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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 [Figure1].**

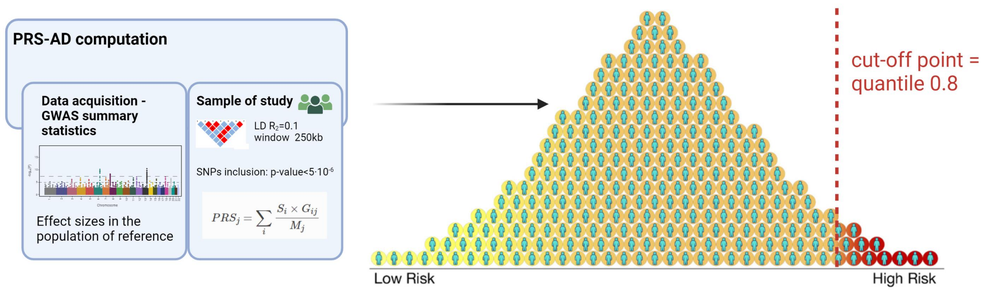
Figure 1. Demographic characteristics of the study populations.

	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 $5{\cdot}10^{-6}$).



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.

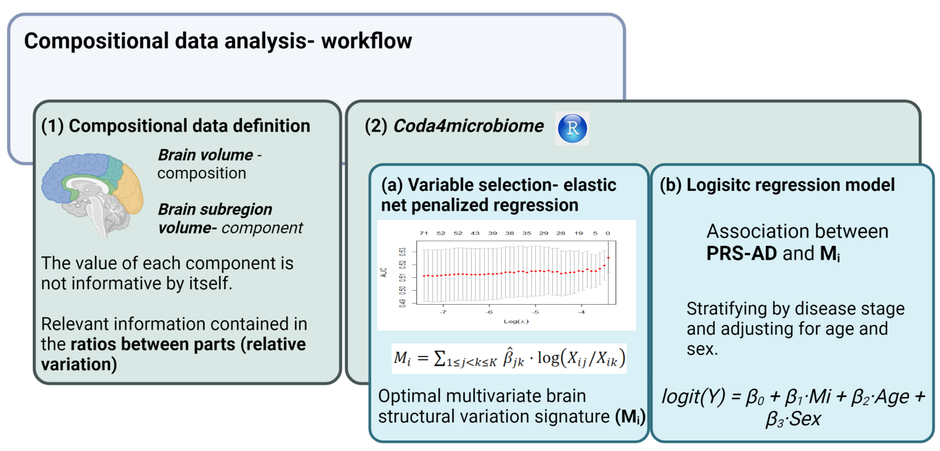
d) Statistical Analysis: Statistical analysis was based on **CoDA [6].** Analyses were performed using ***Coda4microbiome*** R package **[7].**

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 **[Figure 3]**.

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

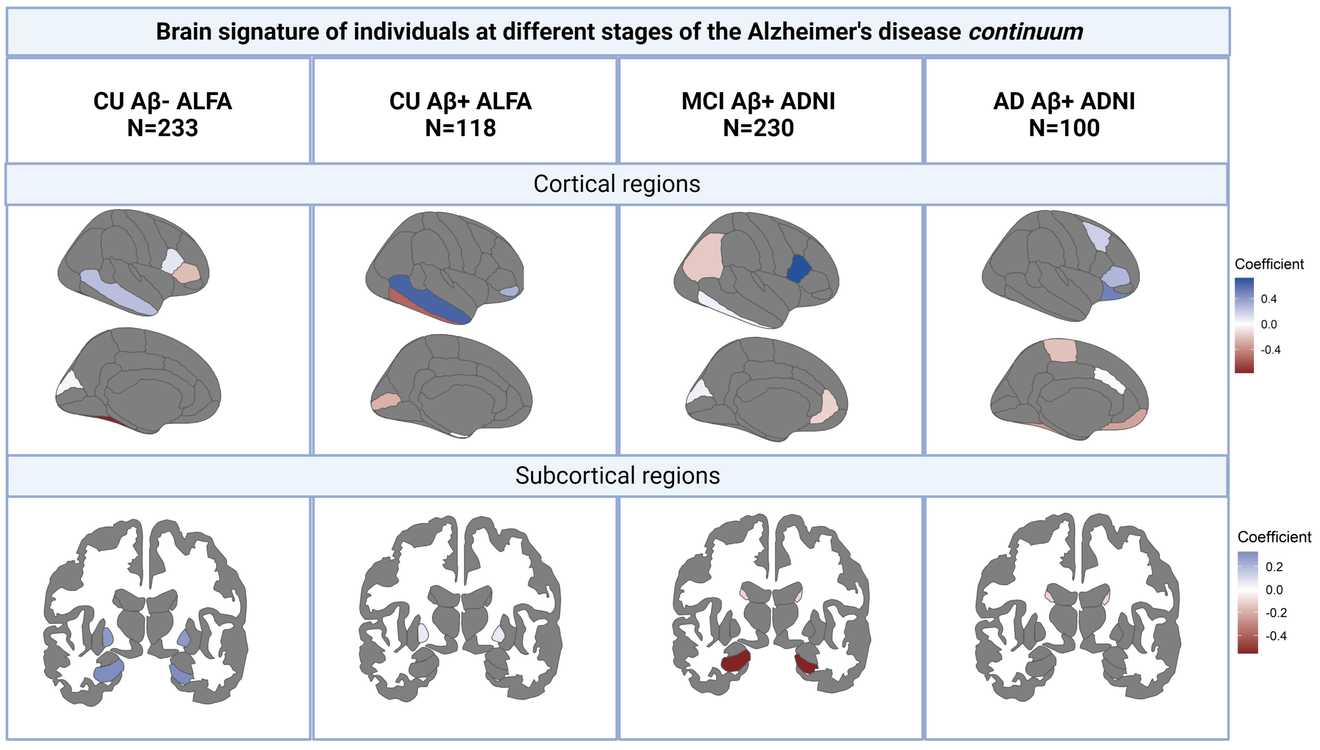
Coda4microbiome: the algorithm was based on two main steps **[Figure 3]**: (2.a) computation of the optimal multivariate brain structural variation signature and (2.b) definition of a logistic model to assess the association with the risk of AD.

Figure 3. Compositional data analysis: working with *coda4microbiome* R package (Calle & Susin, 2022).



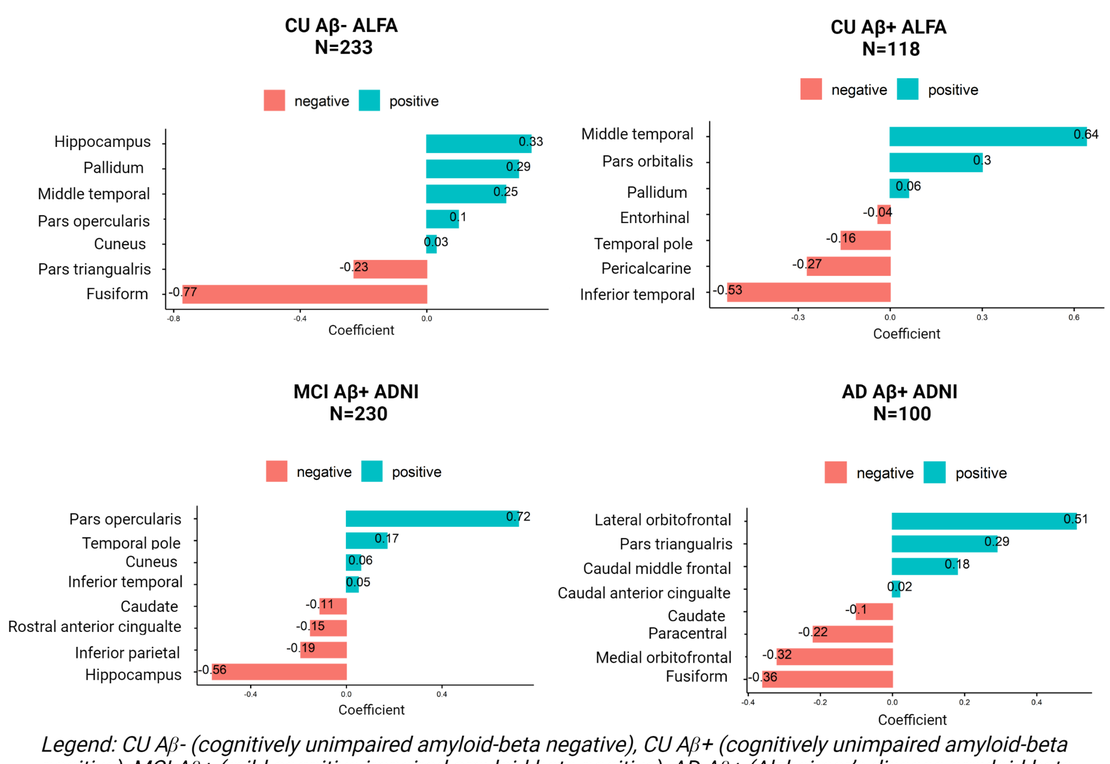
Results

Figure 4. 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 5. 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 4].**

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 5]**.

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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