Multimodal Classification of Cognitive States in Alzheimer's Disease

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***Abstract*—Alzheimer's disease is a neurodegenerative disease which affects the brain and causes memory loss. Today, this is the most affected disease in the world and has been a real struggle to survive. It is a condition which affects a large number of individuals globally, and it's important to diagnose it early and distinguish between different cognitive states such as AD, MCI, and NC. Personality changes, hallucinations, and difficulties speaking and walking may be symptoms as the illness worsens. It is important to ensure that a patient get treatment on time and management of the disease. The accuracy of AD classification can be greatly improved by incorporating different forms of data, including clinical, genetic, imaging and electroencephalogram(EEG) data, according to a recent study. One area of research involves using biomarkers to identify the disease early, before symptoms are evident. In this paper, we suggest a multimodal approach to identifying cognitive states in Alzheimer's disease. Recent research has demonstrated that multimodal classification techniques for AD diagnosis offer both unique advantages and drawbacks. In conclusion,our study highlights the importance of multimodal data in improving the accuracy of AD classification and provides a promising approach for early diagnosis and management of the disease, ultimately offering hope for better outcomes and quality of life for affected individuals.**

***Index Terms*—Alzheimer's Disease(AD), Mild Cognitive Impairment(MCI), Normal Cognition(NC), Neurodegenerative disorder, Multimodal, Imaging, Genetics, Clinical, EEG.**

I. Introduction

Alzheimers is a slowly progressing neurological condition that affects the brain and reduces cognitive function over time. It is the most typical dementia cause and is characterised by memory loss, cognitive impairment, and language issues. [1]Alzheimer's disease is often discovered in older adults, while younger adults can potentially develop the illness's early-onset variants. The illness is progressive, which means that symptoms worsen with time and eventually affect a person's capacity to perform daily tasks. Although the reason behind Alzheimer's disease is still unknown, it is believed to be a cause of a combination of genetic, environmental, and lifestyle factors.

Alzheimer's disease currently has no treatment, although there are few tests that can help to increase the thinking ability of a person. Brain imaging, cognitive testing, physical examinations, [10] medical histories, and physical examinations are frequently used to identify Alzheimer's disease. There is a lot of interest in developing more accurate methods to identify, treat, and ultimately prevent Alzheimer's disease, and research into the condition is still ongoing.

The study uses multimodal analysis, which makes use of many kinds of data from different sources, such as imaging, genetic, and clinical data. By combining these different modalities, [11], we can gain comprehensive understanding and the progression of the disease. This strategy may help in the early detection and treatment of the disease, as well as increase the precision of the classification of AD. Additionally, multimodal analysis may provide new insights into the underlying causes of AD and potential targets for treatment in the future.

II. Literature Review

Many studies have been conducted over the years to discover diagnostic methods, triggers, and possible remedies for Alzheimer's illness. In this study, we attempted to compare, integrate, and evolve all existing studies on Alzheimer's disease. We categorized the linked papers based on the data they utilised, the stages of AD they intended to predict, and the models they incorporated. The model lacks clinical confirmation in [8]. Some Researches have predicted AD stages while some did analysis for early diagnosis.In the table-1(Comparison Of Existing Solutions) EHR stands for Electronic Health Records and corresponds to Clinical Data while SNP stands for Single nucleotide polymorphisms corresponding to genetical Data.The [6] The study's primary objective was to filter out specific genetic variations known as SNPs by carefully choosing files that contain patient data, with each file representing data related to a specific chromosome. For [14] the author classified the stages of AD by pairing two stages together at a time.In [4], the author did not include the AD stage in classification, whereas in [7], the author failed to demonstrate the distinction between a patient with Alzheimer's and a patient who did not have it.The model's performance in [3] is quite poor. We compared our model's outcomes to that of the above studies investigation.

TABLE I
COMPARISON OF EXISTING SOLUTIONS

Author	Database	Model	Group	Evaluation Metrics
Venugopalan *et al.* [3]	ADNI	SDA for EHR and SNP, 3D CNN for MRI	AD,MCI and NC	Accuracy: 78% F1 Score: 78%
Khanna *et al.* [4]	ADNI-1	GBM on MRI,PET and SNP	NC,MCI	c-index: 0.86
M Golovanevsky *et al.* [6]	ADNI	Attention + FCNet for SNP, EHR and 3D CNN for MRI	AD,MCI and NC	Accuracy: 92% F1 Score: 90%
Lawrence Fulton *et al.* [7]	OASIS-1	ResNet on EHR and MRI	4 classes Of Dementia	Accuracy: 98%
Zhang *et al.* [8]	ADNI-1,2	M3TL on MRI,PET and CSF	AD,PMCI and LMCI	Accuracy: 73.9% AUC: 0.80
Giulia Fiscon *et al.* [14]	IRCCS Centro Neurolesi "Bonino-Pulejo"	Supervised ML on EEG	AD,MCI and NC	Avg Accuracy: 74.7% Avg Precision: 76.05%

III. DATASET DESCRIPTION

The Alzheimer's Disease Neuroimaging Initiative (ADNI) [1] website provided the information utilised in this project. ADNI is a long-term, multicenter study that aims to identify biomarkers for early detection and surveillance of Alzheimer's disease (AD), including clinical, imaging, genetic, and biochemical markers.

A. Clinical Data

The clinical datasets were selected because they provide detailed information on the clinical characteristics and cognitive function of study participants. The following datasets were used:

- **PTDEMOG:** This dataset contains demographic information of the participants in the ADNI study, such as age, gender, race, education level, and marital status.
- **NEUROEXM:** This dataset contains neurological examination data for ADNI study participants, including cognitive function, motor function, sensory function, and other neurological assessments.
- **DXSUM_PDXCONV_ADNIALL:** This dataset contains diagnostic information for ADNI study participants, such as their information on the diagnostic criteria used to classify their condition.
- **ADSP_PHC_COGN:** This dataset contains cognitive function data for participants in Alzheimer's Disease Sequencing Project (ADSP).

B. Genetical Data

In this study, the genetic data was obtained using Illumina's non-Clinical Laboratory Improvement Amendments (non-CLIA) [2] platform. This platform is used for research purposes and is not regulated by the Clinical Laboratory Improvement Amendments (CLIA). After obtaining the WGS data, ADNI generated variant call files(VCFs) various pipelining techniques. Out of those we considered the VCFs that are pipelined with Burrows-Wheeler Aligner using Genome Analysis Toolkit and with BWA aligner using the CASAVA Toolkit. A VCF is a standard file format used to store genetic variant information.

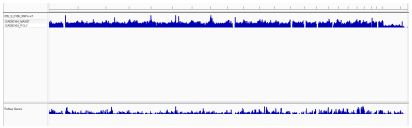


Fig. 1. VCF File Representation

Each study participant's raw VCF file contained about 3 million SNPs. Not all SNPs, though, offer useful information for predicting Alzheimer's disease. A gene file obtained from [2] was also used to further clean up the genetic data used in the study, in addition to the pre-processing methods. Only the SNPs in the genes that causes AD were kept in this file, which contains a list of those genes. The genetic data was an important component of the study, as it provided information on the genetic factors that may contribute to the development and progression of Alzheimer's disease.

C. Imaging Data

The imaging data consists of magnetic resonance imaging (MRI) data from two datasets: ADNI1_Baseline_3T and ADNI1_Baseline_1.5T. These datasets contain .nii files which are three-dimensional images of the brain acquired using magnetic resonance imaging. The ADNI1_Baseline_3T dataset contains data from participants who were scanned using 3 Tesla (3T) MRI machine, while the ADNI1_Baseline_1.5T [1] dataset contains data from participants who were scanned using 1.5 Tesla (1.5T) MRI machine.

D. EEG Data

The subjects in the EEG resting state-closed eyes recordings dataset [16] we used included people with AD, people with frontotemporal dementia (FTD), and some healthy people (NC). Using the international Mini-Mental State Examination (MMSE), each subject's cognitive and neuropsychological condition was assessed; lower scores denoting more severe cognitive decline. The disease's median duration was 25 months, and there were no dementia-related comorbidities detected in the AD group. A clinical reference electrode was used to record the EEG. Participants were asked to close

their eyes during the recording session while sitting still and participating in the activity. For the AD group, each recording lasted around 13.5 minutes, for the FTD group it was around 12 minutes, and for the NC group it was about 13.8 minutes.

IV. Data Preprocessing

A. Clinical Data Preprocessing

The study utilizes clinical data from 2384 patients, including neurological tests like balancing assessments, cognitive evaluations such as memory tests, and demographic information such as age. There are 29 measurable, classified, or binary characteristics in the clinical data. To prepare the data for analysis, categorical information was transformed into features through one-hot encoding, while continuous-valued features underwent normalization [9]. From ADNI1, ADNI2, and ADNI GO, we extracted 1680 common clinical features which included quantitative real values, binary variables, and categorical variables as shown in Fig. 2. The quantitative data is first normalized to the range one and two, then using one hot encoding categorical data is converted to binary , and the binary data is lastly turned into values one and zero [6].

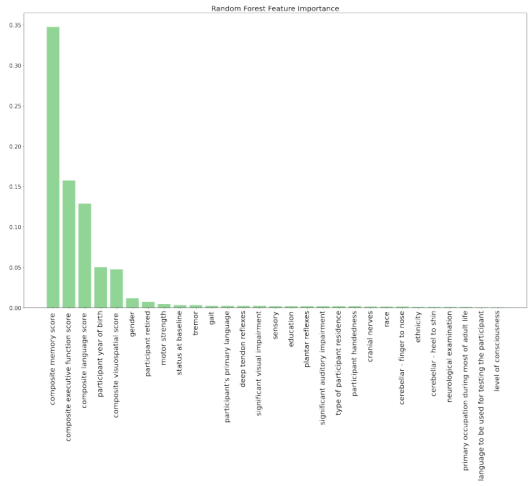


Fig. 2. Clinical Feature Importance

B. Genetic Data Preprocessing

The initial step in preprocessing genetic data (SNPs) is to get VCF files from ADNI. Then use the vcftools [13] package to filter the files based on the Hardy-Weinberg equilibrium (p0.05), genotype quality (Gq20), minor allele frequency (0.01), with high per missing rate, etc. criteria that you have selected. The whole genome sequencing (WGS) data from 805 ADNI participants collected by Illumina under non-CLIA constitutes the genetic data. In 2014, ADNI produced the variant call files (VCFs) as a consequence of employing Burrows-Wheeler Aligner and Genome Analysis Toolkit. The raw VCF file created contains around 3 million SNPs for each individual.

To cut down on the amount of SNPs and maintain only the necessary genetic elements, we adhered to the pre-processing procedures that have been defined and described in [3]. We were left with a matrix that was rather sparse. In order to narrow down the feature space ,we used a classifier.Take note that the classifier was blind to the data points utilised for model testing.

C. Imaging Data Preprocessing

In our study, we used preprocessed images that have undergone a special correction procedure that accounts for certain distortions that may occur during image acquisition as performed in [5]. Gradwarp [6] is the initial step in the rectification process; it eliminates gradient nonlinearity-induced distortion of the image geometry. This bias can differ between different slope models, so correction is necessary for accurate analysis. Additionally, we looked into how the unimodal imaging model might function with more brain slices. We evaluated the model using only the middle three slices, plus an additional two slices each angle (for a total of six), five more angles, ten additional angles, twenty additional angles, and fifty additional angles. We measured the F1 score and accuracy of each variation of the model (average of three validation sets). As slices were added, the model's performance remained relatively constant. The performance difference between using no extra slices (as reported in the study) and 20 extra slices was within 1%.

Below graph shows the unimodal imaging model [14] does not significantly benefit from adding more images.The performance degradation is likely due to slices far from the center not being processed.It adds noise to the model and meaningful information. The centre three slices are displayed in the sample below, followed by the outer 10 slices, and finally the outermost slice.

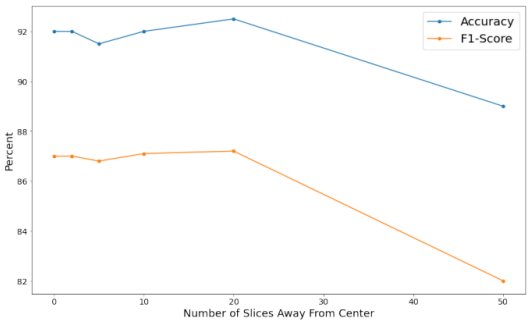


Fig. 3. Validation F1-Score and Accuracy Trend as Number of Images Increases

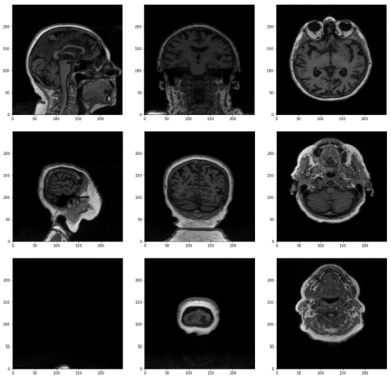


Fig. 4. Examples of MRI slices as distance increases from center

D. EEG Data Preprocessing

On the .SET files Fast Fourier Transform(FFT) [16] is performed to visualize the frequency distribution of data. Those

files are used to store EEG data as well as the information of sampling rate,filter settings and electrode placements. We converted the patients data that are in .SET(Time Domain) into .CSV(Frequency Domain) by selecting a specific channel(have used F4) and applied FFT on them. This makes the data more compatible and accessible for EEG Data Analysis. Data is standardized by applying standard scalar.It is a method for standardising dataset features by scaling them.

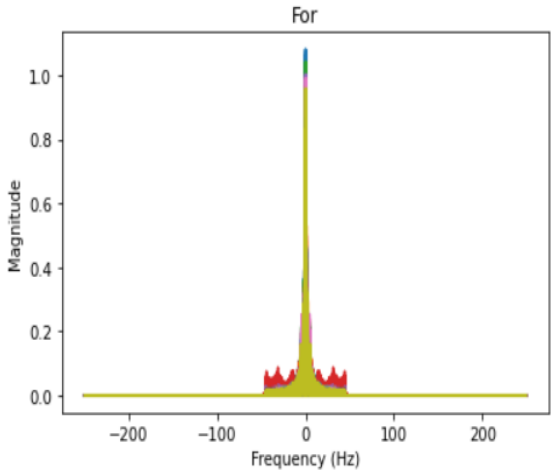


Fig. 5. FFT Magnitude v/s Frequency

V. Methodology

A. Clinical Data Unimodal

In this model the input variables consisted of 185 traits and the output variables were labels representing one of three possible outcomes (normal, risk, disease). One-hot coding [7] was applied to the output variables to allow multiple class classification. Techniques such as batch normalization and dropout regularization have been used to improve model performance.

Inputs for each layer are standardised using batch normalisation, which improves their consistency and reduces their propensity for overfitting. In order to avoid overfitting, dropout regularisation randomly eliminates neurons.Based on the gradient of the loss function, this optimizer modifies the learning rate] [15]. Low-density cross-entropy, a commonly utilised loss function in multiclass classification problems, was employed. 32 batches of 100 epochs each were used to train the model. Overall, the approach taken in this work shows that the machine learning models have the potential to precisely predict clinical outcomes based on unimodal clinical data.

B. Genetic Data Unimodal

The study used a deep learning model with a TensorFlow backend developed in keras to analyse genetic data.In order to avoid overfitting, the model architecture comprises of numerous fully connected layers with a dropout regularisation. By comparing the genetic data of study participants to a reference gene list [2], the study was able to identify potential genetic risk factors and associations with Alzheimer's disease. Gene lists have also been used as a trait selection [8] tool in machine learning models to identify the most meaningful genetic traits that can be used to accurately predict different stages of Alzheimers. In summary, this study used deep learning models to analyze WGS data from 805 ADNI study participants to identify potential genetic risk factors and associations with Alzheimer's disease and related disorders.

C. Imaging Data Unimodal

The methodology used a convolutional neural network (CNN) to map MRI images to healthy or AD impact, using a dataset consisting of T1-weighted and 3-Dimensional images. The model was trained on the ADNI1_Baseline_3T dataset and validated on the ADNI1_Baseline_1.5T dataset. The imaging data consisted of MRI data from two datasets, ADNI1_Baseline_3T and ADNI1_Baseline_1.5T, which contained .nii files, three dimensional images of the brain acquired using magnetic resonance imaging.

T1-weighted imaging provides excellent contrast between the gray and white matter, enabling the detection of structural changes associated with Alzheimer's disease. Various structural features of the brain were extracted from these images, such as the volume and thickness of specific regions of interest. To ensure the quality of the MRI data, ADNI performed quality control procedures before publishing the dataset. Additionally, the MRI data [3] was preprocessed using standard methods to address motion artifacts, bias field inhomogeneity, and other noise sources. Additionally, the model was validated using a cross-validation approach.

D. EEG Data Unimodal

EEG has proven to be a valuable tool in offering essential insights into the brain's electrical activity and cognitive functioning. We tested several algorithms such as Support Vector Machine, Decision Tree (with and without GridSearchCV), Naive Bayes, Random Forest (with and without GridsearchCV), Ada Boost, and Neural Networks. Each of these models has its unique characteristics that impact their performance on the dataset. In our study, we analyzed the performance of each algorithm and identified the best-performing one based on the results. This approach allowed us to gain insights into the strengths and weaknesses of different algorithms and helped us choose the best one for our classification task. Overall, our study provides valuable information for future researchers to use when selecting algorithms for EEG [16] data analysis.

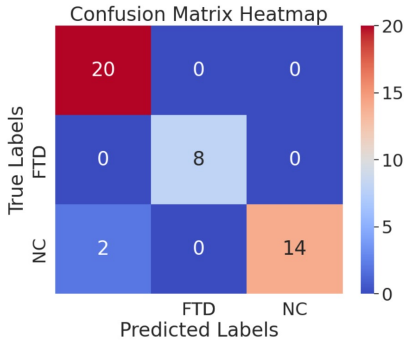


Fig. 6. Random Forest

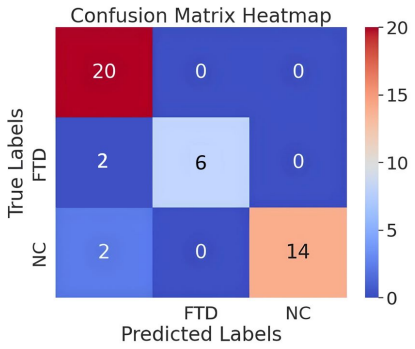


Fig. 7. Random Forest with GridSearchCV

E. Multimodal

This study used three types of data: clinical, genetical (SNPs) and imaging data. Here we had not used EEG data because we dont have data of same patients from whom MRI, clinical and genetical data is considered.

The machine learning model used was a multimodal model that combined information from all three data types. The model [6] was trained using a multilayer deep neural network. The model's architecture included three separate neural networks, one for each data type, combined across the cross-modal attention layer inspired by [17].

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V$$

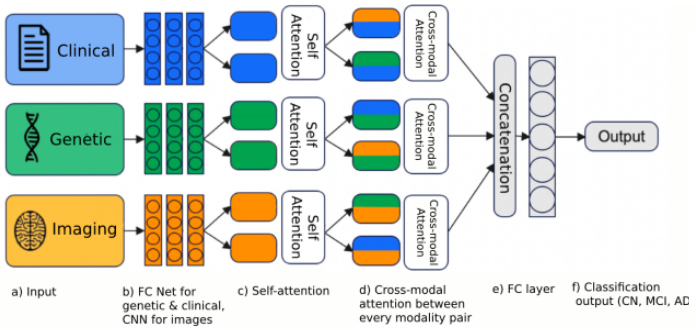


Fig. 8. Model Architecture

In summary, this study used a machine learning approach to predict the stage of Alzheimers based on clinical, Genetical and imaging data. This study combined details from all three data types using a multimodal model with crossmodal attention [12]. This model achieved high accuracy on the test set and showed promise for future use in clinical practice.

VI. Observation

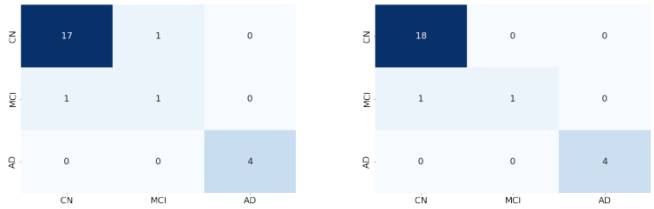
A. Performance of Individual Class

The table illustrates the average performance metrics of the study for each class.The findings reveal that the model accurately predicts Alzheimer's Disease irrespective of the initialization, while its only misclassification occurs in identifying MCI patients as control patients.

TABLE II
Performance Metrics of Individual Classes

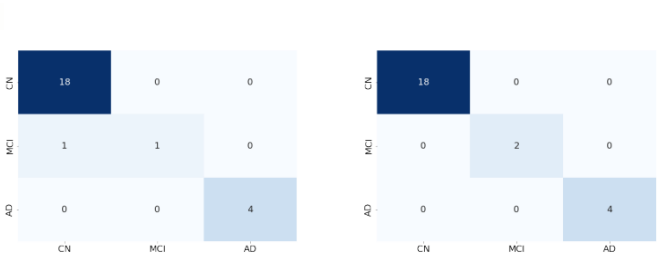
Group	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)
Normal Cognition	96.66	96.78	98.88	97.81
Mild Cognitive Impairment	96.66	90.00	70.77	76.66
Alzheimer's Disease	100	100	100	100

To ensure reproducibility of results, the models was trained and scored using five different random seeds.We included confusion matrices for each of the 5 random initializations to supplement to the above table. Each confusion matrix represents the results of our best multimodal model with respect to a random seed.



(a) Random Seed 1 (b) Random Seed 2

Fig. 9. Random Seed 1 and 2



(c) Random Seed 3 (d) Random Seed 4

Fig. 10. Random Seed 3 and 4

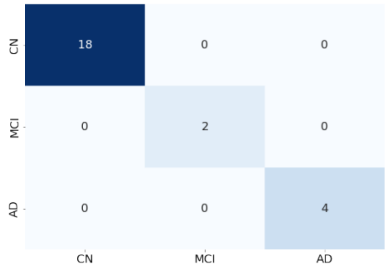


Fig. 11. Random Seed 5

B. Performance of Unimodals

The four evaluation metrics for each modality, namely imaging, EEG, clinical and genetical model are listed in below table.

TABLE III
PERFORMANCE OF UNIMODALS

Data	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)
Clinical	80.71	80.56	80.50	80.47
Imaging	92.31	94.02	90.4	91.83
Genetic	77.78	78.37	76.92	77.24
EEG	95.45	96.97	95.83	96.39

C. Performance of Multimodal

We were able to perform at the cutting edge on the multimodal, three-class classification job in our study. In particular, we deployed an ensemble of deep neural networks to boost the model's prediction capability and improved feature extraction algorithms to collect pertinent elements from the data. In order to provide a more thorough understanding of the underlying illness mechanisms, we also used a more comprehensive dataset that included clinical, imaging, and genetic data.

This below graph represents the assessment of different combinations of modalities. [6] The best results were obtained when using all three modalities together, as measured by various evaluation metrics.

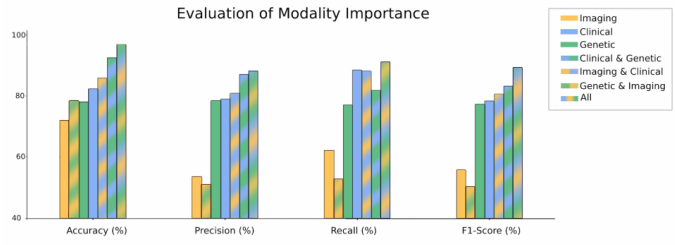


Fig. 12. Bar Plot Comparision

VII. CONCLUSION AND FUTURE SCOPE

In conclusion, our study presents a promising approach for accurately classifying cognitive states in Alzheimer's Disease (AD). Our model has the potential to be used for early diagnosis of AD, as MCI is the initial stage of obtaining AD.So by predicting the MCI stage we are able to predict the early stage of AD.Our study comprises of a total of eight models, including four unimodals, three bimodals, and one trimodal.We were unable to overlap all the four models due to the lack of common ground between the datasets, namely MRI, genetical, clinical, and EEG data.

In our study, we explored various algorithms to analyze the preprocessed EEG data as many researches were done on clincal, imaging and genetic data. Our aim was to identify the algorithm that could best classify the data and provide the most accurate results by making the data more compatible and accessible for EEG Data Analysis. Considered the cognitive functions while dealing with the clinical data. We were successful in analysing genetic variations by using both pipelined files: one based on chromosomes(GATK) and the other on patient data(CASAVA). This approach helped us identify important patterns and mutations in the genome, leading to valuable insights into Alzheimer's condition.

In order to enhance the effectiveness and accuracy of our AD classification model, we can extend our study by incorporating additional data sources such as PET or fMRI data. By including these modalities, we can create a higher-level classification model that can provide a more comprehensive analysis of cognitive states in AD. Furthermore, we can explore the possibility of finding a common data of EEG data that can be used to train and integrate our existing model. This will improve the accuracy of our classification model and also enable us to perform a more detailed analysis of the cognitive state of patients with AD.

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