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Genetic predisposition to Alzheimer's disease is differentially associated with joint volumetric variations in the disease continuum

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Background

- Imaging genetics (IG) studies analyze how genetic information influences brain features by combining neuroimaging-based brain features and genetics data.
- Most IG studies focus on individual analysis of brain structures.
- An alternative is to incorporate compositional data analysis (CoDA) methods to assess the joint modulation of specific brain subregions.

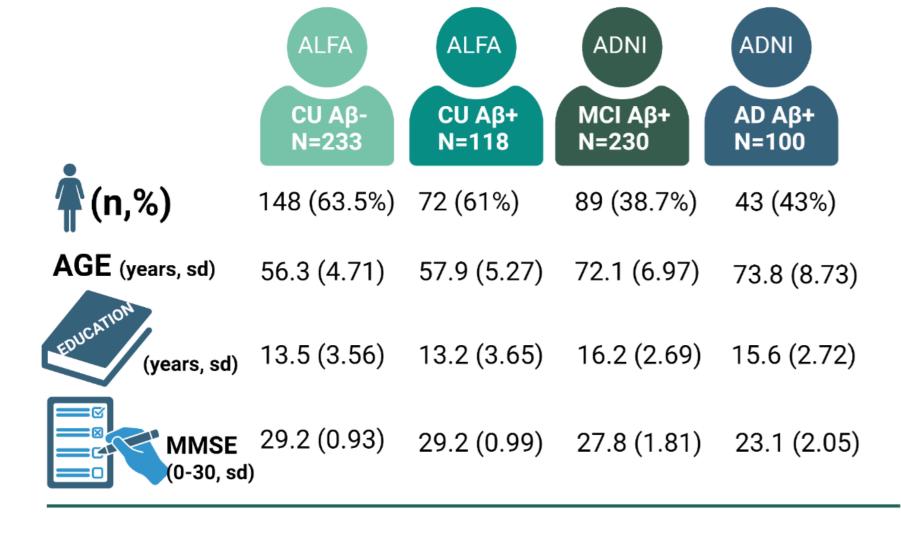
Aim

The main goal of this study is to explore the structural variation of the brain at different stages of Alzheimer's disease (AD) continuum, depending on the genetic predisposition to AD.

Methods

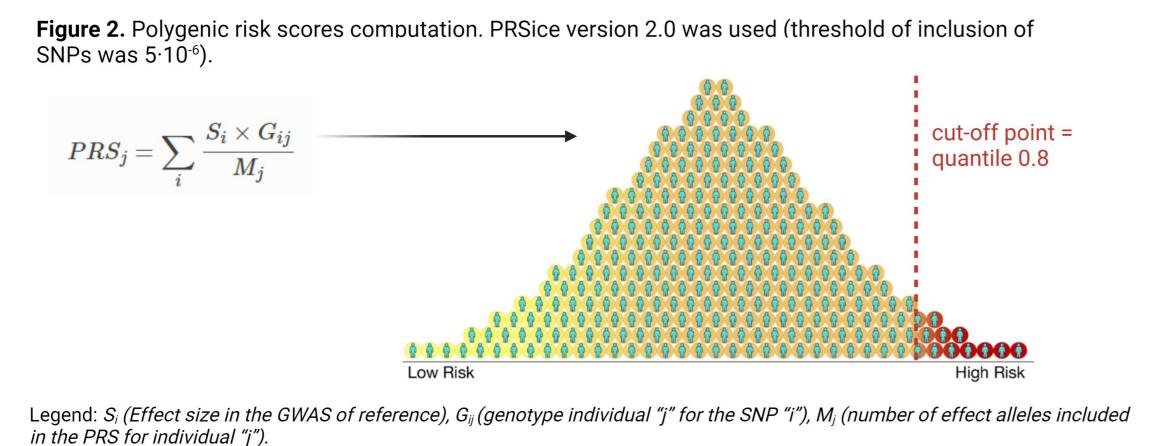
a) Sample: cognitively unimpaired (CU) middle-age participants from ALFA [1] and cognitively impaired participants from ADNI [2] study

Figure 1. Demographic characteristics of the study populations.



Legend: CU Aβ- (cognitively unimpaired amyloid-beta negative), CU Aβ+ (cognitively unimpaired amyloid-beta positive), MCI $A\beta$ + (mild cognitive impaired amyloid-beta positive), AD Aβ+ (Alzheimer's disease amyloid-beta positive), MMSE (Mini Mental State Exam). Counts and percentage per group were reported for categorical variables.

b) Genetic data: The polygenic risk score estimating each participant's genetic predisposition to AD (PRS-AD) was calculated including genetic variants at the genome-wide suggestive level (5·10-6), normalizing by the total number of alleles [3]. Individuals were classified into high/low genetic predisposition groups (cut-off point=quantile 0.8) [Figure 2].



c) Neuroimaging data

- Freesurfer [4] was used to obtain cortical and subcortical parcellations using the Desikan-Killiany atlas [5].
- Volumes were globally quantified by summing the measurements of both hemispheres.

d) Statistical Analysis: Statistical analysis was based on CoDA [6]. Analyses were performed using *Coda4microbiome* R package [7].

Composition: vector of strictly positive real numbers with a constraint or noninformative total sum [8]. In the study, the composition is defined as the whole brain volume, and the components are the brain subregions volumes.

Composition
$$x = [X_1, ..., X_D] \in \mathbb{R}^D$$

for $x_i > 0$, $\sum_{i=1}^{D} x_i = k$, where k is a constant



Key point: the value of each component is not informative by itself and the relevant information is contained in the ratios between parts. The simplest scale invariant function is the log-ratio between components

Coda4microbiome: the algorithm was based on two main steps.

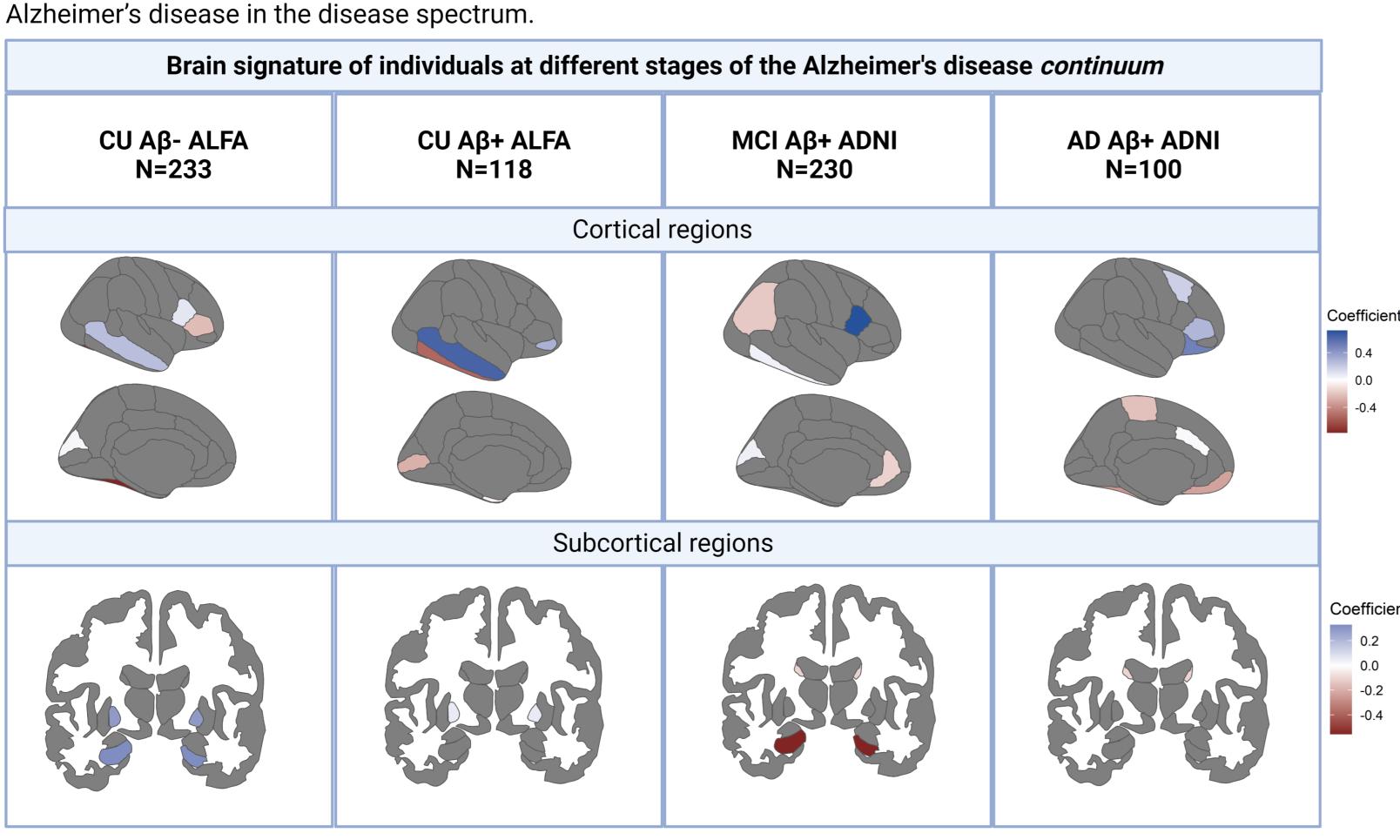
Computation of the optimal multivariate brain structural variation signature (M_i) (elastic net selection).

$$M_i = \sum_{1 \le j < k \le K} \hat{\beta}_{jk} \cdot \log(X_{ij}/X_{ik})$$
 [7]

Logistic regression model to determine the **association** between the **M**_i and the **risk of AD**. Models were stratified by disease stage and adjusted for age and sex.

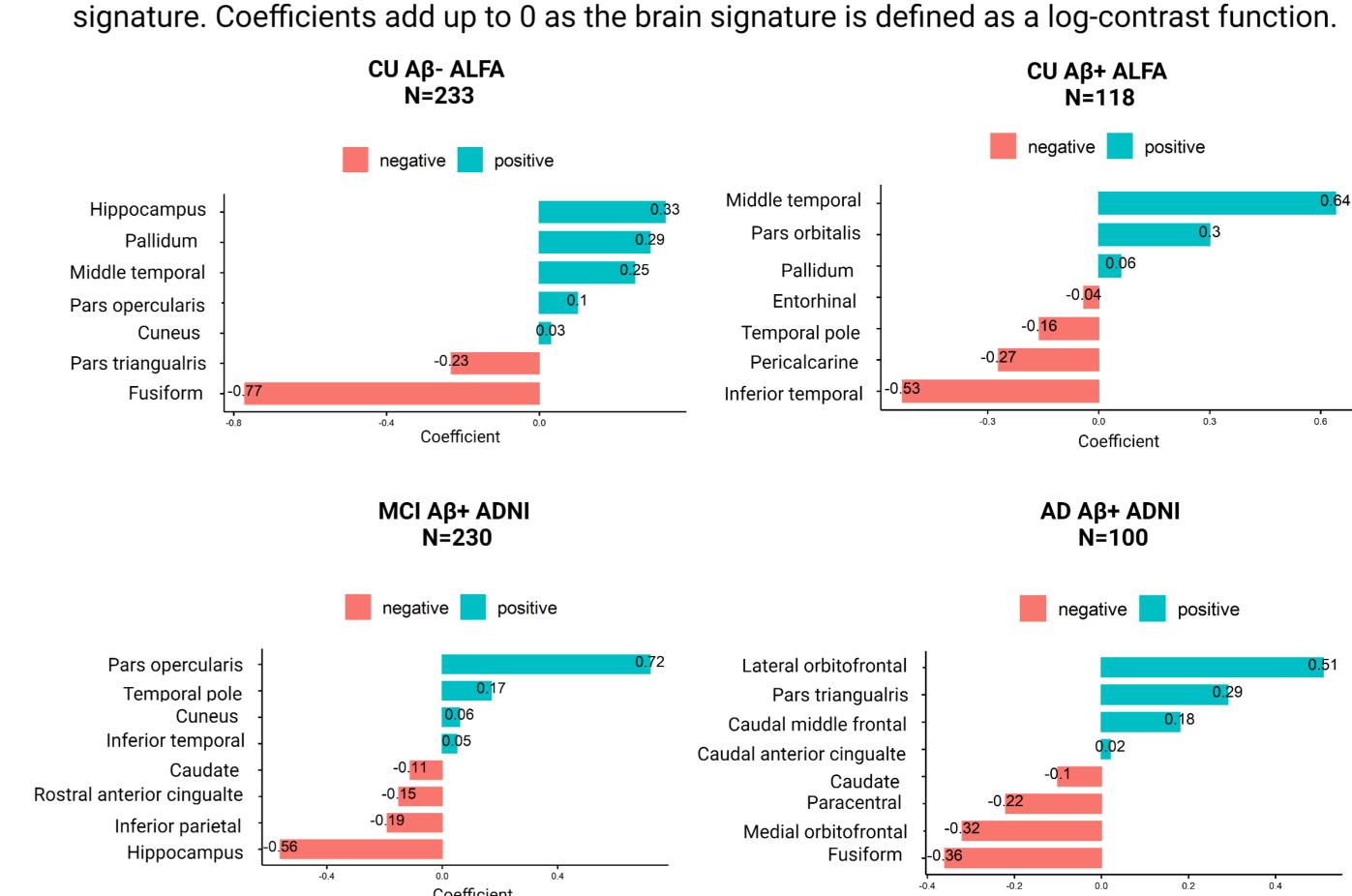
Results

Figure 3. Optimal multivariate structural brain signatures associated with higher genetic predisposition to



Legend: CU $A\beta$ - (cognitively unimpaired amyloid-beta negative), CU $A\beta$ + (cognitively unimpaired amyloid-beta positive), MCI $A\beta$ + (mild cognitive impaired amyloid-beta positive), AD $A\beta$ + (Alzheimer's disease amyloid-beta positive).

Figure 4. Weight of each brain region involved in the optimal multivariate structural brain



Legend: CU $A\beta$ - (cognitively unimpaired amyloid-beta negative), CU $A\beta$ + (cognitively unimpaired amyloid-beta positive), MCI $A\beta$ + (mild cognitive impaired amyloid-beta positive), AD $A\beta$ + (Alzheimer's disease amyloid-beta positive).

Individuals at different stages on the AD continuum displayed different brain volumetric modulations associated with higher genetic predisposition to AD [Figure 3].

The optimal signature associated with a higher risk of AD was characterized by increased hippocampal volumes in ABindividuals, but decreased volumes in MCI Aβ+ along with the modulation of other temporal regions [Figure 4].

Conclusions

- Results showed AD stage-specific multivariate volumetric variation associated with an increased genetic risk of AD.
- The analysis of the joint volumetric variation of brain subregions brings an innovative modeling perspective for neurogenetic studies of AD.

References

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