

Associations between amyloid-positivity, brain atrophy rates and accelerated forgetting in adults aged 70–77

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Background

- Accelerated Long-term Forgetting (ALF) is the phenomenon whereby material is retained normally over short intervals (minutes or hours) but forgotten abnormally rapidly over longer periods (days or weeks).
- There is evidence that ALF is an early marker of cognitive decline in preclinical Alzheimer's disease (AD) [1], but questions remain about its relationships with biomarkers of preclinical Alzheimer's disease pathology.
- We previously reported associations between some measures of ALF and amyloid-positivity and brain atrophy rates in cognitively normal 73-year-olds in the Insight 46 study – a sub-study of participants from the MRC National Survey of Health and Development (also known as the British 1946 Birth Cohort) [2]. Participants were all born during the same week and have completed regular assessments of their health and cognition throughout childhood and adulthood.
- We now report investigation of the relationships between AD biomarkers and ALF from the next time-point of this study at age ~78 years.

Methods

- At age ~78, participants (n=613) completed the ALF assessment comprising verbal and visual memory tasks: the 12-item Face-Name Associative Memory Exam (FNAME-12) [3,4] and Complex Figure Drawing [2] (Fig.1, Fig.2) ALF scores were calculated as % of material retained after 7 days, relative to 30 minutes.
- Plasma p-tau217 was quantified ~8 years earlier (at age ~70 years) and categorised as low, intermediate or high using published cut-points [5]. A sub-sample of participants (n=307) had amyloid-PET status determined at age ~73, and rates of whole-brain atrophy (derived from serial MRI) between ages ~70–78.
- Linear regression models were used to investigate associations between memory performance (trial-by-trial and ALF) and, separately, amyloid status (positive, negative), p-tau217 (low, intermediate, high) and brain atrophy rates, adjusting for relevant covariates. Analyses were repeated including only participants who were cognitively normal at age ~78 (Clinical Dementia Rating (CDR) = 0), to investigate whether subtle ALF was detectable in this group.

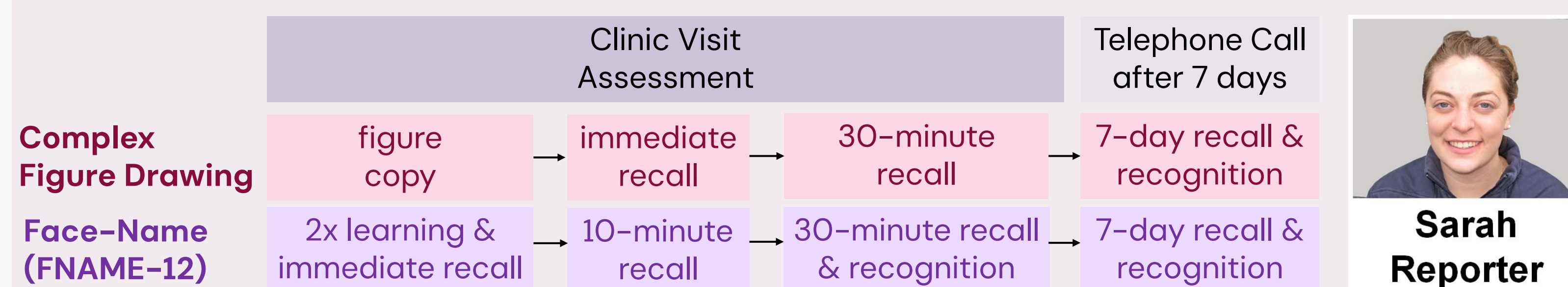
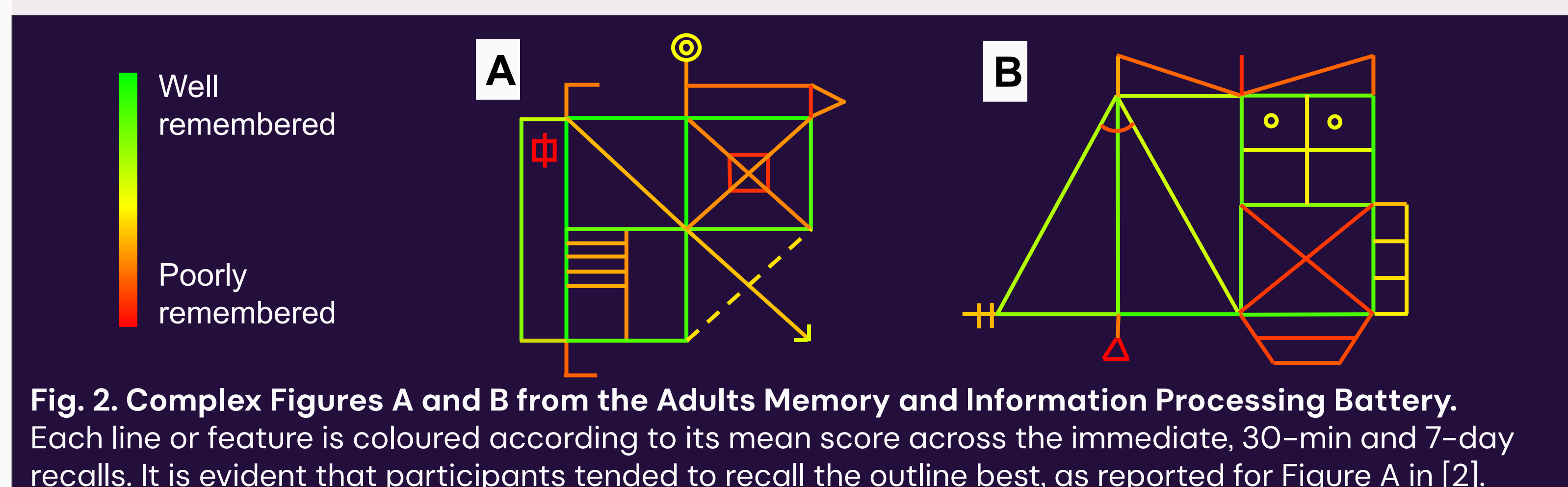


Fig. 1. Accelerated Long-term Forgetting assessment, and an example Face-Name stimulus



Results

- Participants (n=613) were 49.9% female with mean [SD] age of 77.6 [1.2] years. Prevalence of low, intermediate and high p-tau217 were 75.4%, 17.1% and 7.5%. The intermediate and high-p-tau217 groups both performed worse on the verbal and visual memory tests, relative to the low-p-tau217 group. These differences were seen even on the immediate and 30-minute recall tests (Fig.3A, 3B).
- In the sub-sample with prior neuroimaging, amyloid-positivity (prevalence 30.5%) was associated with poorer verbal and visual recall ~4 years later (Fig.3C, 3D). Faster rates of brain atrophy were associated with the same outcomes (Table 1). Again, these effects were seen even on the immediate and 30-minute recall tests.
- Although coefficients for ALF scores were in the expected direction, they were only statistically significant on FNAME-12 for faster brain atrophy.
- When including only participants with CDR=0 (prevalence 81.2%), associations with memory were attenuated for p-tau217 and amyloid-positivity; however, associations with brain atrophy rates remained, including for ALF score on FNAME-12 (data not shown).

Table 1. Associations between whole-brain atrophy rate and memory performance in n=201:

Coefficient [95% CIs] per ml/yr volume change
Outcomes are % correctly recalled.

Complex Figure Drawing	
Immediate	0.8 (–0.4, 2.0)
30-minute	1.3 (0.0, 2.5)*
7-day	1.6 (0.2, 2.9)*
ALF score	0.7 (–0.6, 2.0)
Face-Name	
Immediate	2.7 (1.3, 4.1)**
10-minute	2.7 (1.2, 4.1)**
30-minute	2.8 (1.3, 4.3)**
7-day	3.7 (2.0, 5.3)**
ALF score	2.4 (0.7, 4.1)**

*p<0.05, **p<0.01

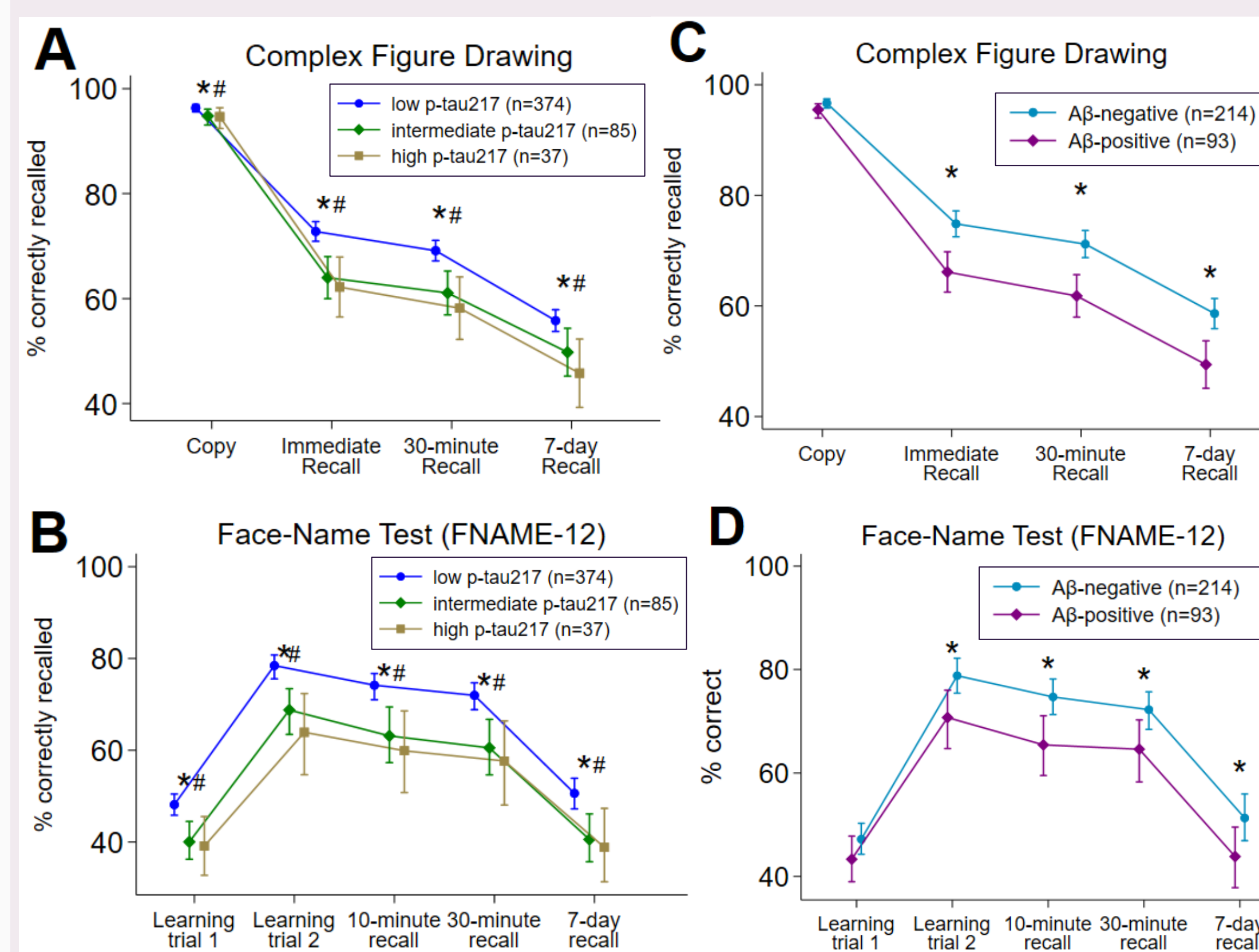


Fig. 3. Performance on the Complex Figure and Face-Name Tests, by amyloid status (A and B) and p-tau217 category (C and D). Plots show adjusted means and 95% CIs from the regression models. In C and D, asterisk indicates significant difference between the low and intermediate groups; hash indicates between the low and high groups.

Conclusions

- Our previous work [2] found evidence of subtle ALF at age ~73 in individuals with biomarkers of preclinical AD. However, by age ~78 years, memory deficits were apparent in immediate and short-delay recall in individuals with biomarkers of Alzheimer's pathology measured up to ~8 years beforehand.
- Among those who were cognitively normal (CDR=0) at age ~78, faster rate of brain atrophy was associated with ALF on a challenging associative memory test.
- These results support the utility of ALF tests for detecting early memory impairment in preclinical AD, but suggest that the prime window for this in population-based samples may be before individuals reach their late 70s.

References: 1. Pizzoni et al. (2026) *JAD* | 2. Lu et al. (2025) *Brain* | 3. Papp et al. (2014) *Clin. Neuropsychol.* | 4. Lu et al. (2026) *Neuropsychology* | 5. Ashton et al. (2024) *JAMA Neurol.*