



Clinical Phenotypes and Longitudinal Trajectories of LATE, AD, and Mixed Pathology Defined by Neuroimaging Biomarkers

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Background

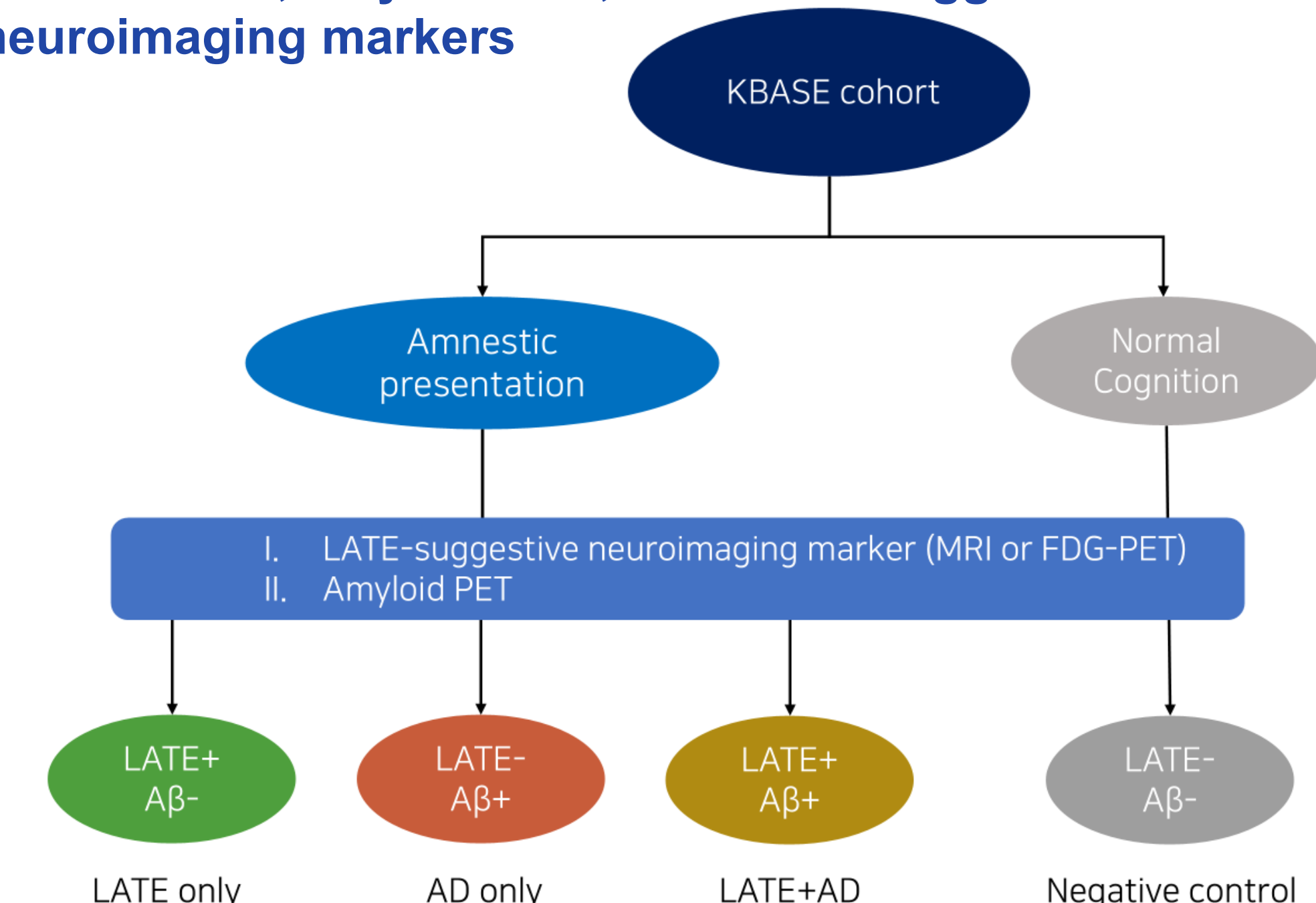
- Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a common age-related proteinopathy that frequently mimics or coexists with Alzheimer's disease (AD).
- Given the absence of definitive in vivo fluid biomarkers for TDP-43, neuroimaging-defined (structural MRI and FDG-PET) phenotypes offer a valid surrogate framework to stratify clinical cohorts.
- **Objective:** To delineate the clinical signature of LATE by comparing cross-sectional and longitudinal profiles of cognition, neuropsychiatric symptoms, and motor function across biomarker-stratified groups.



Methods

- **Cohort Stratification:** Participants with amnesic cognitive disorders from the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE) cohort were classified using Amyloid PET and LATE-suggestive neuroimaging markers (MRI/FDG-PET):
 - LATE-only group: LATE-suggestive positive / Amyloid negative.
 - AD-only group: LATE-suggestive negative / Amyloid positive.
 - Combined LATE+AD group: Concurrent positivity for both markers.
 - Note: A biomarker-negative group served as a descriptive control.
- **Clinical Metrics:** Cognition (MMSE, CERAD battery), Neuropsychiatric symptoms (NPI), and Motor function (Parkinsonian signs).
- **Statistical Analysis:** Covariate-adjusted models for baseline comparisons; linear mixed-effects models (time-by-group interaction) for longitudinal trajectories. Adjustments were made for age, sex, and education.

Figure 1. Operational grouping scheme based on amnesic presentation, amyloid PET, and LATE-suggestive neuroimaging markers



Results

Section A: Cognitive Impairment

- **Cross-Sectional:**
 - The **Combined LATE+AD group** exhibited the most severe global cognitive impairment (MMSE, CERAD total) at baseline.
 - Deficits in the mixed pathology group were broader, significantly impairing non-amnesic domains (language and executive functions).
- **Longitudinal:**
 - The **Combined LATE+AD group** showed the steepest and fastest rate of global cognitive decline over time.
 - Accelerated decline in the mixed group was widespread, spanning memory, language, visuospatial, and executive controls.

Section B: Neuropsychiatric Symptoms

- **Cross-Sectional:** Baseline neuropsychiatric symptom burdens and behavioral profiles did not significantly differ among the pathological groups.
- **Longitudinal:** No distinct or divergent trajectories of neuropsychiatric symptom progression were observed across the groups during follow-up.

Section C: Motor Function (Parkinsonism)

- **Cross-Sectional:** Initial motor function scores and mild Parkinsonian presentations were highly comparable across all disease groups at baseline.
- **Longitudinal:** Amyloid-associated cohorts (**AD-only group** and **Combined LATE+AD group**) demonstrated significantly faster and more severe motor degradation over time compared to the stable trajectory of the **LATE-only group**.

Figure 2. Cross-sectional and longitudinal trajectories of global cognitive impairment across pathology-related groups

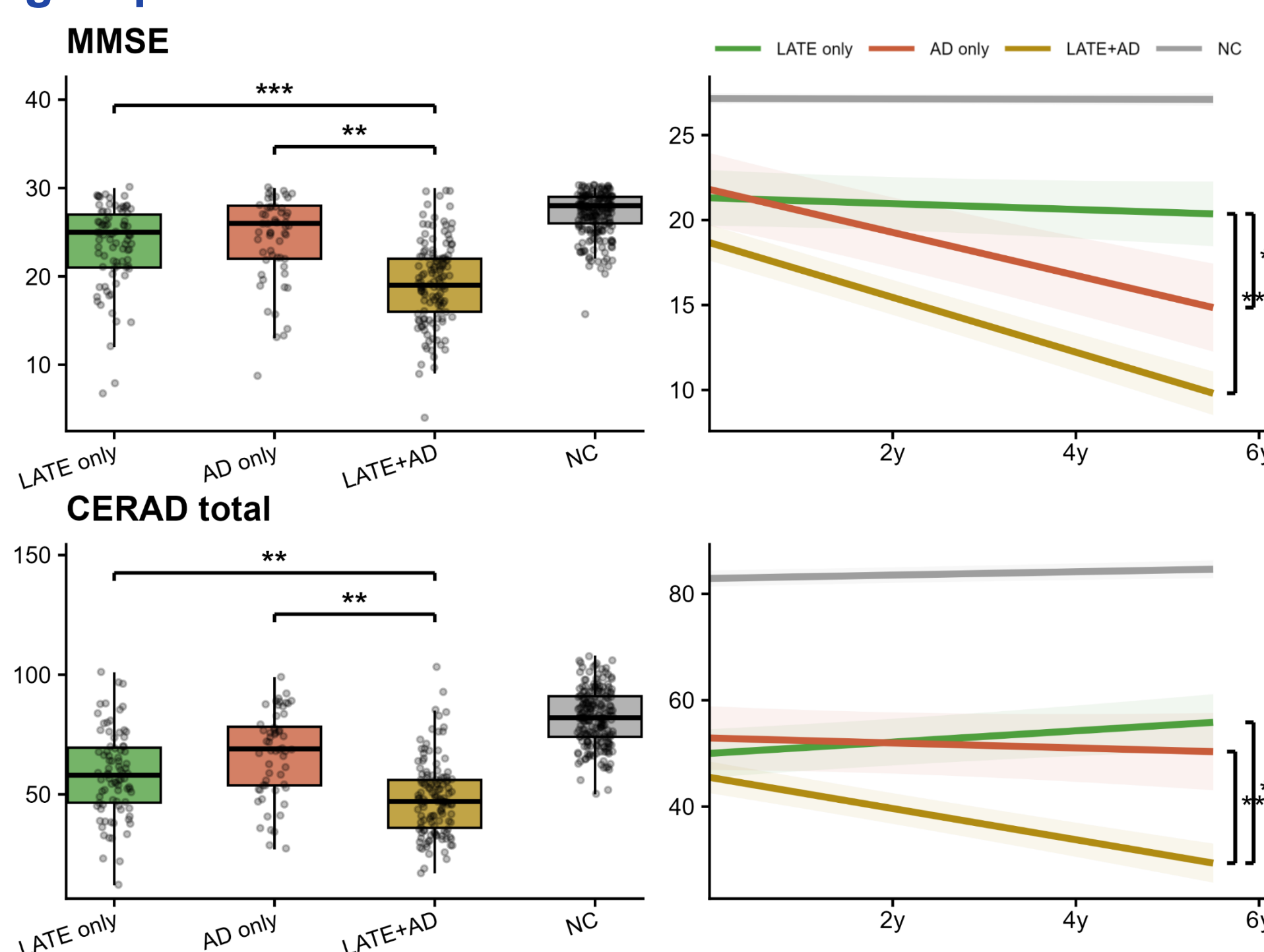
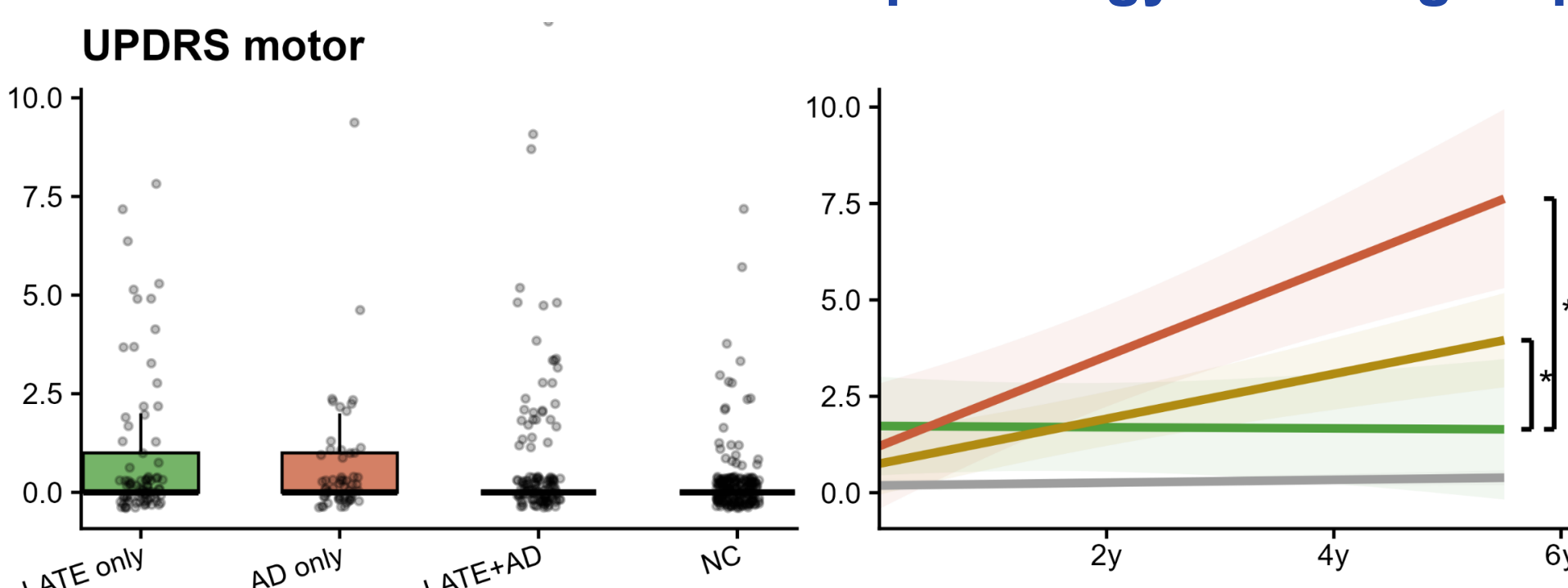


Figure 3. Cross-sectional and longitudinal trajectories of UPDRS motor scores across pathology-related groups



Conclusion

- Coexisting LATE and AD pathologies exert a synergistic burden, causing broader baseline cognitive deficits and accelerated longitudinal decline across multiple cognitive domains.
- While **neuropsychiatric symptoms** overlap heavily and fail to differentiate these pathologies, **longitudinal motor progression** reveals distinct paths: amyloid-driven groups show significantly faster motor deterioration than the LATE-only presentation.
- Tracking image-defined LATE phenotypes provides critical utility for resolving clinical heterogeneity and optimizing patient stratification in late-life amnesic cognitive disorders.

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