Accelerated Forgetting is sensitive to β-amyloid pathology and cerebral atrophy in cognitively-normal 72-year-olds

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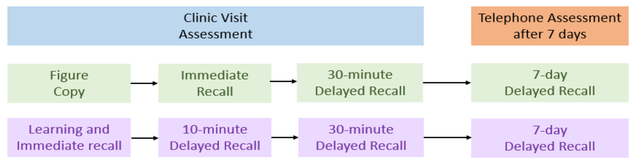
Background

- Accelerated Forgetting is the phenomenon whereby material is retained normally over short intervals (minutes or hours) but forgotten abnormally rapidly over longer periods (days or weeks).
- Accelerated Forgetting has been observed in presymptomatic carriers of mutations causing familial Alzheimer's disease (AD) [1] and in cognitively-normal *APOE*-ε4 carriers [2], but, to our knowledge, no studies have investigated whether Accelerated Forgetting is sensitive to preclinical AD pathology in cognitively-normal older adults.
- We aimed to investigate associations between Accelerated Forgetting and brain pathologies in Insight46, a sub-study of the MRC National Survey of Health and Development (the British 1946 Birth Cohort) [3]. Participants were all born during the same week and have completed regular assessments of their health and cognition throughout childhood and adulthood.
- We previously reported that β-amyloid pathology was associated with subtly poorer cognition in Insight46 participants at age ~70 years, including on the Preclinical Alzheimer's Cognitive Composite [4].

Methods

- Participants attended a baseline assessment at age ~70 years and a follow-up ~29 months later, at University College London.
- For the follow-up visits, we complemented the clinic visit assessments of Complex Figure Drawing [5] and the Face-Name test (FNAME-12) [6] with a 7-day delay version administered by telephone (**Figure 1**).
- Accelerated Forgetting scores were calculated as the percentage of material retained after 7 days, relative to retention after 30 minutes.
- Cerebral atrophy between baseline and follow-up was quantified from T1-weighted MRI using the Brain Boundary Shift Integral (BBSI) [7]. β-amyloid status at baseline (positive / negative) was determined from 18F-Florbetapir-PET, using a cut-point of SUVR>0.6104, based on a reference region of eroded subcortical white matter.
- Multivariable regression models were used to investigate the effects of β-amyloid status and BBSI on Accelerated Forgetting, and to explore interactions between these two predictors. We adjusted for potential confounders including sex, childhood cognitive ability, education, socioeconomic position, *APOE*-ε4 (carrier / non-carrier) and white matter hyperintensity volume (see [4] for details of these variables).

Fig 1. Accelerated Forgetting Assessment



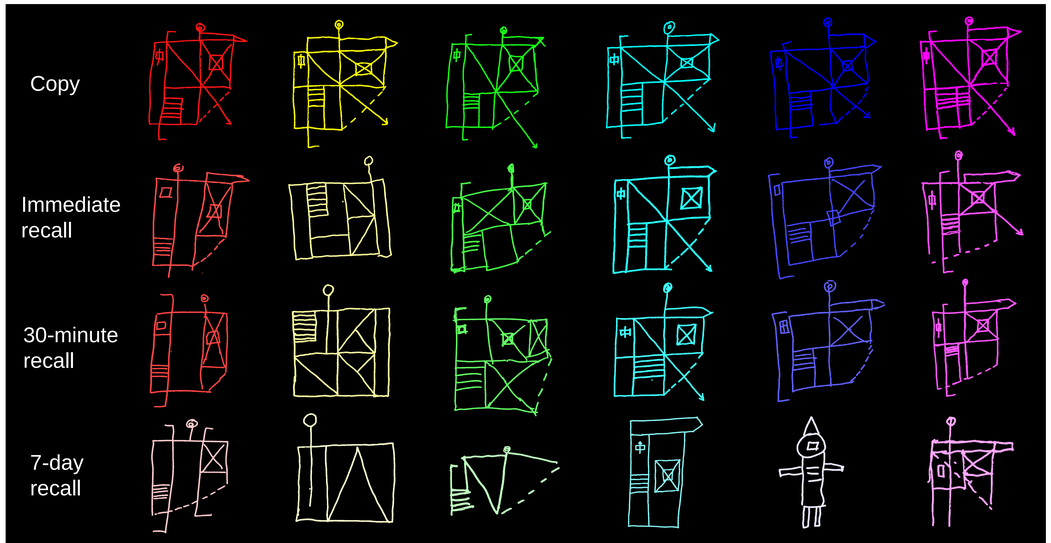


Fig 2. Examples of Complex Figure drawings from six participants (each participant in a different column). The choice of colours is arbitrary, but the colour intensity corresponds to the score received, with paler hues indicating lower scores.

References 1) Weston et al. (2018) Lancet Neurol 17:2:123-132. 2) Zimmerman & Butler (2018) Lancet Neurol 17:5:394-5. 3) Lane et al. (2017) BMC Neurol 17:75. 4) Lu et al. (2019) Neurology 93:e2144-56. 5) The Adult Memory and Information Processing Battery (1985) Coughlin, St James' Hosp. 6) Papp et al. (2014) Clin Neuropsychol 28:5:771-85. 7) Leung et al. (2010) Neuroimage:50:516-23.

Results

- Performance on Complex Figure Drawing is illustrated in **Figures 2-3**.
- Despite no statistically significant differences after a 30-minute delay, amyloid-positive participants retained a lower percentage of Complex Figure material over 7 days (71.8% vs. 80.7%, p = 0.014), and a trend to a lower percentage of FNAME-12 material (69.4% vs. 77.2%, p = 0.083) (**Figure 4**).
- There was an interaction between amyloid status and BBSI, such that greater cerebral atrophy predicted poorer retention of the Complex Figure in amyloid-positive participants only (interaction coef. = -2.3 [95% CIs -4.5 – -0.1], p = 0.038) (**Figure 5**).
- Higher educational attainment was associated with better retention of the Complex Figure (regression coef. = 4.0 per category of educational qualification [95% CIs 1.4 – 6.6], p = 0.002) .

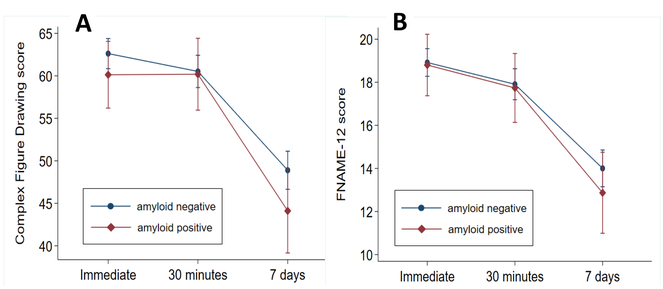


Fig 4. Means and 95% CIs for recall on (A) Complex Figure Drawing, (B) FNAME-12. Range of possible scores is 0 to 80 (Complex Figure) and 0 to 24 (FNAME-12).

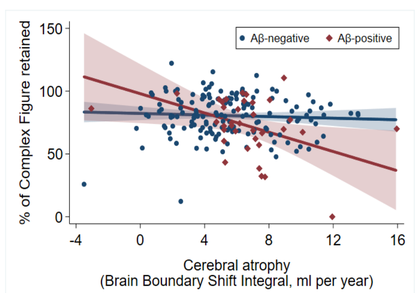


Fig 5. Association between cerebral atrophy and Complex Figure retention. Note that a score of >100% is possible if more material was recalled after 7 days than after 30 minutes. Solid lines represent predictions from the multivariate regression model, and shaded areas represent 95% CIs. Markers show raw data.

Participants

	β-amyloid negative	β-amyloid positive
N	159	36
% female	50.9	36.1
Age (years): mean (range)	72.5 (71.9, 73.1)	72.6 (72.0, 73.1)
Childhood cognition (z-score): mean, *SD* (range)	0.43, *0.76* (-1.59, 2.47)	0.33, *0.73* (-1.08, 2.50)
Highest educational qualification: %		
None	13.8	13.9
Below O-levels (vocational)	3.8	8.3
O-levels or equivalent	34.0	30.6
A-levels or equivalent	34.6	27.8
Degree or equivalent	13.8	19.4

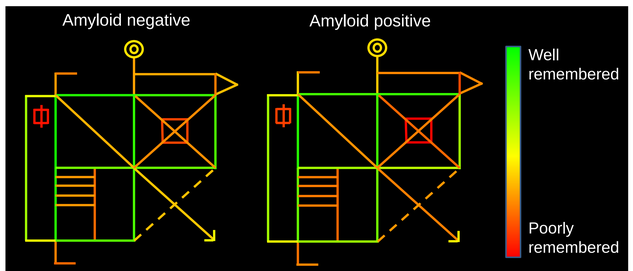


Fig 3. Memory for each part of the complex figure after 7 days. The colour of each line or feature is graded according to its average score. This shows that the overall structure of the boxes was remembered better than the details of the various features.

Conclusions

- These results provide novel evidence of Accelerated Forgetting in cognitively-normal amyloid-positive 72-year-olds, similar to the effect we observed in our previous study of presymptomatic familial AD [1].
- The effect size of the difference between the amyloid groups on the Complex Figure test (equivalent to 0.5 *SD*) was greater than the differences observed on standard cognitive assessments in this cohort at age ~70 [4].
- The association between greater rate of cerebral atrophy and greater forgetting in amyloid-positive participants suggests that these assessments may hold promise as sensitive outcome measures for therapeutic trials in preclinical AD.
- Future work will include repeating analyses with the full sample when data collection is finished (~500 participants), incorporating additional biomarker measures such as rates of amyloid deposition, and conducting longitudinal Accelerated Forgetting assessments to investigate predictors of memory decline.

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