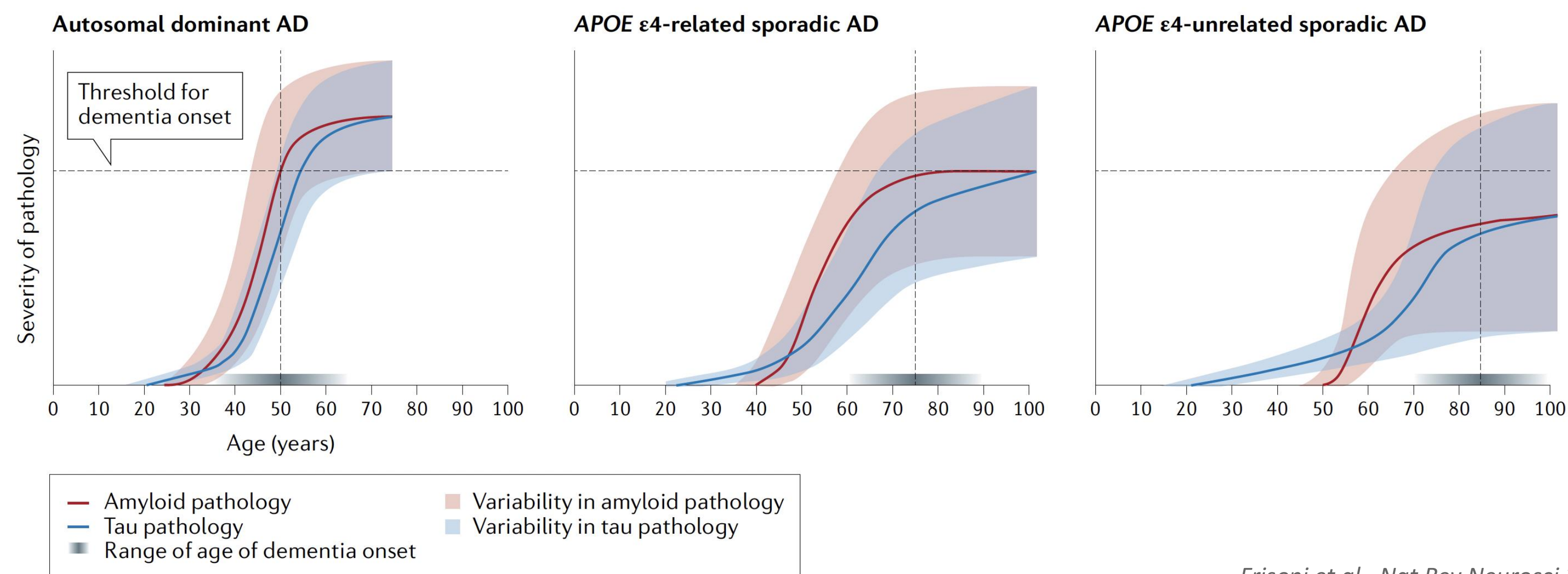


1 Introduction

- **Alzheimer's disease (AD) is heterogeneous:** amyloid deposition varies substantially across individuals in onset, regional distribution, and rate of progression.
- **APOE ε4** is the strongest common genetic risk factor for sporadic AD and a key modifier of amyloid cascade penetrance.
- **Probabilistic model of AD (Frisoni et al., 2022):** genetic factors govern the balance between deterministic and stochastic influences, creating a continuum of pathological predictability.



2 Methods

Participants

- Alzheimer's Disease Neuroimaging Initiative (**ADNI**) and Geneva Memory Center (**GMC**) cohorts
- **Inclusion criteria:** amyloid positive (A+), availability of amyloid-PET, and APOE4
- **APOE4 genotype:** non-carriers (zero alleles), heterozygotes (one allele), and homozygotes (two alleles)

Amyloid PET acquisition

- **ADNI:** [¹⁸F]florbetapir
- **GMC:** [¹⁸F]flutemetamol
- **Preprocessing:** SPM12, MNI normalization, 2mm isotropic, grey-matter masked SUVR maps

Statistical analysis

- 1) **Topographic similarity:** Pearson r between individual voxel-wise SUVR maps and canonical AD amyloid reference map (Centiloid Project)
- 2) **Spatial homogeneity:** Inter-subject Pearson r matrices within APOE4 genotype groups

Linear regression adjusted for age, sex, and global amyloid burden to compare among APOE4 groups

Winner-take-all maps display the voxels which APOE4 genotype dominates in both analysis

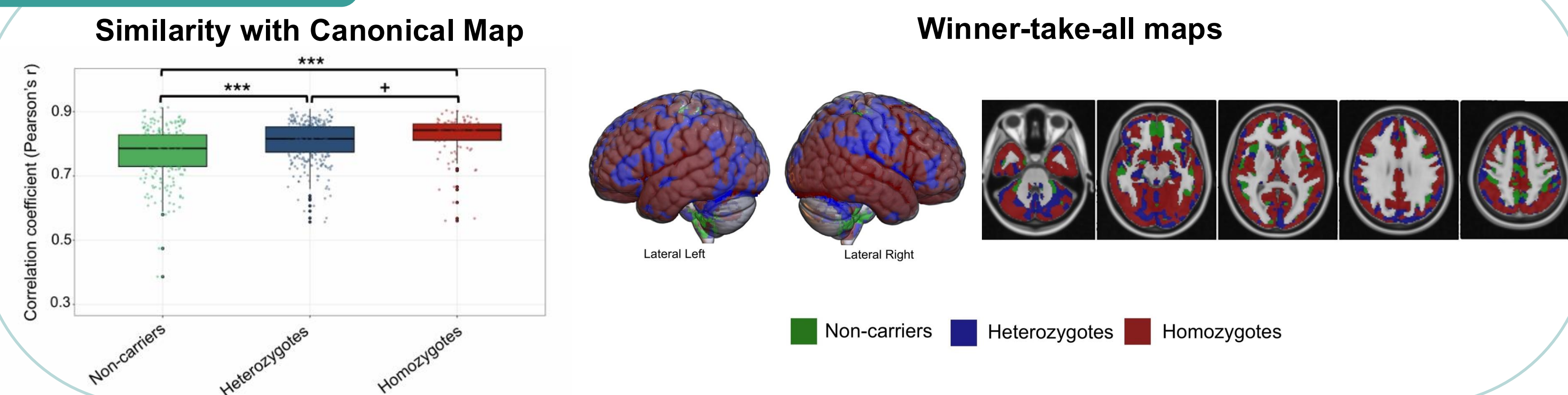
3 Main Results

Participants

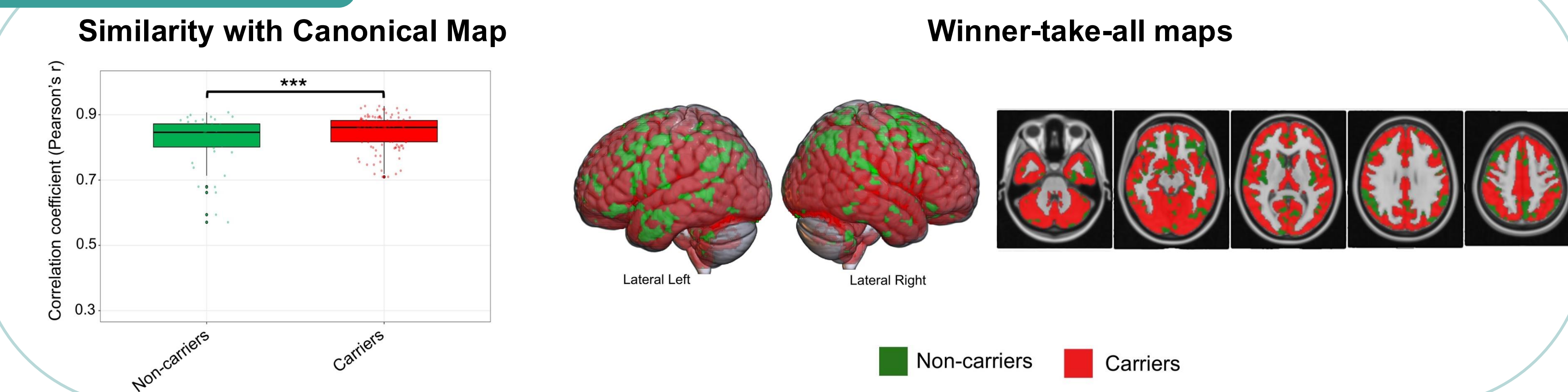
Total	ADNI	GMC
781	676	105
Cognitively unimpaired (CU)	160 (24%)	—
Mild Cognitive Impairment (MCI)	331 (49%)	62 (59%)
Dementia	185 (27%)	43 (41%)
APOE4 carrier	427 (63%)	62 (59%)

1) Determine how APOE4 is aligned with canonical amyloid topography

ADNI cohort

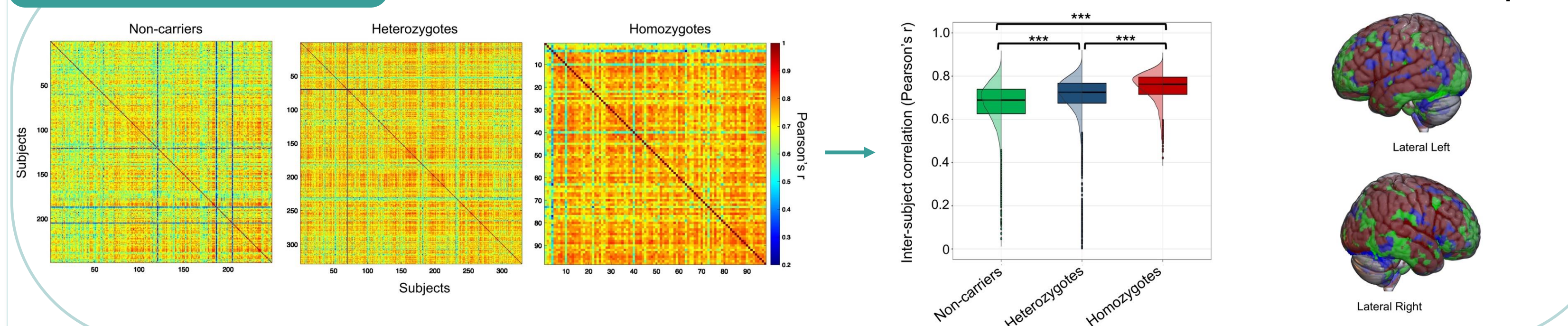


GMC cohort

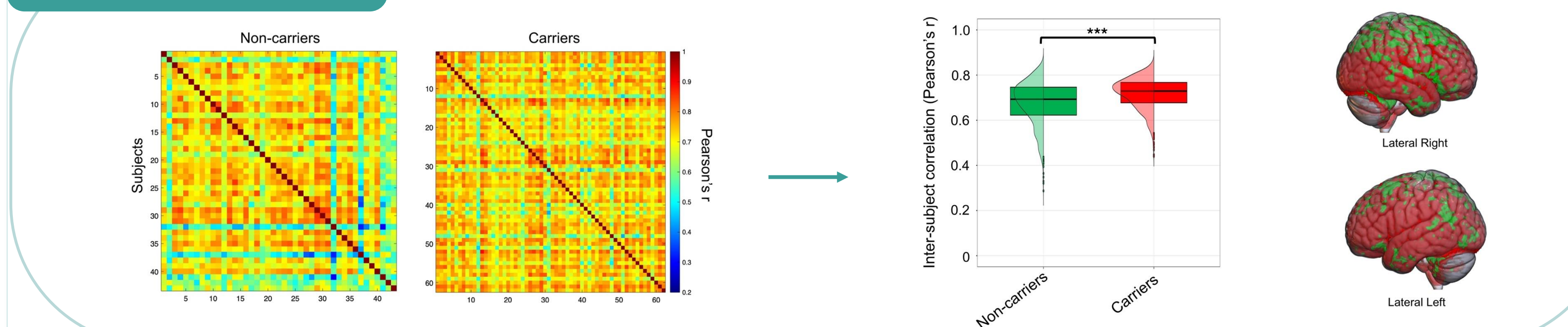


2) Test how APOE4 carriers has greater spatial homogeneity of amyloid deposition

ADNI cohort



GMC cohort



4 Conclusions

- 01 **Dose-dependent effect:** Higher APOE4 dose drives a more canonical and homogeneous amyloid topography
- 02 **Probabilistic model:** APOE4 influences the determinism of pathological penetrance
- 03 **Robust findings:** Results are consistent across cohorts, PET tracers, and independent of global amyloid burden
- 04 **Clinical implications:** Spatial predictability supports genotype-stratified strategies for anti-amyloid therapies

5 Affiliations, funding, and contact

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