

ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI): Clinical characterisation

How can quantitative MRI-derived imaging features serve as reliable biomarkers for the diagnosis of Alzheimer's disease?

INTRODUCTION

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder characterized by progressive loss of cognitive function due to the deterioration of brain tissue, affecting millions of people worldwide.

In this study, we analyzed **longitudinal magnetic resonance imaging (MRI)** scans collected over time from three groups of participants:

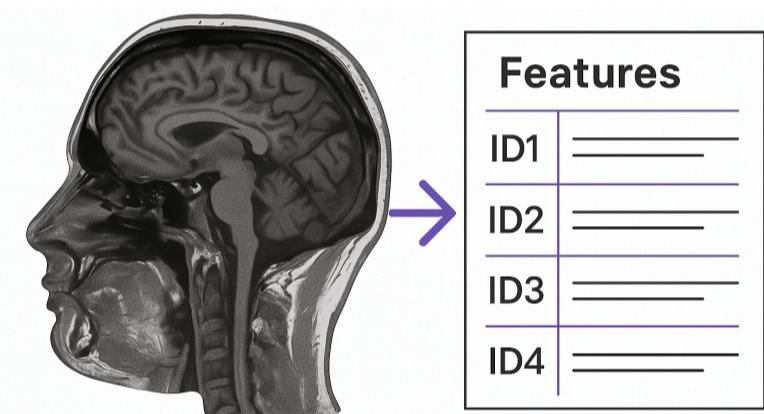
- Cognitively Normal (**CN**)
- Mild Cognitive Impairment (**MCI**)
- Alzheimer's disease (**AD**)

to identify patterns of structural brain change associated with disease onset and progression.

FEATURE ENGINEERING & SELECTION

Preprocessing & Feature Extraction

From raw MRI scans, we processed images and extracted quantitative features into an Excel dataset



Literature-driven preselection

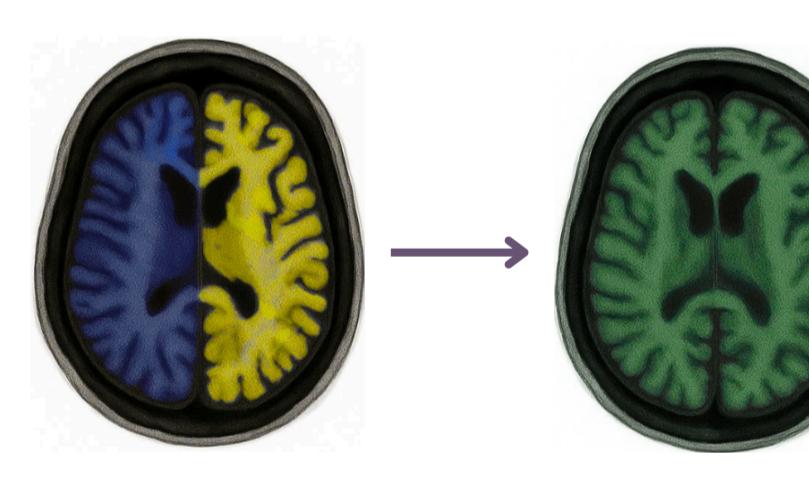
identified key metrics from prior studies

Recursive Feature Elimination (RFE)

iteratively ranks features by importance, removing the least significant until only the most informative remain.

Bilateral aggregation

combined left/right measures to reduce dimensionality and capture overall structural changes



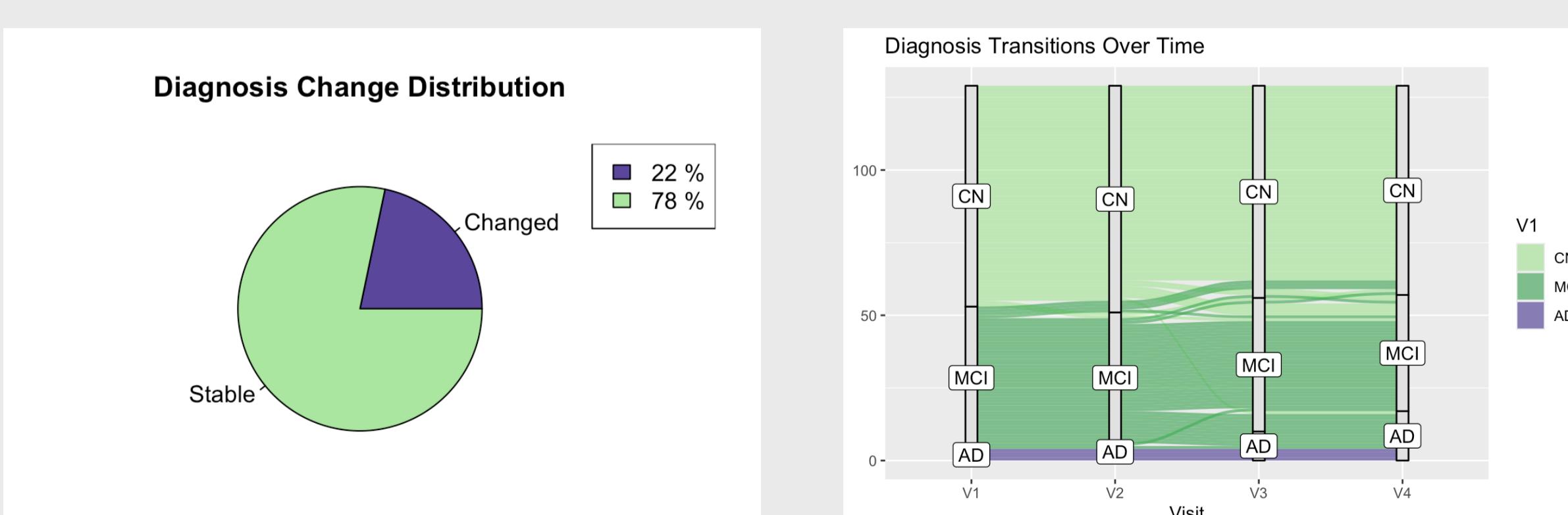
LONGITUDINAL MRI ACROSS FOUR TIMEPOINTS

Objective

To compare structural MRI scans of cognitively normal, MCI, and Alzheimer's cohorts at four distinct timepoints in order to characterize how key quantitative imaging features evolve over time and relate to changes in diagnostic category.

Methods

- We initially applied **linear mixed-effects models (LMMs)** to account for repeated measures of structural MRI features across the four timepoints.
- We also tested **multinomial mixed-effects models** to predict transitions between diagnostic categories



→ Despite efforts to model the temporal evolution of diagnosis, we found that longitudinal models (LMM/GLMM) were unsuitable due to high collinearity, convergence issues, and near-zero intra-subject variability—78% of patients showed no diagnostic change across visits

ATEMPORAL ANALYSIS

MULTINOMIAL ANALYSIS ON ALZHEIMER'S DIAGNOSIS: A COMPARISON OF BALANCING TECHNIQUES

Objective

The aim of this study is to evaluate the effect of brain volumetric measures on the probability of belonging to one of the three diagnostic categories: CN (Cognitively Normal), MCI (Mild Cognitive Impairment), and AD (Alzheimer's Disease), using multinomial regression models and comparing different dataset balancing techniques.

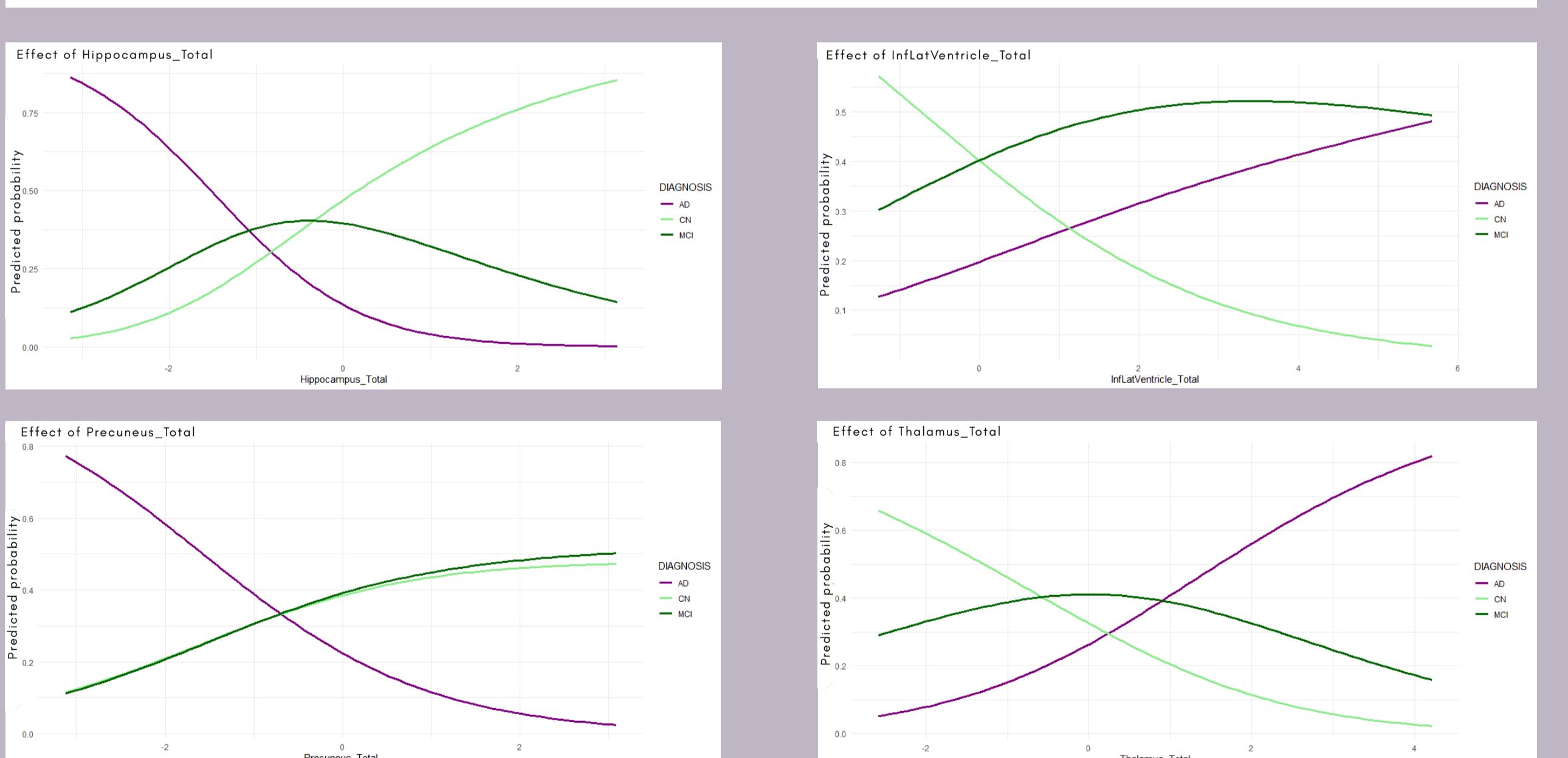
Balancing Techniques

1. Class Weights
2. SMOTE (Synthetic Minority Oversampling Technique)
3. K-Medoids Undersampling

Statistical Significance of the Coefficients (P-Values)

Variables	Class Weights (AD)	SMOTE (AD)	K-Medoids (AD)
Hippocampus_Total	0.6141	0.0000	<0.001
Thalamus_Total	0.8400	0.0005	0.0250
SuperiorTemporal_Total	0.9616	0.5406	0.2100
Insula_Total	0.8910	0.0113	0.0223
Precuneus_Total	0.7660	<1e-8	<0.001
Mammillary_Total	0.9132	0.0263	0.0913
CaudalMiddleFrontal_Total	0.9888	0.6961	0.4467
InfLatVentricle_Total	0.7041	1.02e-10	6.5e-6

Variables	SMOTE (AD)	SMOTE (MCI)	K-Medoids (AD)	K-Medoids (MCI)
Hippocampus_Total	0.0000	0.1006	<0.001	0.127
InfLatVentricle_Total	7.10e-12	0.0051	<0.001	0.128
Precuneus_Total	1.06e-10	0.747	0.0002	0.912
Thalamus_Total	0.0005	0.515	0.0250	0.822

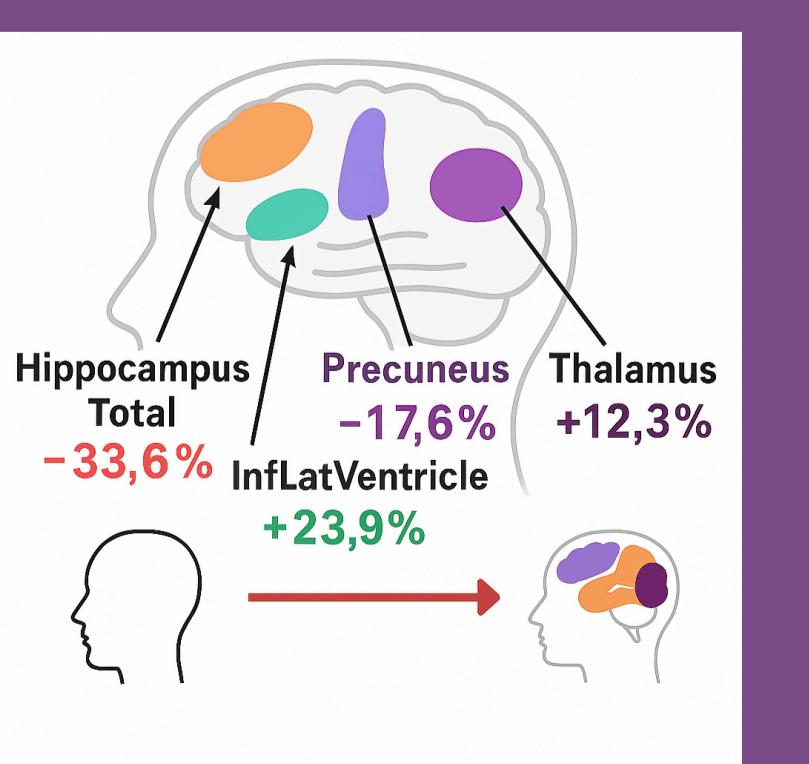


CONCLUSIONS

Balancing techniques have a strong impact on the statistical significance of variables: SMOTE and K-Medoids allowed more **robust** associations between volumetric measures and diagnosis to emerge.

From a **clinical perspective**, the findings align well with the literature, except for Thalamus.

Although **thalamic atrophy** is common in Alzheimer's, we found that higher thalamic volume predicts greater AD risk. This paradox may reflect early swelling in at-risk groups (e.g., APOE ε4 carriers) due to neuroinflammation or gliosis from amyloid buildup.



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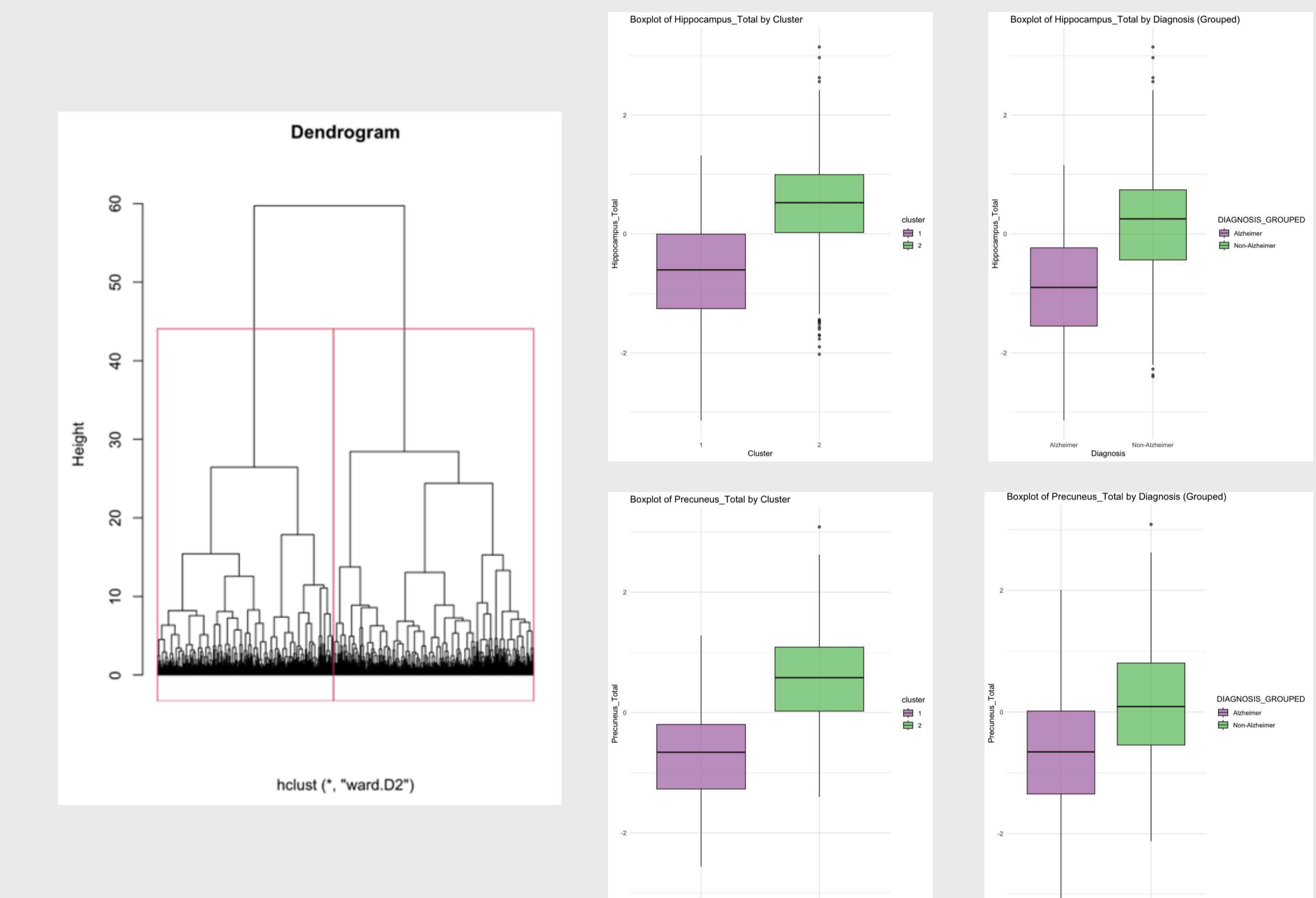
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HIERARCHICAL CLUSTERING: AD VS. CN/MCI

Interestingly, the **lack of discriminative power between MCI and CN** observed in the multinomial model was independently supported by an **unsupervised hierarchical clustering analysis**. Using **Ward's method** on standardized brain measures, the optimal clustering solution consisted of two groups, which aligned closely with the clinical diagnostic split between AD and non-AD (i.e., CN and MCI combined).



→ This convergence of evidence from both supervised and unsupervised methods reinforces the hypothesis that **MCI and CN subjects share overlapping structural profiles**, at least in terms of the brain regions considered in this study. The clustering structure thus mirrored the diagnostic classification, particularly in isolating the AD group from the rest.

GENETIC VARIANTS DRIVING ALZHEIMER'S RISK

We evaluated the **predictive effectiveness of a set of genetic variables** (SNPs and APOE genotype) in the clinical classification of Alzheimer's disease (CN, MCI, AD), using multinomial and binary logistic regression models. This analysis was conducted on a subset of patients for whom complete genetic data were available.

The **baseline model**, which included only brain volumetric variables, achieved an accuracy of 58.1%.

The **joint model** (SNPs + APOE + brain variables) reached a maximum accuracy of 67.4%, suggesting a potential synergistic value of combining genetic and neuroimaging data.

