

Distinct clinical trajectories and tau burden across MRI-derived subtypes and stages of Alzheimer's disease



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Introduction

- While structural MRI is a routine part of clinical Alzheimer's disease (AD) assessment, quantitative morphometric indices (e.g., regional cortical thickness or gray matter volumes) are rarely utilized in routine clinical practice [1]
- Likely reasons for this sparse adoption are:
 - High computational demands and long processing times of standard pipelines [2]
 - Interpretive burden of complex regional data [1]
 - Lack of validated norms that generalize across different scanning environments [3]
- Heterogeneity in AD-related regional atrophy patterns requires a framework that goes beyond reporting individual morphometric indices in order to place an individual within the broader atrophy heterogeneity structure of the disease

Research aim: To establish and validate a framework that translates MRI data into clinically interpretable atrophy subtypes and stages, applicable across diverse acquisition settings without need for site-specific reference data.

Methods

- N = 8,415 participants** from five cohort studies, analyzed as samples grouped by cohort study and scanner field strength (A4/LEARN-3T, ADNI-1.5T and -3T, ARWIBO-1.5T, DELCODE-3T, NACC-1.5T and -3T)
- Inclusion criteria
 - ≥ 60 years of age
 - Cognitively unimpaired (CU) or diagnosed with subjective cognitive decline (SCD), mild cognitive impairment (MCI), or dementia of the Alzheimer type (DAT)
 - Available T1-weighted whole brain MRI acquired at 1.5 or 3 Tesla

Image processing

- Pre-processing and surface reconstruction with FastSurfer ([4], ~55 min. *versus* ~245 min. with FreeSurfer)
- Calculated gray matter volumes of the MTL (entorhinal cortex, amygdala, and hippocampus) and average cortical thickness of the temporal, parietal, frontal, and occipital lobes to serve as regional atrophy markers

Modeling framework

Normative modeling

- Atrophy marker standardization to CU participants using w -scores controlling for age, sex, scanner manufacturer, and field strength

Subtype and stage inference (SuStaln [5])

- Reconstruction of atrophy sequence(s) using events $w = \{-1, -2, -3\}$ for each atrophy marker

Cross-validation

- 10-fold (within-sample and global models) and leave-one-sample-out (LOSO, global model only) cross-validation

Statistical analyses

Clinical correlates of subtype and stage

Cross-sectional demographic and clinical associations of atrophy subtypes and stages were characterised within samples using linear and logistic regression and pooled across samples via REML meta-analysis.

Associations with regional tau burden

The relationship of atrophy subtype and stage with tau PET signal was modelled using linear (regional CentTauR scores) and ordinal logistic (overall tau burden group, cf. TRAILBLAZER-ALZ 2 [6]) regression models.

Two implementation contexts

Within-sample modelling

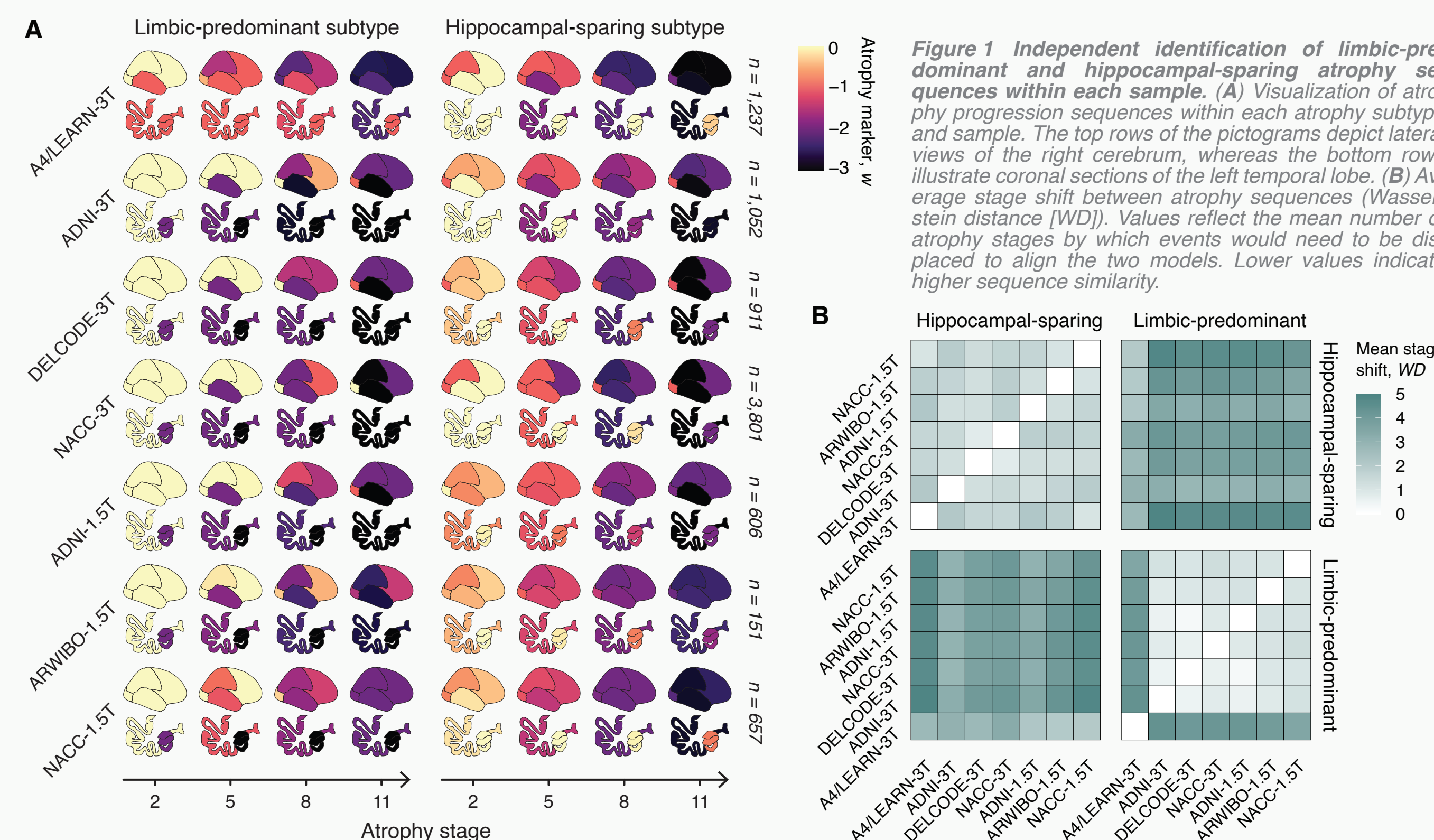


Global modelling

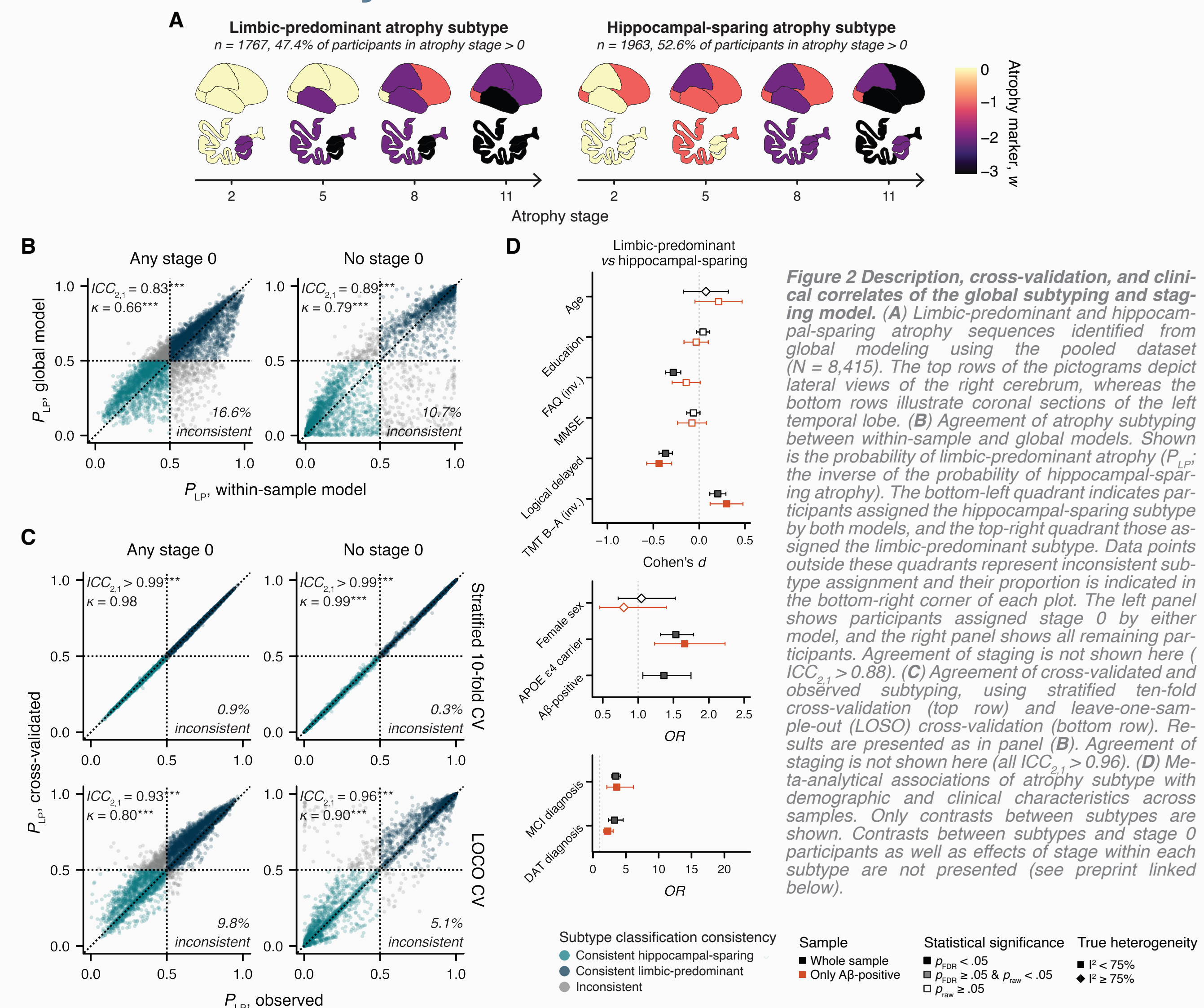


Results

Limbic-predominant and hippocampal-sparing atrophy subtypes are identified across independent samples

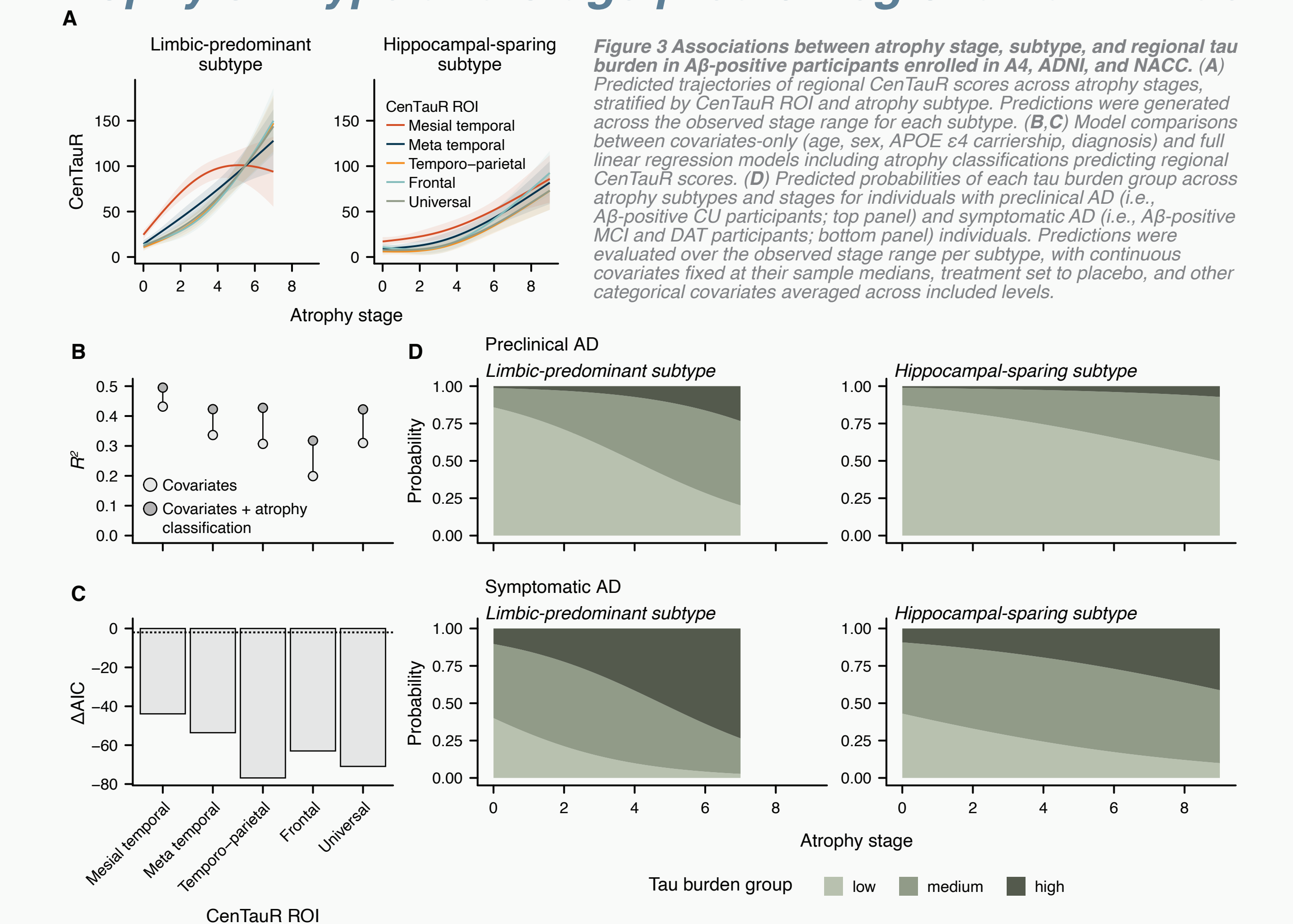


A cohort-independent subtyping and staging pipeline robustly classifies unseen MRI scans

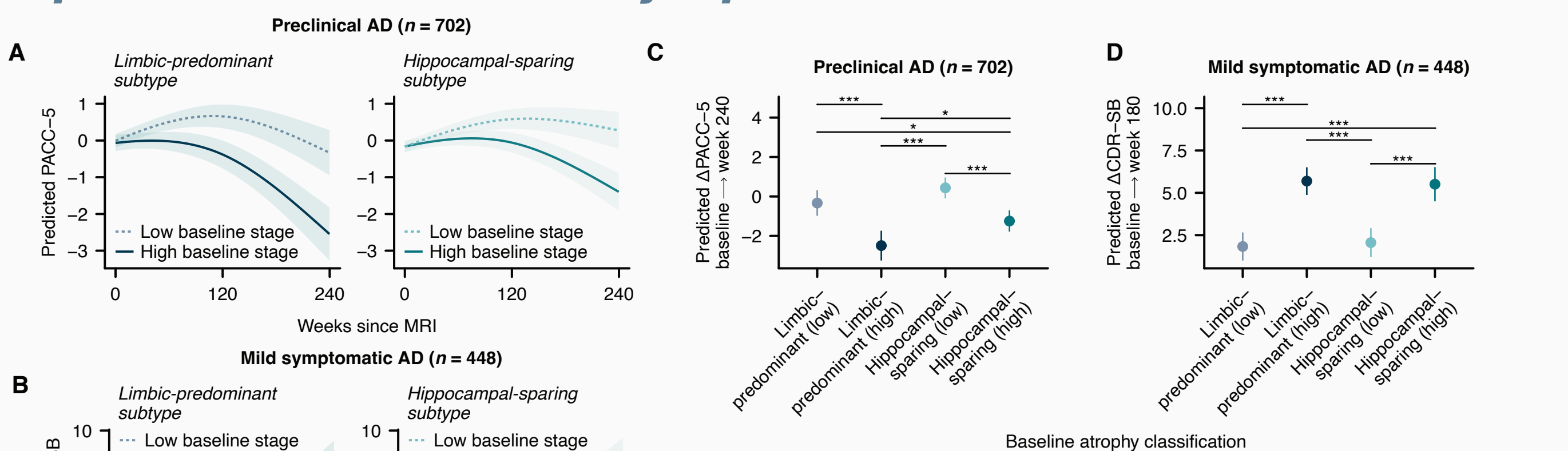


Results

Atrophy subtype and stage predict regional tau burden



Atrophy classifications stratify cognitive decline in preclinical and mild symptomatic Alzheimer's disease



Conclusion

- Limbic-predominant and hippocampal-sparing atrophy subtypes capture **biological heterogeneity in AD** and are associated with **diverging clinical profiles**
- The global model's good cross-validation performance and strong correspondence with within-sample atrophy heterogeneity structures support **robust application in diverse clinical settings without local reference datasets**
- Atrophy classifications may support the **PET-free estimation of regional and global tau burden** as well as **prognostic assessments** in relevant prospective settings, such as clinical trials aimed at implementing enrichment or stratification strategies

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Abbreviations

Aβ, amyloid-β; CV, cross-validation; FAQ, Functional Activities Questionnaire; FDR, false discovery rate; MMSE, Mini-Mental State Examination; TMT, Trail-Making Test.

* $p < .05$. ** $p < .01$. *** $p < .001$.

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