

Short-term and one-week delayed recall latent trajectory analysis as a sensitive cognitive marker of early Alzheimer's disease pathology in cognitively unimpaired individuals

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1. Background

- **Accelerated Long-term Forgetting (ALF)** - disproportionate memory loss over days despite normal short-delay retention [1] - has been proposed as an **early cognitive manifestation of preclinical Alzheimer's disease (AD)** [2, 3].
- **Standard neuropsychological assessments evaluate memory at 30-minute delays** [4, 5], missing the consolidation window in which ALF manifests.
- Existing **retention-ratio approaches overlook the full acquisition-to-consolidation pattern** [4, 5], potentially obscuring heterogeneous memory profiles relevant to early AD pathology characterisation.

2. Aim

To investigate how a one-week delayed memory assessment could be useful for the prompt detection of early Alzheimer's disease pathology, exploring its associations with fluid biomarkers and structural MRI measures.

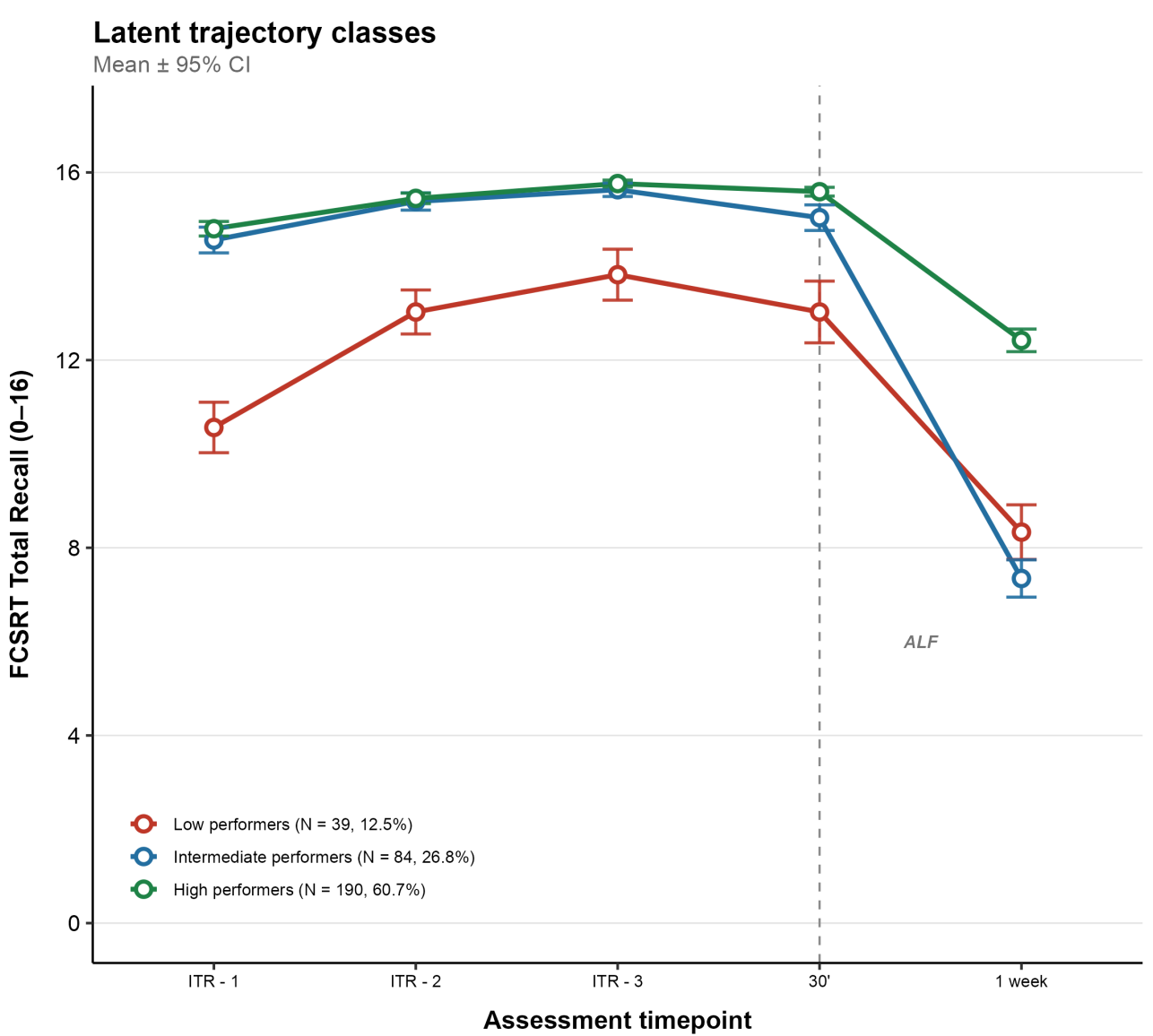
5. Conclusions

- Learning and forgetting trajectories, including delayed recall assessed beyond standard intervals, **relate to early AD pathology**, in particular **plasma p-tau217 elevation and accelerated hippocampal atrophy**.
- Further studies exploring the ability of combined metrics of plasma p-tau217 and long-term recall trials to predict short-term cognitive decline are warranted.

3. Method

- **Cognitive assessment:** Participants completed the Free and Cued Selective Reminding Test (FCSRT) in person. The test required memorizing a **16-word list**, which was then recalled across **three immediate recall trials**, followed by a **delayed recall trial after a 30-minute interval**. An additional, unexpected **one-week delayed recall assessment was conducted by telephone**.
- **Trajectory analysis:** Latent Class Growth Analysis (LCGA) was applied across the five recall time points to identify **distinct memory consolidation trajectory classes**.
- **Fluid biomarkers analysis:** Associations between trajectory classes and Alzheimer's disease biomarkers were examined using **general linear models (ANCOVA)**. Biomarkers included:
 - **CSF A β 42/A β 40 ratio** (Elecsys NTK, Roche; UGOT)
 - **CSF p-tau181/A β 42 ratio** (Elecsys; p-tau181 standard, A β 42 NTK; Roche, UGOT)
 - **Plasma p-tau217** (Elecsys NTK, Roche; UGOT).
- **Neuroimaging analysis:** Retrospective longitudinal MRI data, including **three acquisitions over a six-year period**, were analyzed using **linear mixed-effects models**. Volumes were derived from **T1-weighted MRI** processed with the **ASHS pipeline**. Hippocampal measures included:
 - Bilateral **global** hippocampal volume
 - Hippocampal **subfield** volumes (CA1, CA2, CA3, DG).

4. Results

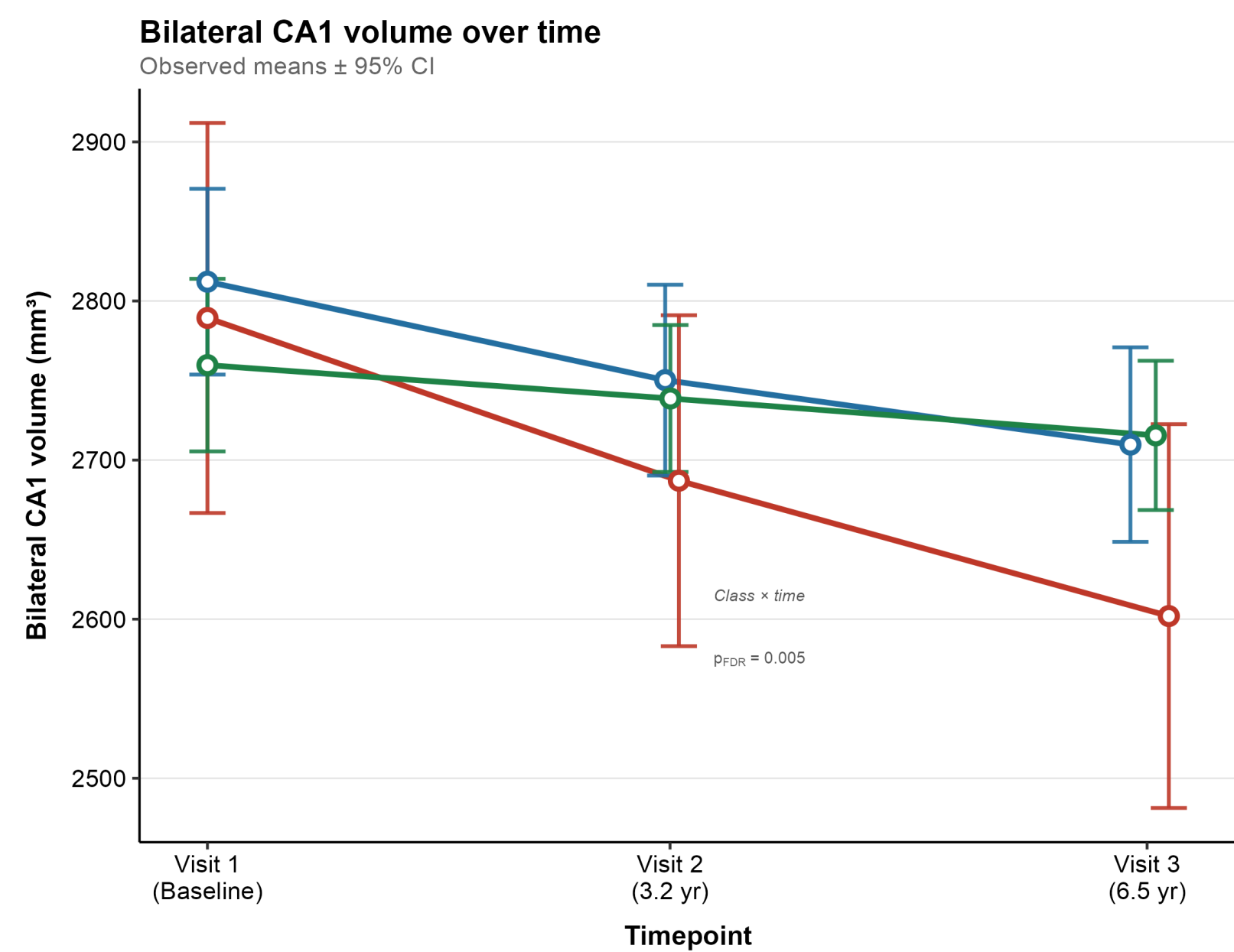
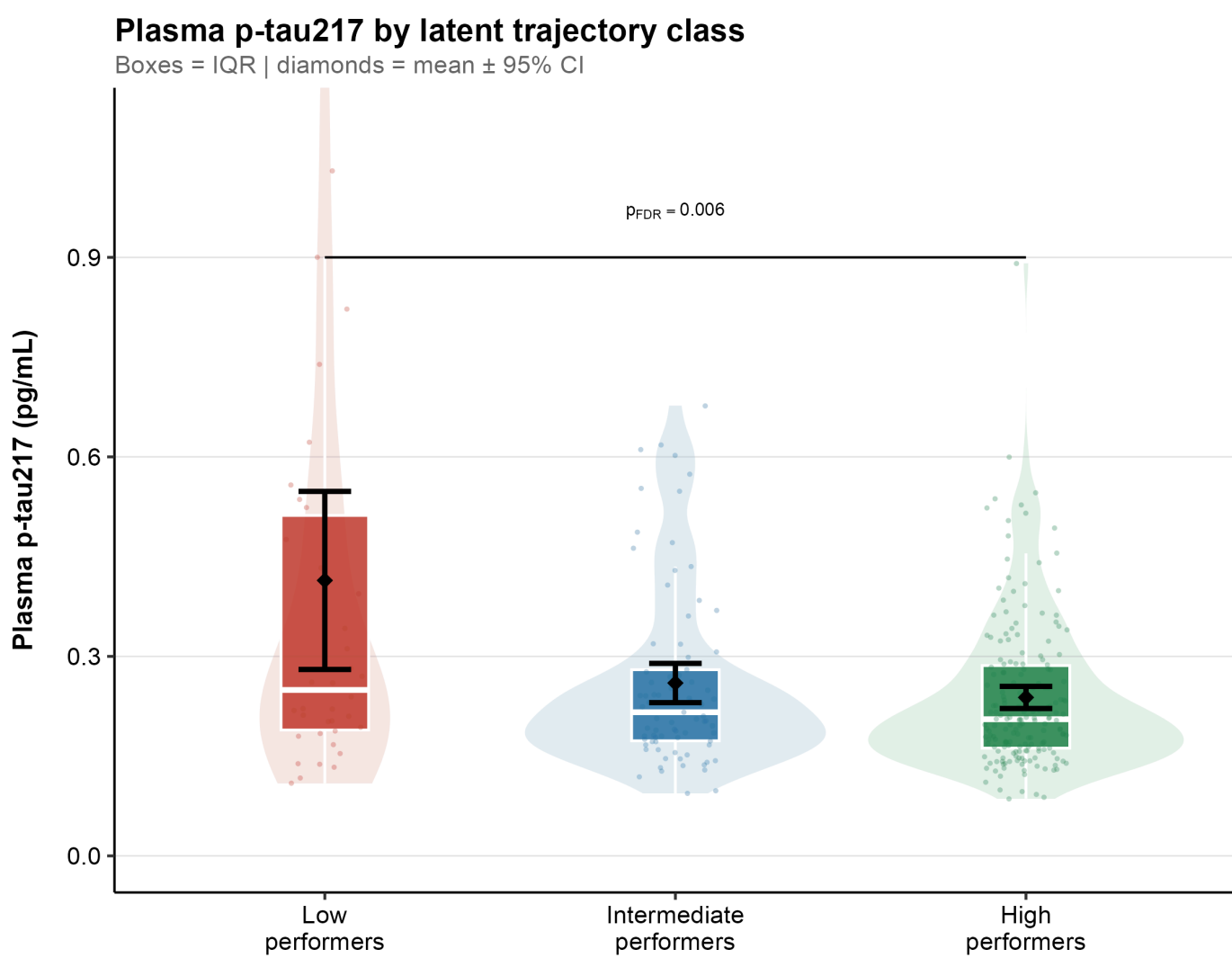


Memory performance profile

Intermediate performers showed preserved learning and 30-minute delayed recall, but exhibited disproportionately greater forgetting after one week compared with High performers (Figure 1).

Plasma biomarkers associated with memory trajectory

- Trajectory classes were significantly associated with plasma p-tau217 levels ($p = 0.006$) (Figure 2).
- **Low performers** showed significantly **higher p-tau217** concentrations than **Intermediate performers** (β STD = 0.54, $p = 0.005$) and **High performers** (β STD = 0.60, $p = 0.0008$).
- Similar patterns were observed for CSF A β 42/A β 40 and p-tau181/A β 42 measures, although these associations did not reach statistical significance.



CA1 subfield shows the strongest atrophy effect

In the retrospective longitudinal analysis the strongest effect was observed in the CA1 subfield ($p = 0.005$) (Figure 3).

- **Low performers** showed **greater annual CA1 atrophy** than **High performers** (β STD = -0.054, $p = 0.001$), corresponding to **x3.3 faster annual volume loss**.
- **Intermediate performers** also showed **greater annual CA1 atrophy** than **High performers** (β STD = -0.028, $p = 0.037$), corresponding to **x2.2 faster annual decline**.

Greater hippocampal atrophy in Low performers

- Retrospective longitudinal MRI analyses revealed a **significant class $\times$ time interaction** for bilateral hippocampal volume ($p = 0.010$).
- **Low performers** exhibited significantly **greater hippocampal atrophy** than **High performers** (β STD = -0.064, $p = 0.004$), corresponding to approximately **x2.5 faster annual volume loss**.