

Elise SAUL, Salma BOUGACHA, Daniel ROQUET, Brigitte LANDEAU, Noémie CORDIER, for the Alzheimer’s Disease Neuroimaging Initiative, the HABS-HD Study Team, the LEADS Study group, Robin DE FLORES & Gaël CHETELAT
Normandie Univ, UNICAEN, INSERM, UA20, NEUROPRESAGE, Cyceron, Caen, France

Amyloid enables, tau organizes, clinical progression amplifies – network-dependent neurodegeneration in AD

INTRODUCTION RESULTS

Neurodegeneration in Alzheimer’s disease (AD) is increasingly framed as a **network-driven process** shaped by **structural** and **functional connectivity**¹⁻². Regional atrophy may reflect complementary mechanisms modelled as network predictors (epicenter proximity³⁻⁴, hub vulnerability⁵, and diffusion-like patterns¹) operating across both modalities. However, their relative contribution may vary across biomarker⁶ strata (amyloid and tau status), clinical stage (minor versus major cognitive disorders; MinCD/MajCD), and age at onset⁷ (early- versus late-onset AD; EAOD <65 years; LOAD ≥65 years). Here, we applied a unified, cross-validated connectome-based framework⁸ to quantify structural and functional predictor contributions across these strata, testing whether they define distinct connectome-based signatures of atrophy in AD.

METHODS

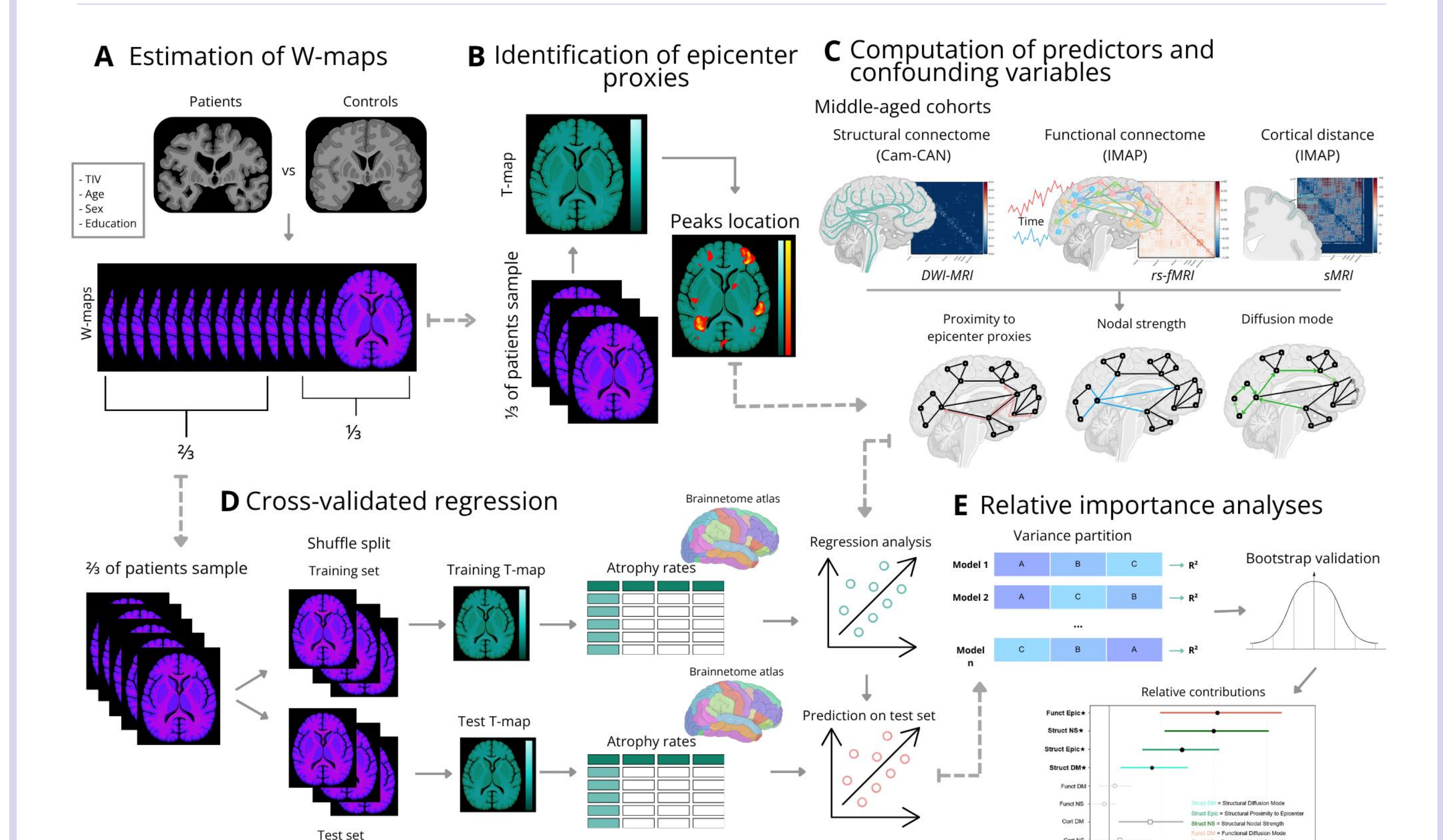
Patients' stratifications according to:

- Aβ status (Aβ+ vs Aβ-)
- Tau status (T+ vs T-)
- Clinical stage (MinCD vs MajCD)
- Age at onset (LOAD vs EAOD)

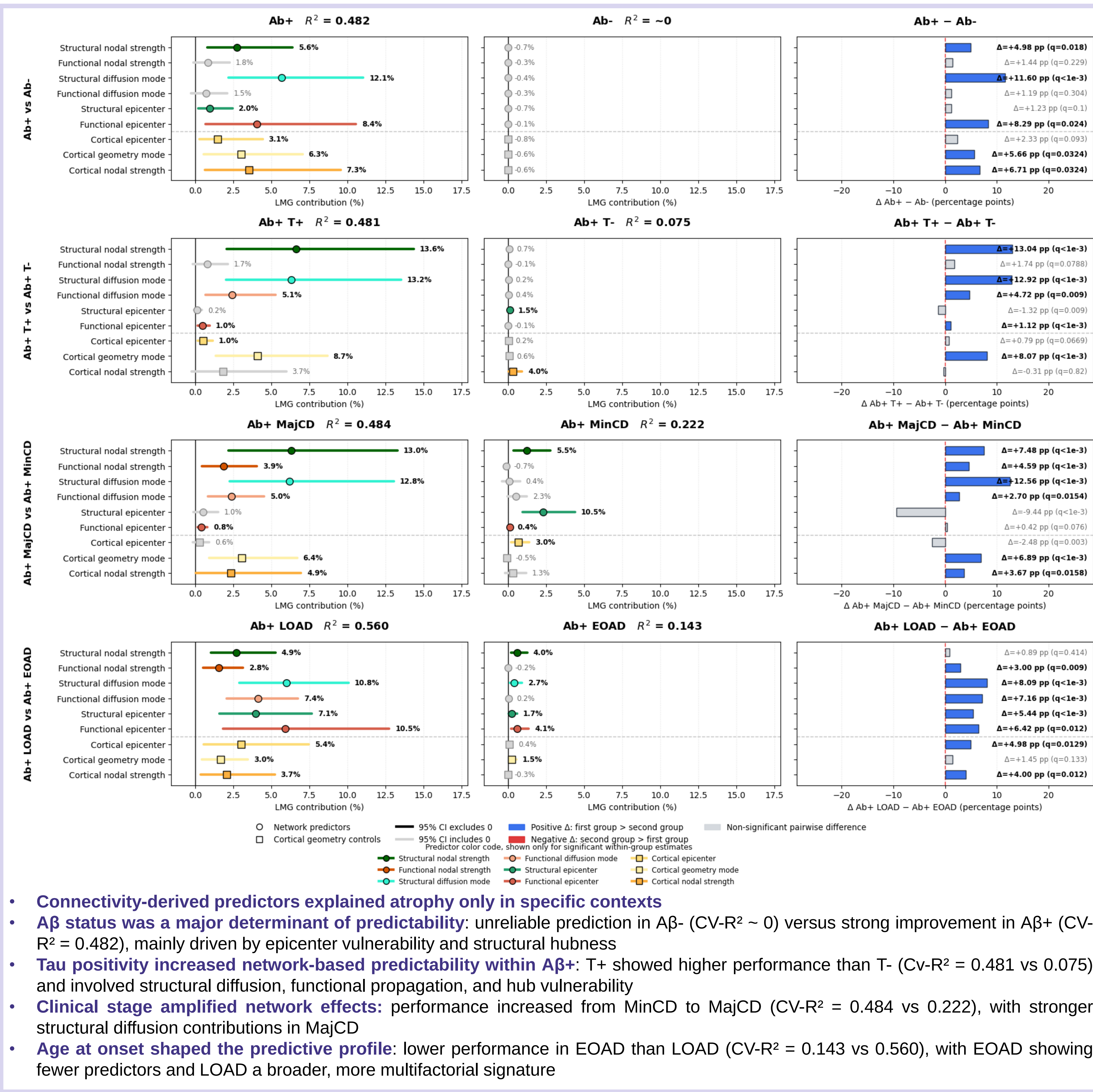
5 cohorts:

- ADNI
- LEADS
- HABS-HD
- Cam-CAN
- IMAP

	Aβ+ patients	Aβ- patients	CU (Aβ-/T-)
N	671	692	441
Sex (female)	326 (48.6)	347 (50.14)	272 (61.7)
Age (years)	70.66 ± 8.86	65.92 ± 9.02	63.4 ± 8
Education (years)	15.48 ± 2.94	14.48 ± 3.39	14.74 ± 3.28
APOE4 carriers	419 (62.4)	176 (28.16)	99 (22.4)
Ethnicity			
Hispanic	36	129	110
Non-hispanic	633	563	331
Asian	103	1	0
Black	49	266	191
Pacific islander	6	0	0
White	475	296	140
Missing	2	0	0
Tau status			
T+	360	-	-
T-	93	-	-
Missing	218	-	-
Age at onset			
EOAD	196 (29.2)	-	-
LOAD	475 (70.8)	-	-
Diagnosis			
MinCD	357 (53.2)	-	-
MajCD	314 (46.8)	-	-



Overview of the analytical framework used to estimate regional biomarker patterns, define maximal atrophy sites, and assess the relative contribution of network-based predictors. (A) W-score maps were estimated for each patient relative to healthy elderly controls, and patients were divided into independent samples for maximal atrophy site identification and regression analyses. (B) Maximal pathology sites, used as epicenter proxies, were identified from group-level maps using a parcel-wise ranking approach. (C) Predictors were derived from healthy middle-aged structural, functional, and cortical distance networks. (D) Repeated train-test splits were used to model regional atrophy patterns with cross-validated Ridge regression. (E) Relative importance and bootstrap analyses were used to estimate and quantify predictor contributions.



- **Connectivity-derived predictors explained atrophy only in specific contexts**
- **Aβ status was a major determinant of predictability:** unreliable prediction in Aβ- (CV-R² ~ 0) versus strong improvement in Aβ+ (CV-R² = 0.482), mainly driven by epicenter vulnerability and structural hubness
- **Tau positivity increased network-based predictability within Aβ+:** T+ showed higher performance than T- (Cv-R² = 0.481 vs 0.075) and involved structural diffusion, functional propagation, and hub vulnerability
- **Clinical stage amplified network effects:** performance increased from MinCD to MajCD (CV-R² = 0.484 vs 0.222), with stronger structural diffusion contributions in MajCD
- **Age at onset shaped the predictive profile:** lower performance in EOAD than LOAD (CV-R² = 0.143 vs 0.560), with EOAD showing fewer predictors and LOAD a broader, more multifactorial signature

CONCLUSION

- A hierarchy of network-driven neurodegeneration emerges, in which Aβ acts as a permissive factor for network-constrained neurodegeneration, while tau organizes propagation through mechanisms extending beyond epicenter effects, including structural diffusion mode, functional spread, and hub vulnerability
- This network signature appears progressively amplified with clinical stage, with a stronger pattern from MinCD to MajCD, suggesting a progressive stabilization and increasing dominance of connectome-driven processes
- Age at onset also shapes the neurodegenerative signature: the lower explained variance observed in EAD may reflect greater heterogeneity and fewer concurrent explanatory mechanisms, whereas LOAD appears more multi-determined, potentially integrating aging-related factors, co-pathologies, and broader multifactorial influences
- **Overall, Aβ may enable network-dependent neurodegeneration, tau may organize its propagation, and clinical progression may amplify connectome-driven mechanisms, while age of onset modulates the balance between AD-specific and multifactorial signatures**