attention towards health. People with mild cognitive impairment and early stages of Alzheimer's can be cured by medication in the early stages. It is expected that the treatment is more effective at an early stage, whereas when detected in the later stages. It is suggested to detect Alzheimer's in the early stages as the patients are found to live with the disease for several years once the symptoms are identified. Alzheimer's leads to other problems like diabetes and heart problems when adequate attention is not provided in the early stages The brain-imaging technologies used to test Alzheimer's are Magnetic resonance imaging (MRI) which uses powerful radio waves and magnets to create a view of the brain, Computerized tomography (CT) a scan which uses X-ray to obtain a cross-section of the brain and Positron emission tomography (PET) scan which uses a radioactive substance to detect substances in the body.

Machine learning can process data beyond human capabilities. It is extensively used in healthcare systems to provide clinical insights and aid for further care. This has been advantageous as it reduces costs, early prediction, better outcomes, and faster aid. Machine learning algorithms play an important role in the detection of Alzheimer's disease in a patient. But due to some problems like imbalance of events with attributes where few instances and too many attributes are observed, the use of pathologically unproven data set, class imbalance, overtraining, and lack of external testing or validation has provided some restriction towards prediction methods. This paper reviews the studies which aim to provide efficient and early detection of Alzheimer's disease to benefit the patients.

II. MACHINE LEARNING

Artificial intelligence has played a major role in revolutionizing the medical industry in the past few years. Machine learning which is a major segment of artificial intelligence has proved to be extremely essential in

diagnosing and predicting advanced diseases. Machine learning algorithms split the available data into test and train data and the system learns from the train data. It then uses this past learning experience to classify the given event. There are various machine learning algorithms, each designed for a certain type of dataset and classification problem, using such algorithms for a different situation may lead to unsatisfactory results.

The two major types of learning are supervised and unsupervised learning algorithms [6]. Supervised learning is used when the data set available for the machine to learn and create a model to map the provided input to the required output. Whereas unsupervised learning is majorly used in areas where machine learning employs self-learning on unclassified and unlabeled data. The most commonly used machine learning algorithms to detect the onset of Alzheimer's are methods such as linear program boosting method (LPBM), linear discriminant analysis (LDA), support vector machine (SVM), and support vector machine recursive feature elimination (SVM-RFE). Before applying the detection techniques on the neuroimages, image processing is done on the obtained MR and PET images of the subject. The anterior and posterior commissure is accomplished and intensity inhomogeneity is corrected. Later the obtained images are classified into different regions such as grey matter, white matter, and cerebrospinal fluid. On further processing, various regions of interest are given as input for the detection algorithm.

III. NEUROIMAGING TECHNIQUES

The reviewed papers have used the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. This is used for clinical testing and to develop newer treatments and efficient solutions. It is also used to further aid research based on different models and testing. Many co-investigators from a wide range of private corporations and academic institutions, and subjects across America and Canada were recruited to develop the ADNI database.

Parameters like blood biomarkers, PET and MRI images, cognitive tests, genetics, and CSF are used as predictors of the disease. The goals of the dataset include early detection of Alzheimer's also known as the pre-dementia stage and using biomarkers to check the on-going progression rate. There are a set data sharing policy and standardized protocols for comparing results from diverse centers which makes all the data on ADNI qualified for research worldwide.

A. MRI

Magnetic resonance imaging is a widely used procedure to generate detailed images of organs or tissues in the human body. It is a non-invasive and painless procedure that uses magnetic fields and radio waves to obtain a comprehensive cross-sectional image of internal organs. According to the author Daoqiang Zhang [1], 1.5T scanners were used to obtain the used MRI images. There are subtle gradient linearity issues observed which create spatial distortions and blurs the edges of the MR image. Various image processing techniques are used by the manufacturers to correct the spatial distortions. The quality of MRI is improved after correcting spatial distortion due to gradient non-linearity and B1 field inhomogeneity.

B. SPECT

Single-photon emission computerized tomography (SPECT) provides the 3D images of the required organs for diagnosis. Tracer is a radioactive material used for SPECT scanning. The Tracer is injected into the subject's bloodstream. The signals are picked up by the radioactive tracer which is later converted into 3D images by the computer. According to R. Chaves [3], the subject is injected with gamma-emitting technetium- 99 m labeled ethyl cysteinate dimer (99mTc-ECD) radiopharmaceutical and the SPECT scan is acquired by using a 3-head gamma camera Picker Prism 3000. Filtered backpropagation and a Butterworth filter are used to obtain reconstructed images of the brain. Spatial normalization is obtained by using statistical parametric mapping to confirm that a particular sub volume region of interest is the same in all the anatomical positions.

C. PET

Positron emission tomography uses a special dye that contains radioactive tracers which when detected by the scanners, helps examine the required tissue. Certain regions of the brain have higher chemical activity during the onset of diseases such as Alzheimer's. The regions with higher chemical activity are collected by the tracer. Bright spots in the PET scan show the region in the brain with high chemical activity. PET scans are usually acquired after 30-60 minutes after injection. Various processing operations such as spatial alignment, intensity normalization, and interpolating to standard voxel size is done on the obtained PET scans. R. Chaves [3] uses an FDG-PET scan which is a sub-type of PET scan, where PET scans use the molecular binder to highlight tissues but in FDG PET, fluorodeoxyglucose is used as a binder.

D. fMRI

Functional MRI is widely used to quantify brain activity based on the amount of blood flow. It is observed that the blood flow is increased to the region of the brain which is in the active state. It can be inferred that the working of fMRI is based on the interlink between cerebral blood flow and neuronal activity.

It is also noted that certain subjects with brain pathological conditions prove to be more difficult when it comes to FMRI scanning and analysis as certain conditions lead to unexpected neuronal activity in the brain and change in the cerebral blood flow.

According to Mohammad Ali Oghabian [11], fMRI has been used to detect impairments in the visual cortex region, impairment in learning ability, and decision making tasks. The test made on Alzheimer's patients using FMRI revealed that during resting state activation size and intensity of the Prothrombin complex concentrate region is

smaller than healthy patients. Research has been going on using fMRI to not just detect Alzheimer's but also predict it.

E. CT

Computerized tomography (CT) makes use of rotating X-ray machines and complex computerized arrangement to obtain detailed cross-section images of the tissues, bones, and various parts of the body. During a CT scan [1], continuous X-ray images are captured which are then processed to form 3D images of the region of interest. It is sometimes combined with a PET scan to obtain a wider range of information. The anatomical information is procured using the CT scan whereas the function information is taken from the PET scan which enables to rightly rule out other causes of dementia or tumors. Features such as loss of gyral volume, enlargement of cerebral sulci, and dilation of the ventricle can be observed in the CT scan.

IV. NEUROIMAGING ANALYSIS

There are four ways [5] that can be used to predict the onset of AD, they are - Hierarchal, Cognitive Impairment, genotype, and age. The organization and development of AD data will be pertinent in recognizing the individuals who are under the shroud of it. A conclusive diagnosis of AD is built on post mortem analysis where they check for pathological damage or abnormal change in the tissue of the brain. These results turn out to be deposition of b-amyloid in the form of blood vessel deposits, extracellular senile plaques, synapse dysfunction and loss. Research has shown that AD is developed in stages over many years before the actual arrival of Alzheimer's and is not instantaneous.

Firstly, the hippocampus gets affected which then spreads to the amygdala and then to the entorhinal cortex and finally attacks the Para hippocampal gyrus. Neuroimaging has been able to detect brain signature of AD parallel to standard elderly controls. It has also been able to transform AD diagnosis from other neurodegenerative diseases and has been able to successfully attain longitudinal imaging studies of disease progression. MRI research in AD patients has shown that there is a comparable pattern between deceased AD patients and patients on the onset of AD, which is the cortical atrophy that comes in stages and accumulates. MRI has been successful in proving that high entorhinal cortex and hippocampal atrophy are congruous in not severe AD patients. As AD comes in stages, neuroimaging can be used to speed up the treatment process and prevention process by detecting the onset of AD in risk patients. Neuroimaging is done to people if their family is prone to AD; where research has shown that the members have more than 50% chance of developing AD. Another way is to read the MRI records of normal aged people who are susceptible to AD.

AD can be developed through hierarchy; through mutations of three genes which are amyloid precursor protein (APP) and presenilin (PS-) 1 and 2 genes. MRI scans of "suspected" AD patients showed that the mutation in genes was already in the process along with parietotemporal, posterior cingulate, and frontal cortex hypometabolism and mild atrophy. Many members of AD prone families were already victims of dementia and the studies illustrated a rapid and belligerent development of brain damage. People suffering from mild cognitive impairment are not always prone to AD, some portion of MCI patients regress to their former selves whereas some affected by mild global and regional atrophy and hypometabolism develop AD, which can be predicted using MRI-PET scans along with check-ups in cordial regions, as cortical regions are of utmost important in differentiating AD and MCI.

Abnormal cortical activities may lead to MCI transforming into AD. Longitudinal MRI and FDG-PET research in mild cognitive impairment were congruous in illustrating that the surplus atrophy/hypometabolism are related with incipient AD, and can be predicted and detected before the onset of AD with accuracies orbiting between 75% to 100%.

MRI along with FDG-PET research have inspected the effects of inbuilt genetic risk factors for sporadic AD, which include Apolipoprotein E. Subjects who carried E4 illustrated low metabolism rates and higher atrophy in the same spots where AD patients were showing. These abnormalities were seen before the development of cognitive problems. These patterns are very similar to the development stages of AD and have a high chance to morph into AD under severe circumstances.

V. LITERATURE REVIEW

Wide range of research has been made on classification of neuroimages using machine learning techniques to detect Alzheimer's disease. This section reviews and compares the work of most commonly used methodologies.

A. Support vector machine

The research by [1] is based on using multiple modalities of biomarkers for brain atrophy measurement, functional imaging for hypometabolism quantification, and cerebrospinal fluid (CSF) for quantification of specific proteins. According to [1], A comparison of multimodality methods kernel combination is done with the single modality approach to discriminate between AD (or MCI) and healthy controls Subjects with the baseline data of MRI, PET, CSF are used which constitute up to a total of 202 subjects including 51 AD patients, 99 MCI patients consisting of 43 MCI converters who had converted to AD within 18 months and 56 MCI non-converters who had not converted to AD within 18 months, and 52 healthy controls. The atlas warping algorithm is used on MRI and FDG-PET where 93 volumetric features are extracted from the 93 regions of interest (ROIs). For each of the 93 features in MRI, the volume of GM tissue in that ROI region is computed as a feature. For PET image, alignment

is done for the same MR image, and using a rigid transformation average intensity of each ROI region in the PET image is computed as a feature. For CSF biomarkers no feature extraction is done and values are directly considered of a total of 3 features.

The method proposed combines multiple types of data such as numeric data, string, and graph in contrast to other combination methods that process only one kind of data. SVM classifier is used for high-dimensional pattern classification which is embedded with the multiple biomarkers (MRI, CSF, and PET) to discriminate between AD (or MCI) and healthy controls. In SVM, mapping of linearly non-separable samples is done to higher or infinite space where they can be separated linearly through a kernel-induced implicit mapping function. Further, the maximum margin hyperplane is obtained in space. This SVM model is further used to integrate the multiple model biomarkers (MRI, CSF, and PET) to classify AD and healthy controls. Classification accuracy, as well as the sensitivity and the specificity, is computed using the 10-fold cross-validation strategy. A comparison of results is done with the multi-modality approach and methods using each modality only. The combined measurements of MRI, PET, and CSF consistently achieve more accurate discrimination between AD patients and healthy controls.

Further according to [1], classification accuracy of 93.2%, a sensitivity of 93%, and a specificity of 93.3% are obtained for a multimodal approach while the best accuracy on individual modality is only 86.5% (when using PET). Classification of MCI from healthy controls, multimodal classification method achieves a classification accuracy of 76.4%, a sensitivity of 81.8%, and a specificity of 66%, while the best accuracy on individual modality is only 72% (when using MRI). It can be efficiently concluded from the results that the multimodal system proves to be more efficient when compared to the individual modality. There are many advantages in the method used compared with the direct feature concatenation method, it provides a unified way to combine heterogeneous data when a different type of data cannot be directly concatenated; it offers more flexibility by using different weights on biomarkers of different modalities. Further research extends to the usage of both baseline and longitudinal data to predict the conversion from MCI to AD by finding the spatiotemporal pattern of brain atrophy in multiple modalities. Usage of more modalities like APOE is further checked for better results. This aims to provide better results altogether overcoming all parameters.

The author Christian Igel [2], states the importance of assessing the texture of the hippocampus through MRI biomarkers. Hippocampus is a major region of interest when detecting AD as it is not only one of the first affected regions but also one of the drastically affected regions. Static hippocampus volume, shape, and its changes with time are used as MRI biomarkers. A textural analysis is executed over some time and the textural changes in the hippocampal structure of a healthy human are found differentiable from that of an AD patient. The paper also uses textural studies to find changes in glucose metabolism in FDG-PET scans. The paper uses datasets from the ADNI database. They have used MRI images of 504 patients and classified it into 3 required datasets where the first dataset is for diagnosis and the other two are for prognosis. 281 subject's data are obtained for CSF measurements from ADNI. the paper has used log(t-tau/Aβ1-42) along with MRI biomarkers.

AIBL data of 141 subjects taken over a period of 18 months and metropolis data is used. Pre-processing includes bias field correction and intensity normalization. To obtain the bilateral hippocampal texture score, they use texture descriptor and SVM. the descriptor majorly consists of 3D histograms which are rotation invariant and multiscale Gaussian derivative-based filters. The paper says that both conformation and filtering are linear processes and hence their combination will result in a linear process as well. To remove noise, the hippocampal surface is removed by the means of morphological erosion. Soft margin SVM with the radial Gaussian kernel is used as a classifier with 20-fold cross-validation. SVM provides a single texture score that divides AD patients from CTRL. The model achieves an accuracy of 85.6% on the ROC curve. The paper optimizes markers based on AUC. The paper also achieves a prognostic AUC of 0.74. in discriminating CTRL from AD concerning texture, an AUC of 0.912 was attained. Whereas, for volume, it was 0.909.

The paper further uses logistic regression and combines both texture and volume to obtain an AUC of 0.915. Using logistic regression over CSF and MRI datasets, they have achieved an AUC of 0.932 for CTRL vs AD. The FDG-PET scans are used to find that there exists a negative correlation of -0.57 for texture and -0.54 for volume, which shows a degrading glucose metabolism and deterioration in the hippocampus. It can be concluded that hippocampal texture and volume show the visible difference between AD and CTRL patients and have been separated with effective efficiency using logistic regression and SVM models.

B. AR mining

The author Chaves [3] has used AR mining to detect AD patients from the association of the attributes between SPECT and PET functional images. The paper computes the fisher discriminant ratio (FDR) which denotes the relationship between discriminant areas in the brain. Medical imaging has been a challenging field for AR mining. To execute content-based retrieval of images, firstly the dimensionality is reduced and the similarity between queries is improved. The paper uses Computer-Aided designing and AR mining to differentiate AD patient's neuroimages from normal patients. The patient is given a feature vector that has the region of interest which is computed using FDR and Activation estimation. The database used is obtained from ADNI. This paper used

SPECT data of 97 patients in which 42 were normal and 55 where AD patients. They used PET scans consisting of 75 normal and 75 AD patients making a total of 150 patients.

The paper uses AR-based mining to segregate the AD patients from normal patient's SPECT/PET database. The process uses two major factors which are S%- support, which is the frequency of the rule and C%- confidence, which is the strength of the relation between two sets. The paper extracts and analyses the discriminant AR.FDR masking is accomplished to obtain a discriminant capability and reduce computational cost.

The paper sets the FDR threshold to be 0.2 for dimensionality reduction and good classification. The size of the block and the step size which is the number of voxels between different blocks is used to divide the images. It is found that the location of one block is overlapped with adjacent blocks. the block is said to be activated if the ratio of the number of activated voxels is greater than the threshold.

The model consists of two phases, training and testing phase. ROI extraction, FDR, and AE followed by AR mining takes place in the training phase. The paper designs the system to mine AR for control/ normal subjects as the pattern in them is less variable. About 67860 rules are obtained for SPECT and 7482 for PET databases. Support and confidence must exceed the set threshold for correct classification. In the model used, the threshold is set close to 100% to obtain well discrimination. Further, in the testing phase, the mined rules are used on the subjects and they are checked for the number of times they exceed the threshold.

The accuracy obtained for the SPECT database is 92.78%, sensitivity is 100% and specificity is 87.5%. For the PET database, the accuracy obtained is 91,33%, sensitivity is 100% and specificity is 82.67%. It can be observed that the reduced number of rules for the PET section has created a trade-off in the specificity. In conclusion, the paper states that the model proves efficient as it reduces the complexity of decision rules. The masking of brain regions using FDR plays a major role in decreasing complexity and computational costs and thus achieving impressive accuracy.

C. Conditional Restricted Boltzmann Machine

The paper [4] briefs about the inability of previous approaches to providing personalized medicine for AD with the help of machine learning. The reason for the failures being the lack of ability of previous models to simulate numerous patient characteristics simultaneously. AD is a disease where multiple people with it can show different symptoms, respond to treatment differently and this presents a dire need for a model to simulate multiple patient trajectories in detail. The authors [4] propose an unsupervised machine learning model to achieve this called the Conditional Restricted Boltzmann Machine.

This method has an edge over other generative models as it can sample from any conditional distribution. The model utilizes a dataset comprising 44 clinical variables across eighteen-month trajectories from 1909 patients with either AD or cognitive impairment to train the model and produces accurate predictions of the progression of AD taken from the Coalition Against Major Diseases Online Data Repository for AD. This also includes individual components of the AD Assessment Scale-Cog and Mini-Mental State Exam scores, laboratory tests, and background information of the patient.

The paper [4] presents a disclaimer that these computational models may be used to guide clinical decisions in the future but the current applications are limited both by the availability of data and by the ability of algorithms to extract insights from those data. The authors achieve Generative modeling by randomly generating patient profiles with the same statistical properties as real patient profiles and then simulating the evolution of these patient profiles through time. In any stochastic process, the CRBM can accumulate the values of an underlying time-dependent probability distribution for the disease progression.

The paper [4] concludes by stating the model accurately constructs patient trajectories. The ability to simulate the stochastic disease progression of individual patients in high resolution could have a transformative impact on patient care by enabling personalized data-driven medicine. Each individual diagnosed has distinctive risks and a different response to therapy. Due to this heterogeneity, predictive models cannot currently make individual-level forecasts with a high degree of confidence. Tools that use simulations to forecast risks for specific individuals could help doctors choose the right treatments for their patients. Progress towards these goals is slowed by the limited availability of high-quality longitudinal health datasets and the limited ability of current methods to produce insights from these datasets

D. Convolutional Neural Networks

The paper [7] is based on an algorithm that can detect and predict the development and status of AD or the onset of AD in a patient with the help of deep learning techniques in association with 3D convolutional neural networks. The algorithm takes its foundation from an MRI scan of the patient and builds it on from that approach. The authors [7] then shine a light on the topic of AD and also provide information about MCI and the relationship between AD and MCI. The main objective of the paper is to utilize and produce positive results by implementing 3D convolutional neural networks on MRI images.

The paper uses a dataset which was mainly derived from ADNI. The study has a total of 755 patients who are under either AD, MCI or HC. The research consisted of a total of 2,265 scans. The normalization of data into an International Consortium for Brain Mapping template which was achieved using Statistical Parametric Mapping

(SPM) is done. Firstly, the system uses a space autoencoder to comprehend the filters for convulsion operations, the autoencoder consists of a 3 layered neural network that can absorb features from an input image. The autoencoder consists of an encoder that can map the input image to its hidden equivalent and the decoder does the opposite task, i.e., extracting the image from its hidden equivalent.

The autoencoder can be trained to do the following with a large enough data set. The next step is to construct a convolutional neural network whose first layer will be composed of the filters which have been trained along with the autoencoder. This layer has been of paramount importance in the field of handwritten digit recognition and object recognition. The artificial neural networks are distinguished by local connectivity of the hidden units, parameter sharing along with the use of pooling operations. The main function of this layer is to take the receive MRI scan, these networks are built on three pertinent layers, convolutional, pooling, and finally fully connected layers. The units in the hidden layer are not fully connected to its predecessor layer, this helps in the reduction of parameters, relieving the system of space complexity. It also aids in the detection of local patterns which play a huge hand in the distinguishing process.

The hidden layer also comprises many feature maps, which near each other share the same parameters. A convolutional layer is acquired by stacking numerous feature maps. The convolutional layer is responsible for detecting local patterns and frameworks from the inputted image, which aids the algorithm to benefit from the 3D topological details of the MRI image and consists of 150 feature maps of size 64 x 91 x 75.

The next layer is the pooling layer which consists of 150 feature maps of size 12 x 18 x 15. The pooling layer is used to minimize the number of units in the hidden layer. Pooling is also significant in constructing vigor to images which consist of distortions. A 5×5×5 max-pooling approach is used to minimize the space consumed by the convolutional layer. To expedite the training of the networks, a momentum method is brought into action. Mini-batch gradient descent is used to train the algorithm, the convolutional layer is benched in the last training as it will be pre-trained with an autoencoder.

The paper then compares 3D and 2D convolutions, contrary to the belief that 3D boasts of higher performance, in the actual working, both 3D and 2D convolutions were neck and neck, though, in a pragmatic way, 3D convolutions do hold an upper hand but in a slim way.

When the above algorithm was set up with actual data, it was able to distinguish between AD, MCI, and HD with 2D convolution having an accuracy of 85.53% and 3D convolution with 89.47%. When setting up with AD and HC, 2D gave an accuracy of 95.39%, which was also the same result when tested with 3D convolution. In classifying AD and MCI, 2D convolution generated an accuracy of 82.24% whereas 3D returned an accuracy of 86.84%. In HC and MCI classification, 2D convolution produced an accuracy of 90.13% and 3D gave an accuracy of 92.11%.

The authors [7] conclude that though the framework generates outstanding accuracy, it still is possible to go past it and improve the results by constructing a much-sophisticated structure. The table [1] shows the comparison between all the reviewed methodologies.

VI. CONCLUSION

This review compares the research based on their performance, accuracy, methods employed, and the approach towards detection. Machine learning techniques like SVM, logistic regression, and CRBM are applied for different neuroimages to provide accurate results. deep learning neural networks are also used to detect Alzheimer's disease in a patient effectively. Single and multimodality have been applied to conclude that the multimodality approach leads to better results. SVM machine learning methods have been applied and have provided good accuracy, but the used data set is seen to be very small. CBRM provides a more unique and personalized approach compared to other supervised learning algorithms. whereas the convolutional neural network built and trained for a bigger dataset provides a higher accuracy which is important in the medical field. To improve the research further, the dataset has to be efficiently pre-processed and class imbalance should be avoided as it can reduce the accuracy. Pathologically proven datasets should be considered which validates the obtained results, reduces imbalance and overtraining issues. These ideas will lead to an efficient model for implementation to detect Alzheimer's disease.

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