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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.

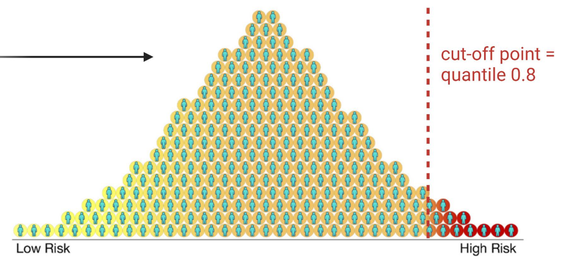
	ALFA CU Aβ- N=233	ALFA CU Aβ+ N=118	ADNI MCI Aβ+ N=230	ADNI AD Aβ+ N=100
(n,%)	148 (63.5%)	72 (61%)	89 (38.7%)	43 (43%)
AGE (years, sd)	56.3 (4.71)	57.9 (5.27)	72.1 (6.97)	73.8 (8.73)
EDUCATION (years, sd)	13.5 (3.56)	13.2 (3.65)	16.2 (2.69)	15.6 (2.72)
MMSE (0-30, sd)	29.2 (0.93)	29.2 (0.99)	27.8 (1.81)	23.1 (2.05)

Legend: *CU Aβ- (cognitively unimpaired amyloid-beta negative), CU Aβ+ (cognitively unimpaired amyloid-beta positive), MCI Aβ+ (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** ($5 \cdot 10^{-6}$), 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].**

Figure 2. Polygenic risk scores computation. PRSice version 2.0 was used (threshold of inclusion of SNPs was $5 \cdot 10^{-6}$).

$$PRS_j = \sum_i \frac{S_i \times G_{ij}}{M_j}$$



Legend: *S_i (Effect size in the GWAS of reference), G_{ij} (genotype individual "j" for the SNP "i"), M_j (number of effect alleles included in the PRS for individual "j").*

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 non-informative total sum **[8]**. In the study, the composition is defined as the whole brain volume, and the components are the brain subregions volumes.

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

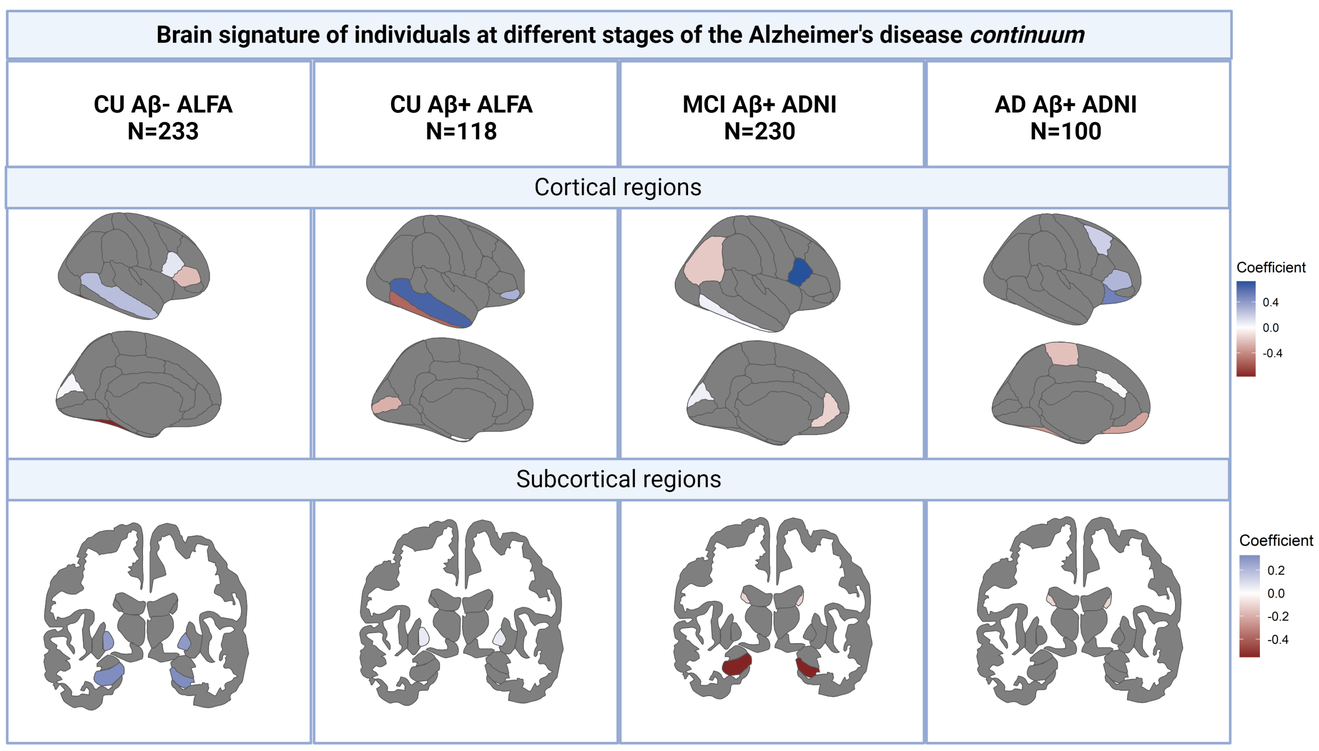
1) Computation of the **optimal multivariate brain structural variation signature (M_i)** (**elastic net selection**).

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

2) **Logistic regression model** to determine the **association** between the $\mathbf{M_i}$ and the **risk of AD**. Models were stratified by disease stage and adjusted for age and sex.

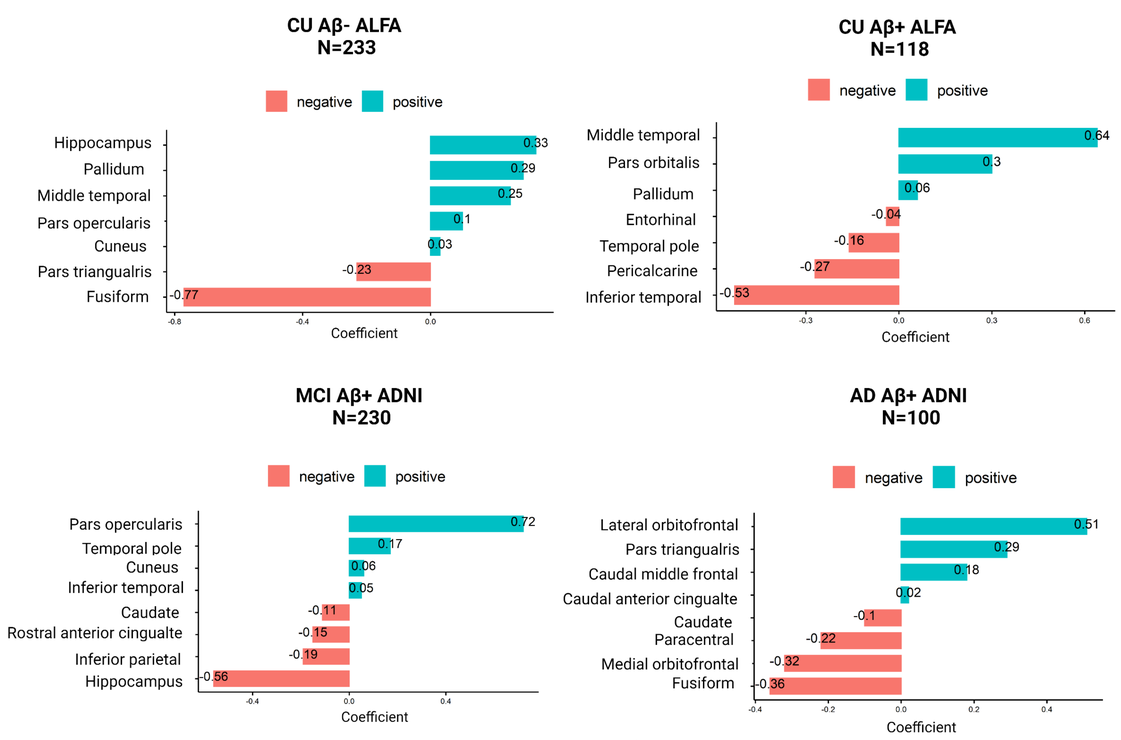
Results

Figure 3. Optimal multivariate structural brain signatures associated with higher genetic predisposition to Alzheimer's disease in the disease spectrum.



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

Figure 4. Weight of each brain region involved in the optimal multivariate structural brain signature. Coefficients add up to 0 as the brain signature is defined as a log-contrast function.



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

Individuals at **different stages on the AD *continuum*** displayed d**ifferent 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 **Aβ-** individuals, 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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