# Alzheimer's Disease

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## Objective

Alzheimer's Disease (AD) is one of the leading causes of dementia worldwide, but the link between genetic risk factors and the development of key AD features—such as brain atrophy and amyloid/tau accumulation—is still unclear. While some alleles like APOE4 are known genetic risk factors, how they drive disease progression and lead to physical changes in the brain hasn't been fully mapped out. This lack of understanding makes it difficult to improve early detection and develop targeted treatments.

The goal of this project is to explore the relationship between genetic variations and critical AD biomarkers, including brain atrophy (measured by MRI) and amyloid/tau build-up (measured by PET scans). By analyzing how genetic and imaging data relate, we aim to uncover biological pathways that link genetic predisposition to brain changes. This research could improve our understanding of how genetics influence AD progression and help in designing more personalized treatment strategies.

## Dataset

The primary dataset used for this project is the Alzheimer's Disease Neuroimaging Initiative (ADNI) Merge dataset. This is essentially a vast dataset combining key predictors from all four distinct phases of the ADNI study– ADNI1, ADNIGO, ADNI2, and ADNI3 – in each of which new participants were recruited while existing participants from earlier phases continued to be monitored.

### Dataset Overview:

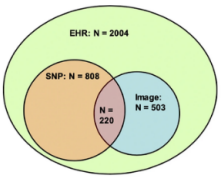
- **Genetic Data:**
  ApoE Genotype: The dataset includes ApoE genotyping, which is critical for Alzheimer's research as the presence of the APOE4 allele is one of the strongest genetic risk factors for late-onset AD.

| | Example Data Types/ Features |
|---|---|
| **Clinical Data** | Demographics, neurological exams, cognitive assessments, bio-markers (e.g. alanine, choline), medication (e.g. levodopa), imaging summary scores (e.g. brain are volumes) |
| **Imaging** | Cross-sectional MRI data |
| **Genetic** | Whole genome sequencing (WGS) data |

**a:**

| | CN | MCI | AD |
|---|---|---|---|
| **Clinical Data** | 598 | 699 | 707 |
| **Imaging** | 132 | 104 | 266 |
| **Genetic** | 245 | 338 | 226 |

**b:**




**c:**

Figure 1: Venugopalan, J., Tong, L., Hassanzadeh, H.R. et al. Multimodal deep learning models for early detection of Alzheimer's disease stage. Sci Rep 11, 3254 (2021). https://doi.org/10.1038/s41598-020-74399-w

Whole Genome Sequencing (WGS) Data: In addition to the APOE genotype, the ADNI dataset provides more comprehensive genetic data through WGS, allowing for the exploration of rare variants and single nucleotide polymorphisms (SNPs). This enables the study of lesser-known genetic risk factors and their interaction with known markers such as APOE4, giving a broader picture of genetic susceptibility to AD.

- **Neuroimaging Data:**
  1. MRI Scans:
  Structural MRI data is used to assess brain atrophy, particularly in regions known to be affected by AD, such as the hippocampus, entorhinal cortex, and temporal lobes. The dataset includes both 1.5T and 3T MRI scans, providing high-resolution images to measure cortical thinning and volume loss in these critical areas.
  Brain atrophy measurements derived from these MRI scans are valuable for correlating genetic factors with structural changes in the brain, especially in early-stage AD.

  2. PET Scans:
  The dataset includes Amyloid-PET and Tau-PET scans that allow visualization of amyloid-beta and tau protein buildup, two hallmarks of AD pathology. The amyloid-beta data is captured using tracers like Florbetapir (AV-45), while tau accumulation is detected through tracers such as Flortaucipir (AV-1451).

These PET scans provide quantitative measures of amyloid and tau burden, which are crucial for linking genetic risk factors with the biochemical processes driving AD.

- **Biomarkers:**
  Cerebrospinal Fluid (CSF) Biomarkers: CSF samples are used to measure key AD biomarkers such as amyloid-beta 42, total tau, and phosphorylated tau (p-tau), which complement the imaging data from PET scans.

  Blood Biomarkers: Emerging biomarkers in blood samples, such as neurofilament light (NfL) and plasma p-tau, are also included in the dataset. These blood-based markers may serve as early indicators of neurodegeneration, enabling an exploration of genetic factors that might predispose individuals to abnormal levels of these proteins.

- **Clinical Assessments:** The dataset contains comprehensive clinical evaluations, including cognitive assessments like the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). These clinical measures are used to track cognitive decline over time and can be correlated with genetic predispositions and imaging data to assess how genetic variations may influence cognitive deterioration.

## Input and Labels

- **Inputs:** Multi-modal data, including MRI scans, PET scans, genetic variants (APOE, SNPs), and biomarker levels.

| VARIABLE | DESCRIPTION | RANGE OF VALUES PRESENT (MIN-MAX) | % MISSING AT BASELINE |
|---|---|---|---|
| **Primary psychometric exams given:** | | | |
| **CDRSB** | Clinical Dementia Rating - Sum of Boxes: measures dimentia progression, especially for patients with early- to mid-level cognitive impairment | 0 - 18 | 0 |
| **ADAS11/ADAS13** | Alzheimers Disease Assessment Scale, 2 versions (11 items, 13 items): relatively detailed exam to measure cognitive and non-cognitive symptoms of AD. Scores range from 0 (no impairment) to 70/85 (severe impairment) | 0 - 70 (11-question)/ 85 (13-question) | 0.53/1.05 |
| **MMSE** | Mini Mental State Examination: quick, widely-used assessment of cognitive function. Scores of 25-30 are considered normal, 21-24 mild, 10-20 moderate, and <10 severe | 0 - 30 | 0 |
| **RAVLT** | Rey Auditory Verbal Learning Test: measures auditory learning and memory | 0 - 75 | 0.53 |
| **FAQ** | Functional Activities Questionnaire: measures a patient's ability to perform everyday functions independently. Scores range from 0 (normal) to 30 (highly dependent) | 0 - 30 | 1.05 |
| **MOCA** | Montreal Cognitive Assessment: 10-minute screening for mild cognitive impairment. Scores range from 0 (severe impairment) to 30 (normal) | 0 - 30 | 40.44 |
| **EcogPt/EcogSP** | Measurement of Everyday Cognition (ECog), a short questionnaire filled out by the patient (Pt) and spouse (Sp), rating the patient's performance in different cognitive areas (memory, language, visuo-spatial abilities, planning, organization, divided attention) relative to his/her performance 10 years prior. Scores range from 1 (no change) to 4 (much worse), or 5 (unknown) | 1 - 4 | Various (depends on Ecog measure) |

| VARIABLE | DESCRIPTION | RANGE OF VALUES PRESENT (MIN-MAX) | % MISSING AT BASELINE |
|---|---|---|---|
| **Primary PET measures:** | | | |
| **FDG** | Measured uptake of Fluorodeoxyglucose (FDG), found to be a strong differentiator between AD and other forms of dimentia, as well as to predict progression of dementia | 0.637 - 1.751 | 35.23 |
| **AV45** | florbetapir (AV45) is used to detect the presence of beta-amyloid, which is a key marker of AD | 0.805 - 2.669 | 51.77 |
| **Primary MRI measures** | | | |
| **Hippocampus** | Hippocampal volume | 2219 - 11207 | 28.73 |
| **WholeBrain** | Entire brain volume | 649091 - 1486040 | 19.17 |
| **Entorhinal** | Entorhinal cortex volume | 1041 - 6711 | 29.88 |
| **MidTemp** | Middle temporal gyrus volume | 8044 - 32189 | 29.88 |
| **Primary biomarker measures from CSF:** | | | |
| **ABETA** | Amyloid-beta peptide level. Higher levels are associated with presence of AD | 828.7 (plus 1 '<200' and 351 '>1700') | 40.06 |
| **TAU** | Tau protein level. Higher levels are associated with presence of AD | 293.4 (plus 8 '<80' and 1 '>1300') | 41.92 |
| **PTAU** | Phosphorylated tau level. Higher levels are associated with presence of AD | 28.1 (plus 11 '<8' and 1 '>120') | 40.06 |
| **Primary risk factors:** | | | |
| **APOE4** | Presence of APOE gene that makes the ApoE4 protein, associated with late-stage AD | 0-2 | 17.54 |
| **Age** | Patient age at time of visit | 54.4 - 91.4 | 0.096 |

Figure 2: Detailed overview of the key variables present in our dataset, the range of values that these variables take on and the percentage of missing values, which is a key component to take into consideration with this dataset

- **Output Labels:** By using a multimodal classification model, our labels will correspond to the diagnostic categories: Cognitively Normal, MCI, and AD, and using the classifications, we can derive insights about the correlation between input variables.

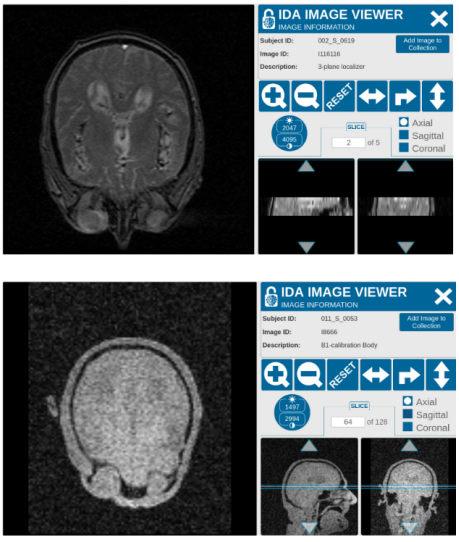
## Data Splits

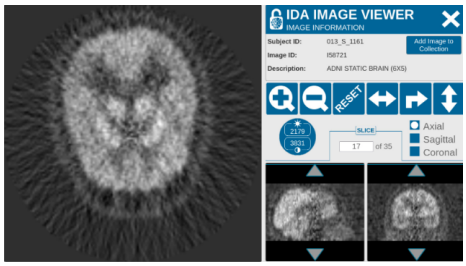
For this project, the data will be split on a patient-wise basis to ensure that no information from the same patient is used in both training and testing phases. This approach helps to better generalize the model's performance to unseen patients and avoids overfitting to specific individuals. The splits are as follows:

- **Training Set (70%):** 70% of the patients will be used to train the machine learning models. This includes all available data (e.g., MRI, PET scans, genetic information) for these patients across multiple time points.
- **Validation Set (15%):** 15% of the patients will be used to fine-tune model hyperparameters and assess performance during training. Importantly, none of the patients in this set overlap with those in the training set.
- **Test Set (15%):** The remaining 15% of patients will be reserved for final model evaluation.

## Sample Data

Example MRI images: Example PET image:






| Data Type | File Type |
|---|---|
| APOE Genotype | .csv |
| Whole Genome Sequencing (WGS) | .vcf |
| MRI Scans | .nii, .dcm |
| PET Scans | .nii, .dcm |
| Cerebrospinal Fluid (CSF) Biomarkers | .csv |
| Blood Biomarkers | .csv |
| Cognitive Tests (MMSE, ADAS-Cog) | .csv |

Table 1: Data types and corresponding file formats in the ADNI dataset.

# Introduction

Alzheimer's Disease (AD) remains one of the most complex and poorly understood neurodegenerative conditions, affecting millions globally. Traditional approaches to diagnosing and treating AD often focus on single biomarkers or symptoms, but the disease is multi-factorial, involving a combination of genetic, molecular, and cognitive factors. Recent advancements in multi-modal data analysis have demonstrated the potential to integrate genetic, imaging, and biomarker data, leading to more accurate diagnostic models and the potential for personalized treatments.

In this project, we aim to explore these complex interactions using a combination of advanced neuroimaging techniques and genetic analyses to uncover the biological pathways through which genetic factors influence the physical manifestations of AD. The goal is to improve early diagnosis and to support the design of targeted therapies based on individual genetic risk profiles.

## Literature Review

Initially, we reviewed classification papers for Alzheimer's Disease (AD) and found that many achieved extremely high accuracies, often exceeding 97%. This highlighted that the current state-of-the-art (SOTA) in AD classification is already very advanced. Despite this, our goal was to explore the biological insights of AD through deep learning. We then read studies using multimodal approaches, combining MRI, PET, and genetic data to enhance prediction. We also found work leveraging GWAS data from resources like ADNI, linking ge-

netic variants with neuroimaging biomarkers, which aligned perfectly with our interest in understanding how genetics and brain changes interact in AD progression.

| Paper | Date | Objective | Input | Dataset | Methodology | Result |
|---|---|---|---|---|---|---|
| "Deep learning-based identification of genetic variants: application to Alzheimer's disease classification" | March, 2022 | "(SWAT-CNN) to identify genetic variants associated with Alzheimer's and create an accurate disease classification model." | "Genome data of AD and CN patients" | "ADNI GWAS data: 981 participants, 650 cognitively normal older adults, 331 AD patients. 5,398,183 SNPs analyzed." | "Three-step process: (1) Genome divided into fragments, CNN run to identify phenotype-associated fragments (2) Sliding Window Association Test (SWAT) to calculate phenotype influence scores (PIS) and identify SNPs (3) CNN applied to SNPs to develop a classification model." | "Identified APOE as the most significant locus. Achieved 75.02% accuracy for AD classification using CNN, outperforming random forest and XGBoost." |
| "A Machine Learning Approach to Unmask Novel Gene Signatures and Prediction of Alzheimer's Disease Within Different Brain Regions" | July, 2021 | "To identify gene signatures for AD and create a classification model for predicting AD in different brain regions" | "Gene expression data from Prefrontal Cortex, Middle Temporal Gyrus, Hippocampus, and Entorhinal Cortex" | "NCBI-GEO database (GSE33000, GSE44770, GSE118553, GSE132903, GSE5281, GSE48350)" | "- Feature selection using Random Forest (varSelRF) and LASSO models - Classification using SVM, Random Forest, and Elastic Net" | "- Novel biomarkers identified: CORO1C, SLC25A46, RAE1, ANKIB1, CRLF3, PDYN - Achieved 99% accuracy in cross-validation (Elastic Net model performed best). The model's biomarkers were further validated using gene expression data from Visual Cortex and Cerebellum regions, achieving over 90% classification accuracy." |
| "Genetic and clinical correlates of two neuroanatomical AI dimensions in the Alzheimer's disease continuum" | Oct, 2024 | "To identify two distinct neuroanatomical dimensions in Alzheimer's disease progression: R1 (diffuse-AD), characterized by widespread brain atrophy, and R2 (MTL-AD), marked by focal atrophy in the medial temporal lobe. The study aims to explore the genetic associations (including APOE 4 for R2) and clinical implications of these dimensions, particularly their presence in both symptomatic and asymptomatic stages of Alzheimer's disease." | "Brain imaging data (MRI) from patients with AD, MCI, and asymptomatic individuals" | "ADNI, UK Biobank, BLSA, PREVENT-AD cohort" | "- A semi-supervised representation learning technique (SurrealGAN) was employed to identify brain atrophy dimensions - GWAS to associate genetic markers to dimensions - Clinical association studies conducted to examine links to AD biomarkers - Longitudinal analysis to track changes over time." | "- Two dimensions identified: R1 (diffuse atrophy) and R2 (focal medial temporal lobe atrophy) - R2 is associated with APOE 4 and AD-specific biomarkers - R1 linked to cardiovascular disease and inflammation - 77 genes unrelated to APOE found to be differentially associated with R1 and R2 - Dimensions are present in both symptomatic and asymptomatic populations." |
| "An Explainable AI Paradigm for Alzheimer's Diagnosis Using Deep Transfer Learning" | Feb, 2024 | "AI-based model for Alzheimer's diagnosis using deep transfer learning and explainable AI (XAI)." | MRI Scans | OASIS dataset | "- Pre-trained CNNs: VGG16, VGG19, DenseNet169, DenseNet201. - Ensemble models: VGG (VGG16 + VGG19) and DenseNet (DenseNet169 + DenseNet201). - Introduced saliency maps and Grad-CAM for explainability. - Data augmentation for imbalanced dataset." | "Achieved 96% accuracy with the proposed model. Improved interpretability with XAI techniques, aiding clinicians in visualizing key regions in MRI scans." |
| "Machine learning with multimodal neuroimaging data to classify stages of Alzheimer's disease: a systematic review and meta-analysis" | August, 2023 | "To assess the contribution of machine learning (ML) methods in accurately classifying Alzheimer's Disease (AD) stages using multimodal neuroimaging data" | "MRI, PET, DTI, fMRI, CSF, EEG, blood biomarkers" | "ADNI, OASIS" | "- Systematic review of 47 studies from IEEE Xplore, PubMed, ScienceDirect, ACM Digital Library - Meta-analysis using a bivariate model with hierarchical summary receiver operating characteristics (HSROC) - Sensitivity, specificity, and statistical tests (Wilcoxon signed-rank) to evaluate model performance" | "- Sensitivity: 83.77% (MCI vs NC), 94.60% (AD vs NC), 80.41% (pMCI vs sMCI), 86.63% (EMCI vs NC) - Specificity: 79.16% (MCI vs NC), 93.49% (AD vs NC), 81.44% (pMCI vs sMCI), 85.68% (EMCI vs NC) - Emphasized variability in models and the importance of feature-level fusion (used in 75% of studies) - Identified a gap in XAI adoption; suggested more research into explainability for clinical relevance." |

Figure 3: Literature survey

## State of the art

The review paper "Machine learning with multimodal neuroimaging data to classify stages of Alzheimer's disease: a systematic review and meta-analysis" by Modupe Odusami, Rytis Maskeliūnas, Robertas Damaševičius, and Sanjay Misra provides an overview of state-of-the-art (SOTA) classification techniques for Alzheimer's Disease (AD).

It highlights that current ML models achieve high accuracy, with classification tasks like AD vs. healthy controls reaching up to 94-97% sensitivity and specificity. Some examples are:

- **Suk et al. (2016):** Modality: MRI, PET, and genetics.
  Fusion Method: Sparse multi-task learning.
  Model: Deep-weighted model.
  Diagnosis: AD vs. NC, MCI vs. NC.
  Accuracy: AD classification had a sensitivity of 92% and a specificity of 90.7%, with an overall accuracy of 98%.

- **Zheng et al. (2016):** Modality: sMRI, PET.
  Fusion Method: Stacked deep polynomial network.
  Model: Support vector machine (SVM).
  Diagnosis: AD vs. CN.
  Accuracy: Achieved an accuracy of 97.3% for AD vs CN with a sensitivity of 96.8% and specificity of 97.5%.

- **Lei et al. (2016):** Modality: PET, sMRI.
  Fusion Method: Multi-kernel learning.
  Model: SVM.
  Diagnosis: AD vs NC, NC vs MCI.
  Accuracy: High accuracy for AD vs NC (97.8%) but moderate for MCI classification (86.5%).

The paper also emphasizes the use of multimodal neuroimaging data (MRI, PET, DTI, EEG, and CSF biomarkers) and advanced fusion methods, with feature-level fusion being the most effective. While the SOTA models show remarkable accuracy, the paper also points out the need for further research into model explainability and external validation to make these methods more clinically applicable.

The paper "An Explainable AI Paradigm for Alzheimer's Diagnosis Using Deep Transfer Learning" by Tanjim Mahmud et al. explores a SOTA approach to Alzheimer's diagnosis by integrating deep transfer learning models and explainable AI (XAI) techniques.

The authors achieve SOTA accuracy of 96% by using an ensemble of popular pre-trained convolutional neural networks (CNNs), including VGG16, VGG19, DenseNet169, and DenseNet201. Two ensembles—Ensemble-1 (VGG16 + VGG19) and Ensemble-2 (DenseNet169 + DenseNet201)—demonstrate that combining multiple architectures yields superior results compared to individual models.

The standout feature of this paper is its use of explainable AI techniques, such as saliency maps and grad-CAM, which enhance the transparency and interpretability of the models. This addresses a challenge in medical AI and ensures that clinicians can understand and trust AI-generated insights by visualizing the neural regions influencing diagnoses.

## Key Insights That Have Driven Progress in This Domain in Recent Years

There has been a notable shift towards multimodal data integration. Multiple data sources like MRI, PET, genetic data, and cognitive assessments are being combined to improve AD progression research since they use diversity to capture patterns that single-modality approaches do not. Feature fusion allows models to fully exploit the strengths of each modality for better diagnostic outcomes.

Incorporation of explainable AI is making models more adoptable by having the outputs be more interpretable. For example, Saliency maps and Grad-CAM visualize which brain regions influence AI predictions, increasing model transparency.

There is also a strong reliance on transfer learning. For example, VGG and DenseNet are being used to improve AD classification. Smaller models are being fine-tuned using AD datasets to boost performance without requiring extensive labeled medical data.

# Approach

## Approach 1: Multimodal Deep Learning with Explainable AI

In this approach, we'll build a multimodal deep learning model that integrates genetic data (e.g., APOE, SNPs), neuroimaging (MRI/PET), and biomarkers (e.g., CSF amyloid, tau) to classify Alzheimer's Disease (AD) stages. The innovation lies in combining these diverse data sources for high-quality prediction while using Explainable AI (XAI) techniques like SHAP and Grad-CAM to identify which genetic variants, brain regions, or biomarkers drive disease progression. While the exact usage and insight derived from XAI may be unclear, we hope to learn about AD through the lens of an extremely accurate predictor/classifier.

## Approach 2: Ensemble Model for Genetic Data with Explainable AI

This approach focuses on building an ensemble model using multiple classifiers (e.g. CNNs for Imaging data, MLP for genetic data, etc) to classify AD stages. This approach will allow us to use multiple methods to visualize embeddings and understand the complexities of various models for various data modalities. This method will also help us gain insight into the relationship between different indicators, such as which SNP or gene contributes to which type of brain atrophy. Even though this method might not give the best classification accuracy, we hope it could help us gain insight into Alzheimer's disease and its contributing factors.

# Github Link

`https://github.com/coolperson111/Alzheimers_is_Deep`

# References

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