

Background and Objectives

Early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD) exhibit distinct clinical and neuroanatomical characteristics, suggesting potential differences in underlying neurodegenerative processes¹. While cortical mean diffusivity (cMD), cortical thickness (CTh), and gray matter volume (GMV) provide complementary measures of microstructural and macrostructural integrity, their spatial patterns across EOAD, LOAD, and normal aging remain incompletely understood^{2,3}. This study aimed to identify reproducible multimodal cortical signatures of EOAD, LOAD, and aging across two independent cohorts and to investigate their associations with age, amyloid- β (A β), and tau pathology.

Methods

- A total of 783 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and 128 participants from the Chinese Geriatric Health and Aging Brain Study (GHABS) were included, comprising young controls (YC), older controls (OC), patients with EOAD, and patients with LOAD.
- Surface-based analyses were performed to evaluate group differences in cMD, CTh, and GMV for EOAD versus YC, LOAD versus OC, and OC versus YC comparisons.
- For each modality and disease contrast, cortical regions were ranked according to the absolute t-values obtained from general linear models in each cohort separately. Regions consistently ranked among the top ten in both cohorts were defined as candidate signature regions of interest (ROIs).
- Individual signature scores were subsequently calculated as weighted averages of regional measurements using the mean cross-cohort t-statistics. This procedure generated nine multimodal signature ROIs representing EOAD-, LOAD-, and aging-related alterations across cMD, CTh, and GMV.
- Multiple linear regression models examined associations between each signature-ROI and A β PET, tau PET, and age within EOAD, LOAD, and aging groups.

References

- Jack CR Jr et al., Alzheimer's & Dementia, 2018, Vol 14, Pages 535–562.
- Ossenkoppele R et al., Brain, 2016, Vol 139, Pages 1551–1567.
- Ferreira D et al., Neurology, 2020, Vol 94, Pages 436–448.

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Results

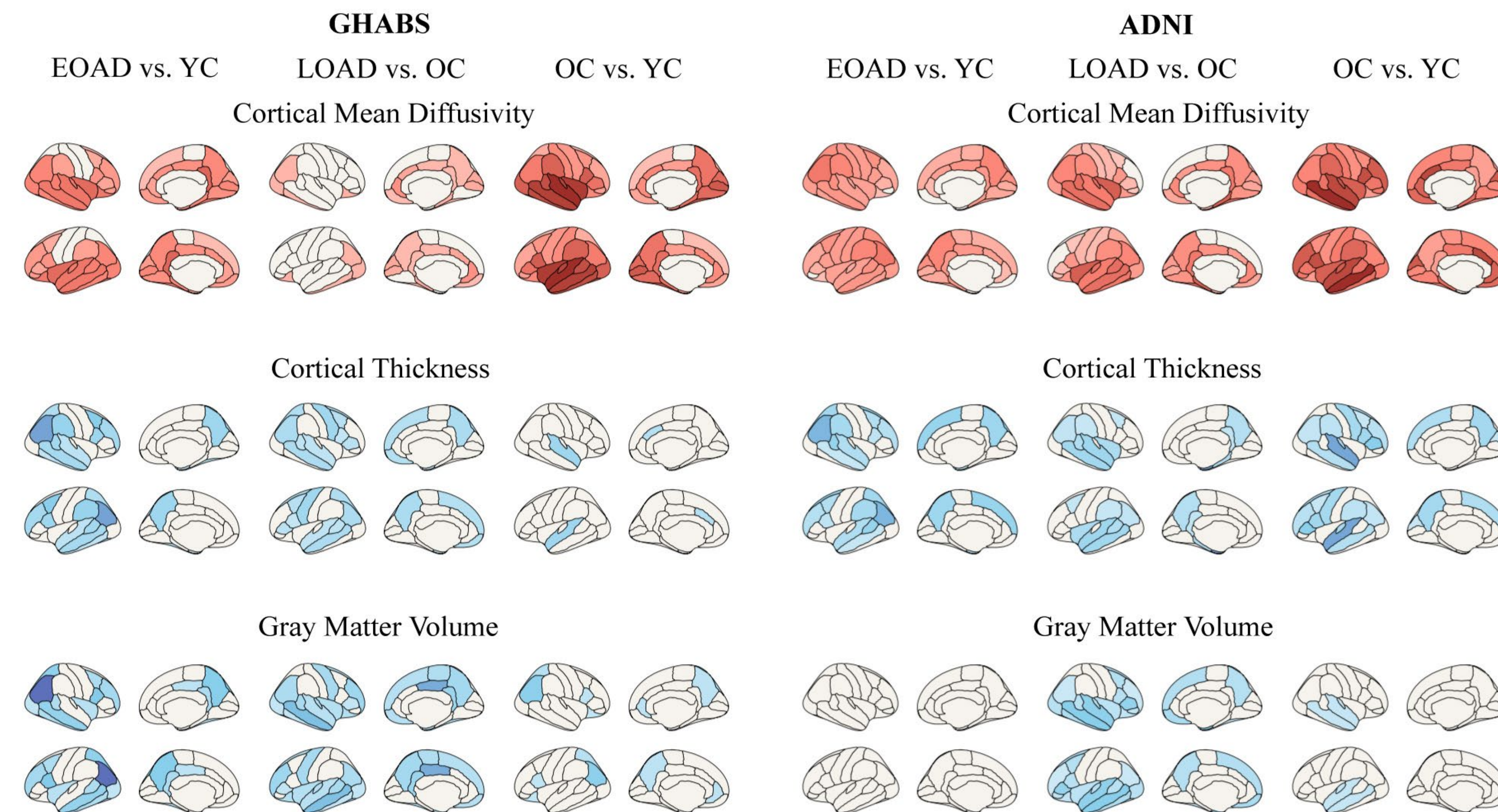


Figure 1. Distinct multimodal structural damage patterns in EOAD, LOAD, and normal aging across ADNI and GHABS

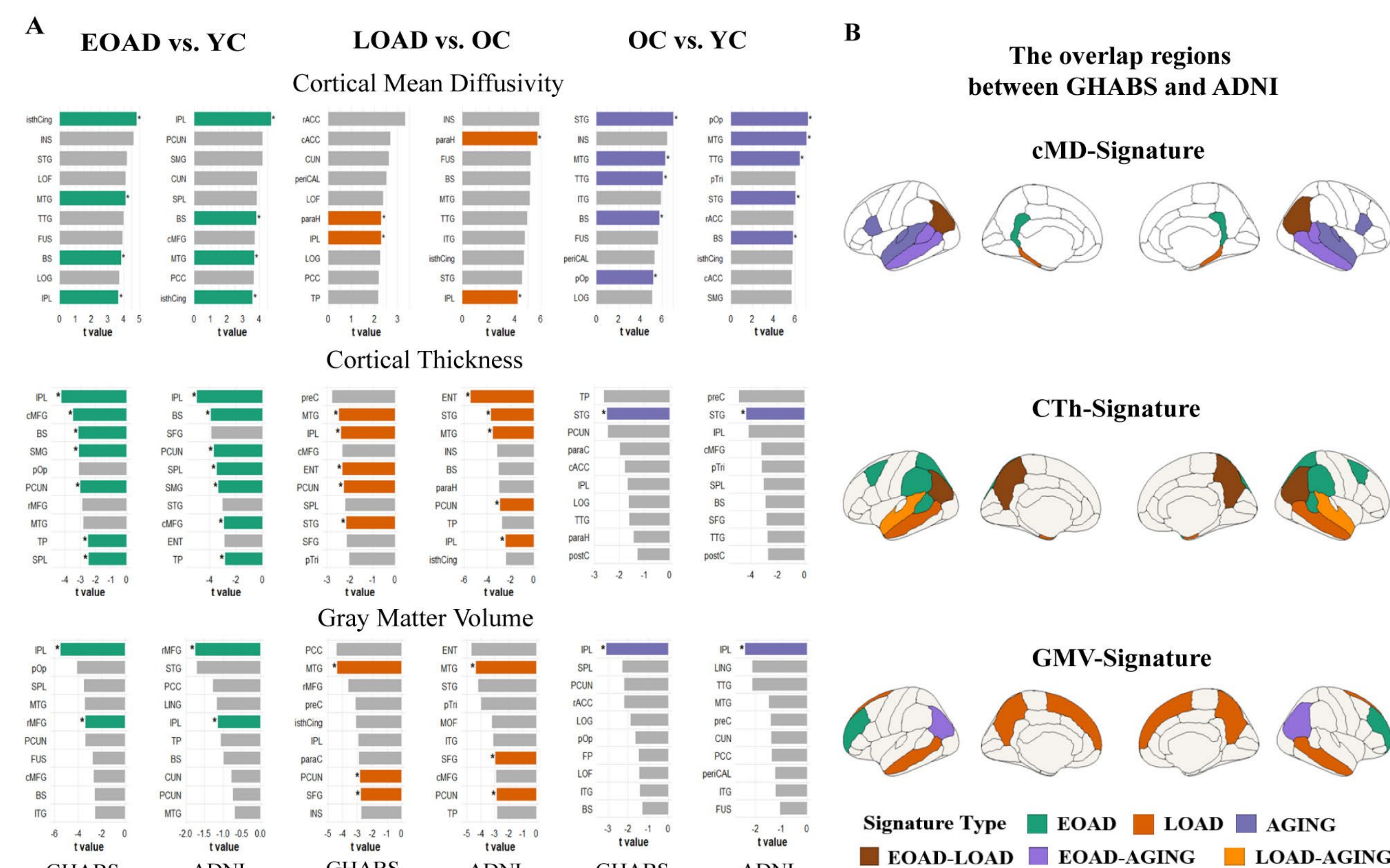


Figure 2. Identification of multimodal neurodegenerative signatures for EOAD, LOAD, and aging

EOAD, LOAD, and aging exhibited distinct multimodal patterns of cortical degeneration. EOAD was characterised by prominent involvement of posterior association cortices, whereas LOAD showed preferential alterations within limbic-temporal regions. Aging-related changes were mainly distributed across sensorimotor and temporal areas (Figure 1). Cross-cohort overlap analyses identified robust and reproducible multimodal signatures (Figure 2). Tau pathology was the primary determinant of all imaging signatures in EOAD. In LOAD, both tau pathology and age contributed independently to structural alterations, whereas age was the sole significant predictor in the aging group (Figure 3).

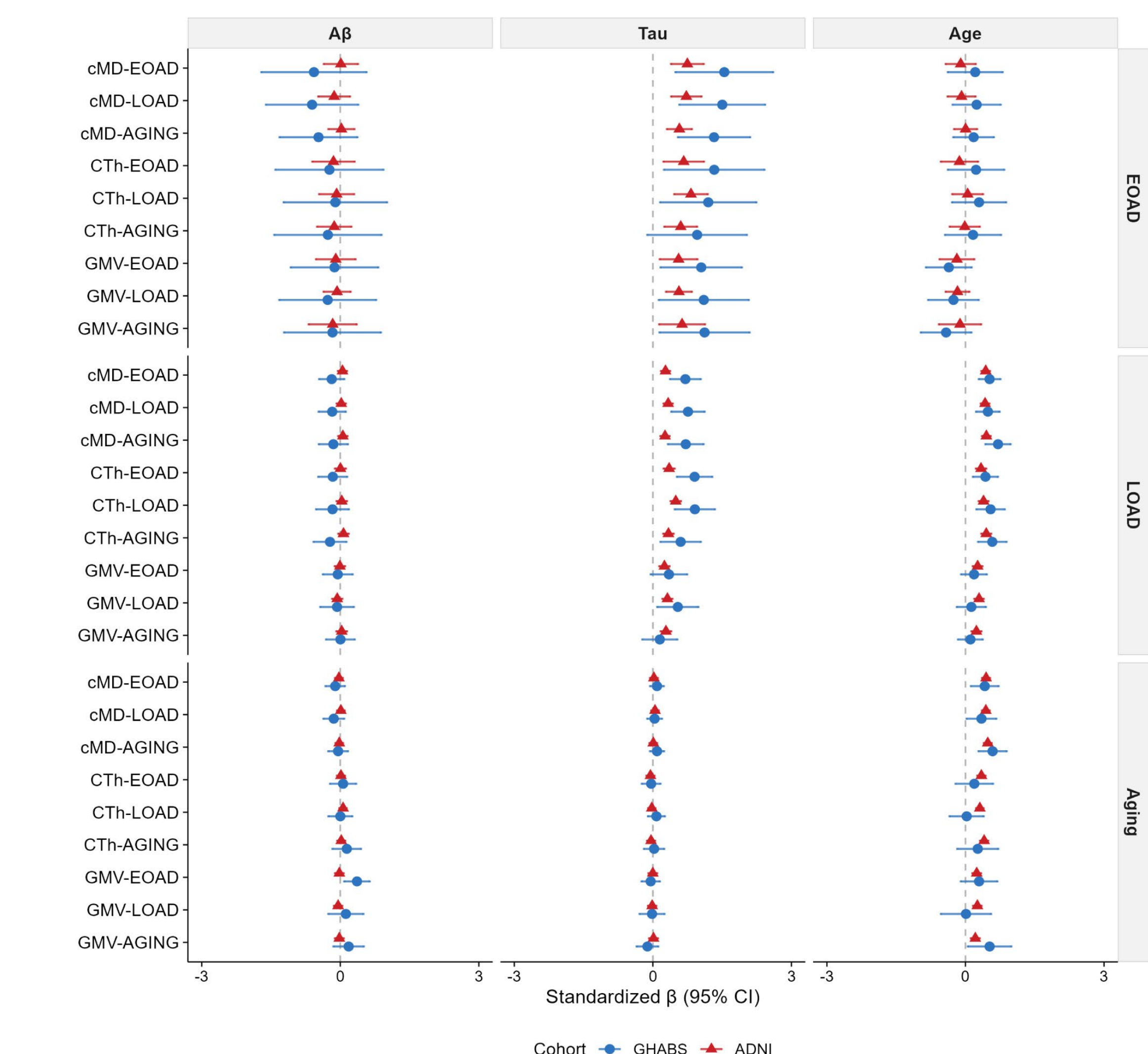


Figure 3. Distinct pathological drivers of multimodal neurodegenerative signatures in EOAD, LOAD, and aging

Discussions

Multimodal MRI identified reproducible cortical signatures that distinguish EOAD, LOAD, and normal aging across independent cohorts. Distinct contributions of tau pathology and aging to these signatures highlight divergent biological mechanisms underlying EOAD, LOAD, and age-related brain changes.