Associations between accelerated forgetting, amyloid deposition and brain atrophy in older adults

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Abstract

Accelerated long-term forgetting (ALF) is the phenomenon whereby material is retained normally over short intervals (e.g. minutes) but forgotten abnormally rapidly over longer periods (days or weeks). ALF may be an early marker of cognitive decline, but little is known about its relationships with preclinical Alzheimer's disease pathology, and how memory selectivity may influence which material is forgotten.

We assessed ALF in 'Insight 46', a sub-study of the MRC National Survey of Health and Development (a population-based cohort born during one week in 1946) (n=429; 47% female; assessed aged ~73 years). ALF assessment comprised visual and verbal memory tests: Complex Figure Drawing and the Face-Name Associative Memory Exam (FNAME). ALF scores were calculated as the percentage of material retained after 7 days, relative to 30 minutes. In 306 cognitively-normal participants, we investigated effects on ALF of β-amyloid pathology (quantified using 18F-Florbetapir-PET, classified as positive/negative) and whole-brain and hippocampal atrophy rate (quantified from serial T1-MRI over ~2.4 years preceding the ALF assessment), as well as interactions between these pathologies. We categorized Complex Figure Drawing items as 'outline' or 'detail', to test our hypothesis that forgetting the outline of the structure would be more sensitive to the effect of brain pathologies. We also investigated associations between ALF and Subjective Cognitive Decline, measured with the MyCog questionnaire.

Complex Figure 'outline' items were better retained than 'detail' items (mean retention over 7 days = 94% vs 72%). Amyloid-positive participants showed greater forgetting of the Complex

Figure outline, compared to amyloid-negatives (90% vs 95%; $P<0.01$). There were interactions between amyloid pathology and cerebral atrophy, such that whole-brain and hippocampal atrophy predicted greater ALF on Complex Figure Drawing among amyloid-positives only (e.g. 1.9 percentage-points lower retention per ml/year of whole-brain atrophy [95% confidence intervals 0.5, 3.7]; $P<0.05$). Greater ALF on FNAME was associated with increased rate of hippocampal atrophy. ALF on Complex Figure Drawing also correlated with subjective cognitive decline (-0.45 percentage-points per MyCog point [-0.85, -0.05], $P<0.05$).

These results provide evidence of associations between some measures of ALF and biomarkers of brain pathologies and subjective cognitive decline in cognitively-normal older adults. On Complex Figure Drawing, 'outline' items were better remembered than 'detail' items – illustrating the strategic role of memory selectivity – but 'outline' items were also relatively more vulnerable to ALF in individuals with amyloid pathology. Overall, our findings suggest that ALF may be a sensitive marker of cognitive changes in preclinical Alzheimer's disease.

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Introduction

Accelerated long-term forgetting (ALF) is the phenomenon whereby information is retained normally over short intervals (minutes) but forgotten abnormally rapidly over longer periods (days or weeks).[1] Although the mechanistic basis – whether ALF represents an impairment of memory consolidation, or a failure of retrieval processes – and neurobiological underpinnings of ALF are poorly understood,[2,3] the phenomenon highlights a critical phase of normal memory processing that is almost entirely ignored in routine clinical assessment. ALF has been predominantly described in people with epilepsy,[4] including children,[5] most commonly resulting from seizures affecting the temporal lobes, particularly in transient epileptic amnesia.[6] It has also been described after minor stroke or transient ischemic attack,[7] and childhood traumatic brain injury.[8] Recently there has been increasing interest in whether ALF could be a useful early clinical marker of memory impairments in Alzheimer's disease (AD) – impairments that would be missed by standard memory tests which typically assess recall over short delays (often up to 30 minutes). Three recent literature reviews on this topic[9–11] present a mixed and nuanced picture of results, but suggest that ALF appears to be an early feature of cognitive decline in the preclinical and prodromal (mild cognitive impairment) stages of AD.

The concept of preclinical AD has evolved considerably in recent years and is now applied to cognitively unimpaired individuals with biomarker evidence of AD pathology: amyloid and tau (usually identified from PET neuroimaging and/or CSF), and neurodegeneration (primarily identified from volumetric structural MRI).[12] These pathological accumulations are detectable years, perhaps decades, before onset of symptoms.[13,14] However, studies investigating ALF in the preclinical stage of AD have often lacked biomarker evidence of pathology and have instead been based on risk factors including age, *APOE*-ε4 genotype (the strongest genetic risk factor for AD)[15], family history of dementia, and subjective cognitive decline (i.e. self-reported decline in cognition despite normal performance on objective cognitive tests)[16]. Evidence from these studies suggests the presence of ALF in *APOE*-ε4 carriers[17,18] and in individuals with subjective cognitive decline.[19–21] One study of healthy older adults found that 4-week delayed verbal memory recall was better than standard memory tests at predicting cognitive decline after 12 months.[22] Other relevant studies have detected ALF in cohorts carrying rare genetic

mutations causing autosomal dominant AD, but who have not yet developed symptoms,[23–25] with one concluding that ALF may be detectable up to a decade before symptom onset, earlier than other neuropsychological tests.[25] To our knowledge, only one study has investigated associations between ALF and a biomarker of AD pathology, reporting greater forgetting rates over one week in individuals with abnormal levels of CSF amyloid-β_{42}.[20] However, this group only contained ten individuals who also had subjective cognitive decline and performed more poorly than their amyloid-negative counterparts on the initial learning and recall tests, suggesting that their memory impairment was not specifically ALF.

There is therefore a need for evidence regarding whether ALF may be a sensitive marker of early subtle cognitive deficits in individuals with biomarker evidence of AD pathology. This question is especially important in this new era of approved disease-modifying treatments, as sensitive cognitive measures are required for diagnosis and tracking of patients, and for use as screening and outcome measures for clinical trials that will increasingly focus on preclinical populations including those with subjective cognitive decline. Furthermore, through the identification of ALF in specific populations, and a careful consideration of what is and is not recalled on a specific cognitive test (e.g. overall gist vs peripheral detail)[26], especially with tasks used to detect ALF often differing markedly between studies,[3,10] we may improve not only the sensitivity of these tests but also gain insight into what drives this phenomenon.

This study assessed ALF in the Insight 46 sub-study[27] of the MRC National Survey of Health and Development (NSHD; the British 1946 birth cohort), a population-based cohort of individuals who were all born during the same week in March 1946. We investigated relationships between ALF and biomarkers of brain pathology in cognitively-normal individuals, addressing the following questions: (1) Do participants with elevated amyloid show evidence of ALF? (2) Is ALF associated with neurodegeneration, as indexed by whole-brain and hippocampal atrophy rates? (3) Does ALF correlate with subjective cognitive decline? Specific hypotheses addressing these questions are set out in the methods.

Materials and methods

The NSHD is the world's longest continuously running birth cohort, with 25 data collections across childhood and adulthood.[28] For the Insight 46 sub-study[27], 502 NSHD participants

completed a baseline assessment at University College London between 2015-2018, at age ~70 years. 442 of these participants completed follow-up assessment at age ~73. As detailed below and in **Supplementary Fig. 1**, this study focuses on cognitively-normal participants. Detailed recruitment procedures and protocols have been described previously.[27,29] At both baseline and follow-up, measures included cognitive tests, clinical history and examination, β-amyloid-PET imaging, brain MRI, and other biomarker (blood; CSF) and genetic measures as detailed elsewhere.[27,30–32] The study was approved by the Queen Square Research Ethics Committee - London (reference 14/LO/1173). All participants provided written informed consent according to the declaration of Helsinki.

The cognitive battery comprised paper-and-pencil tests and more novel computerised tasks, detailed in previous publications where we have reported cross-sectional associations between baseline cognition and biomarkers of brain health.[32–35] At follow-up, the cognitive battery was complemented with the addition of an accelerated long-term forgetting (ALF) assessment, so only cross-sectional data are currently available for this test.

Accelerated long-term forgetting assessment

Our ALF assessment used two memory tests: the 12-item Face-Name Associative Memory Exam (FNAME-12)[36], which requires learning and recall of names and occupations associated with pictures of faces, and Complex Figure Drawing from the Adult Memory and Information Processing Battery (AMIPB).[37] The rationale for not including the list learning task used in our original study of ALF in presymptomatic dominantly inherited AD[23] was to avoid interference and potential contamination with an existing 15-item list learning test embedded in the longitudinal NSHD assessments at ages 43, 53, 62, and 69.

Both tests included immediate recall and 30-minute delayed recall, as well as 7-day delayed recall and recognition captured using a telephone assessment (**Fig. 1**). This complies with guidance from Elliott et al.[3], that assessments of ALF should use both verbal and non-verbal material, with testing of recall and recognition.

On the day of their assessment at the clinic, participants were given a sealed envelope containing the paper stimuli needed for the telephone call to take place 7-days later; they were instructed not to open this envelope in advance of the call. They were not warned to expect any cognitive tests – they were simply told that the purpose of the call was to follow up on some aspects of the clinical visit. Within the envelope was a set of further sealed envelopes, each

containing material for one task, so that each task could be completed sequentially according to the assessor's instructions. Due to restrictions during the coronavirus pandemic, 22 participants were assessed via video-call instead of in-person assessment, so their testing procedure deviated slightly from the descriptions below, in that the stimuli for the main assessment and the 7-day assessment were presented to them via screenshare.

Face-Name test

FNAME-12[36] is a paired associative memory test, which was chosen as it meets the criteria of Elliot et al.[3] and was already part of the existing cognitive battery, so could be adapted into an ALF assessment without adding to the length of the main battery or conflicting with existing memory tasks. We used FNAME-12 version A (version B is also available). The procedure (summarised in **Figure 1**) was as follows: Participants received two exposures to twelve faces, each with a name and occupation (e.g. Nancy, Doctor). The faces were presented one-by-one for 8 seconds each, on a computer screen. Each exposure was followed by an immediate recall test where participants were shown the twelve faces one-by-one and asked to state the name and occupation of each one. A third recall trial was administered after a delay of ~10 minutes. After a ~30-minute delay, participants were shown twelve sets of three faces and asked to identify each previously learned face from the two distractors (facial recognition) and to state the name and occupation (the fourth recall test). They were then asked to select the correct name and occupation from three options comprising the correct answer, a distractor (a name or occupation that belongs with a different face in the set), and a name or occupation that did not feature in the set. During the 7-day telephone call we repeated the same procedure as at the 30-minute delay, with the stimuli presented on printed worksheets provided in the sealed envelopes. For each of the five recall trials (immediate 1; immediate 2; 10-minute delay; 30-minute delay; 7-day delay), the score is the number of names and occupations correctly recalled (maximum 24). For each of the two facial recognition tests (30-minute delay; 7-day delay), the maximum score is 12. For each of the two name and occupation recognition tests (30-minute delay; 7-day delay), the maximum score is 24.

Complex Figure Drawing

Complex Figure Drawing was chosen based on its sensitivity to ALF in presymptomatic individuals carrying mutations causing Familial Alzheimer's Disease,[23] and because it did not conflict with any existing memory tests in the battery. Complex Figure Drawing tests are

widely used as measures of visual memory.[38] We used AMIPB Complex Figure version A,[37,39] which was presented to participants on a laminated card. First, participants were asked to copy the figure while it was directly in front of them, without a time limit. They were then asked to draw it from memory immediately after it had been removed from sight, and again after a delay of ~30 minutes. During the 7-day telephone call, participants were asked to make a further drawing from memory, which they were then instructed to seal inside an envelope. To test recognition memory, they were subsequently shown four sets of three similar illustrations (on printed worksheets provided in the sealed envelopes) and were asked to identify which images exactly matched part of the original figure (with a maximum score of 4). The four figure drawings (copy; immediate recall; 30-minute recall; 7-day recall) were scored according to the AMIBP manual, which breaks the figure down into 36 items (lines or features). Most of the items are worth up to 2 points each, but four of the more complicated features are worth up to 4 points each, giving a maximum total score of 80. Points are deducted for items that are missing or are inaccurate (e.g. wrong size, wrong orientation, wrong position). Five raters carried out the scoring, meeting regularly to discuss queries and ensure consistent application of the scoring guidelines. We created a spreadsheet to record item-level scores (**Supplementary File**). All raters were blind to the amyloid status of participants.

When scoring the drawings, we noticed that the outline of the figure (i.e. the general box-like structure) tended to be preserved whereas the internal details (e.g. internal lines and small features) were more likely to be forgotten (**Fig. 2A**). We also noticed that for some participants there appeared to be a qualitative shift after 7 days whereby the outline was no longer well reproduced (see **Figure 3** for some individual examples). This shift was apparent both from visual examination of the drawings and also from the particular challenges of applying the scoring guidelines to some of the 7-day drawings. The scoring procedure requires raters to decide whether each item is present or absent, and (if present) whether it is accurate or distorted in some way (e.g. too big, rotated, embellished). The manual advises raters to start by identifying a 'reference set' – a part of the drawing that can be treated as an anchor for other items to be judged in relation to; for most drawings, this was the outline of the four boxes (**Fig. 2A**). For some 7-day drawings the scoring was difficult and time-consuming, because there was no clear 'reference set' and the lines on the page did not have an obvious or unambiguous mapping onto the original diagram. This experience, along with seeing the outline stand out so distinctively in **Figure 2A** (an earlier version of which we produced as an interim analysis for a conference poster)[40] prompted our idea that there may be distinct processes underlying recall

of the outline and recall of the detail after an extended (7-day) delay. We saw a parallel here with the premise of ALF, namely that the processes of memory storage and recall are somehow functioning differently over a long delay compared to a short delay.

Based on this, we hypothesised that such a breakdown in memory for the outline may reflect a more problematic – and potentially pathological – type of forgetting, potentially reflecting the cognitive consequences of preclinical AD pathologies. To test this hypothesis, we created separate 'outline' and 'detail' scores, by categorising each of the 36 items as either 'outline' or 'detail'. We first converted the scores for each item to a proportion (between 0 and 1), to allow all the items to be compared against each other (**Fig. 2C**). Visually examining these bar charts (**Fig. 2C**) we perceived a step decrease in the frequency of full-mark responses after the highest-scoring eleven items, and we noticed that these eleven items were consistent across all three delay trials (despite minor variations in their ordering). These eleven items correspond to the outline of the Complex Figure (**Fig. 2B**). Thus, we categorised these eleven items as 'outline', creating a score out of 22 (since all of these items were worth up to 2 points each). The remaining 25 items were categorised as 'detail', creating a score out of 58 (since twenty-one items were worth up to 2 points and four items were worth up to 4 points).

ALF scores

Using a method derived from previous studies,[3,23] ALF scores were calculated as the percentage of material recalled after 7 days, relative to the proportion recalled after 30 minutes (i.e. 7-day score / 30-minute score, multiplied by 100). This gives a 'percentage retention' score, which is preferable to simply using the 7-day recall score, as that does not capture forgetting itself[3]. Previous studies have identified testing at 30 minutes and 7 days to be sufficient for identifying ALF.[23,41] The Complex Figure Drawing had three ALF scores reflecting overall retention of the diagram, retention of the 'outline' and retention of the 'detail': $\text{Drawing}_{\text{total}}$, $\text{Drawing}_{\text{outline}}$, and $\text{Drawing}_{\text{detail}}$. The Face-Name test had a single ALF score based on total names and occupations correctly recalled – hereafter referred to as ALF-FNAME.

Of the 442 participants in the follow-up assessments, ALF scores were available for 429 participants. Reasons for missing data are detailed in **Supplementary Figure 1**.

Biomarker measures

At both baseline and follow-up, participants underwent simultaneous β-amyloid-PET and multimodal MRI during a 60-minute scanning session on a single Biograph mMR 3T PET/MRI scanner (Siemens Healthcare, Erlangen, Germany), with intravenous injection of 370 MBq of the β-amyloid PET ligand, 18F-Florbetapir (Amyvid). Detailed imaging protocols have been described elsewhere.[27,31]

β-amyloid deposition was quantified using the Standardised Uptake Value Ratio (SUVR) calculated from a composite of cortical regions of interest with a reference region of whole cerebellum, with partial volume correction. A cut-point for amyloid status (positive / negative) was determined using a mixture model to define two Gaussians, and taking the 99th percentile of the lower (amyloid-negative) Gaussian at SUVR>1.032.[42] In all analyses involving SUVR, we have used the follow-up value, as this was contemporaneous to the ALF assessment. In all analyses involving amyloid status, we have used the follow-up data for the same reason, but for 3 participants with missing follow-up PET data, we have substituted baseline status (positive n=1; negative n=2). This maximises the sample size and is based on our finding that few participants changed amyloid status between baseline and follow-up: of 269 amyloid-negatives at baseline, only 21 (7.8%) converted to amyloid-positive at follow-up.

Changes in whole-brain and hippocampal volumes between baseline and follow-up were quantified from T1-weighted MRI using the Boundary Shift Integral (BSI).[43] BSI allows for comparison of brain volumes on serial imaging through a process of semi-automated brain segmentation and edge detection of the boundaries between brain and CSF.[44] Annualised whole-brain and hippocampal atrophy rates were calculated by dividing the BSI by the interval between the two scans. Negative BSI values represent volume loss (atrophy).

Global white matter hyperintensity volume (a marker of cerebral small vessel disease that is common in older people and is associated with poorer cognition)[32,34,45] was quantified from T1 and FLAIR images using an automated segmentation algorithm – Bayesian Model Selection – followed by visual quality control.[46] Total intracranial volume (TIV) was generated using statistical parametric mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm).[47]

APOE genotype was classified as ε4 carriers or non-carriers.[27]

Subjective Cognitive Decline questionnaire

Subjective cognitive decline at baseline and follow-up was measured using the MyCog questionnaire, which is part of the SCD-Questionnaire (SCD-Q).[48] MyCog comprises 24 'yes/no' questions about instrumental activities of daily living, and assesses perceived decline over the preceding 2 years (e.g. "I find it harder to follow the plot of a book."). Scores range between 0 to 24, with higher scores indicating greater perceived cognitive decline.

We have previously reported cross-sectional results from our baseline assessments, showing that MyCog scores correlated with trait anxiety scores,[49] measured using the State and Trait Anxiety Inventory (STAI).[50] Our proposed explanation for this is that MyCog (like other SCD measures) captures some general aspects of anxiety traits, such as a low estimation of one's own abilities. Now that we have longitudinal MyCog data, this allows us to look at *change* in MyCog score, which should be a purer measure of SCD, assuming that the contribution of anxiety traits remains stable. In our Statistical Models (see below), we have adjusted for trait anxiety score, which has a possible range between 20 to 80 (with higher scores indicating greater anxiety). The score is derived from 20 questions asking participants about how they feel generally (e.g. "I lack self-confidence").

Life-course and clinical variables

The nature of the NSHD has facilitated prospective collection of extensive life-course data. We included the following variables as they have previously been shown to correlate with cognitive function in later life.[32,51]

Childhood cognitive ability was measured with tests of verbal and nonverbal ability at ages 8, 11 and 15, standardised into z-scores as previously described.[32] We have used the z-score from age 8 (or ages 11 or 15 if earlier data were missing).

Education was classified into five categories based on highest qualification at age 26: no qualification, below O-levels (vocational), O-levels and equivalents (ordinary), A-levels and equivalents (advanced), higher (degree and equivalents).

Socioeconomic position was derived from participants' occupations (based on data collected at age 53, or earlier where this was missing), classified into six categories: unskilled, partly skilled, skilled manual, skilled nonmanual, intermediate, professional.[32]

Participants were classified as having a neurological or major psychiatric condition (including dementia and mild cognitive impairment) using previously described criteria[32] (see **Supplementary Figure 1** for specific diagnoses). We refer to participants not meeting these criteria as cognitively normal. This does not imply that all participants with a neurological or major psychiatric condition necessarily had a measurable cognitive impairment.

Statistical analysis

Analyses were conducted using Stata 18 (StataCorp, College Station, TX). Statistical significance was set at $P<0.05$. Model assumptions were checked by examination of residuals.

Amyloid pathology and brain and hippocampal atrophy

We tested the following hypotheses in cognitively-normal participants with complete biomarker data (n=306; **Supplementary Fig. 1**): (1) poorer performance on the ALF test (i.e. greater forgetting) would be associated with amyloid pathology and brain and hippocampal atrophy; (2) ALF-Drawing$_{outline}$ would be more sensitive to these pathologies than ALF-Drawing$_{total}$ and ALF-Drawing$_{detail}$.

Multivariable regression models were used to investigate associations between ALF and amyloid pathology and cerebral atrophy rates (whole-brain and hippocampal), and to explore interactions between these predictors. Eight models were fitted for each of the four ALF scores (ALF-Drawing$_{total}$, ALF-Drawing$_{outline}$, ALF-Drawing$_{detail}$ and ALF-FNAME). Models 1-4 use amyloid status (positive / negative) as a dichotomous measure of amyloid pathology. Models 5-8 essentially repeat models 1-4 but with SUVR as the continuous measure of amyloid pathology.

Model 1: amyloid status and whole-brain atrophy rate

Model 2: amyloid status and hippocampal atrophy rate

Model 3: interaction between amyloid status and whole-brain atrophy rate

Model 4: interaction between amyloid status and hippocampal atrophy rate

Model 5: SUVR and whole-brain atrophy rate

Model 6: SUVR and hippocampal atrophy rate

Model 7: interaction between SUVR and whole-brain atrophy rate

Model 8: interaction between SUVR and hippocampal atrophy rate

As the distributions of the outcome variables were somewhat skewed, bootstrapping was used to produce bias-corrected and accelerated 95% confidence intervals (CIs) from 2,000 replications. All models adjusted for the following potential confounders: sex, age at ALF assessment, childhood cognitive ability, education, socioeconomic position, *APOE*-ε4 genotype (carrier or non-carrier), white matter hyperintensity volume and total intracranial volume (an index of head size)**.**

While our main outcomes were the ALF scores, we also examined performance on each trial of the tasks, including the recognition tests (described above and summarised in **Figure 1**) Our purposes were to build on our findings of associations between these pathologies and ALF, by addressing the following questions: (1) Did the difference between the amyloid groups on Complex Figure Drawing only emerge after 7-days (i.e. no evidence of differences after a short delay of 30 minutes, consistent with the definition of ALF)? (2) Were amyloid-related deficits after 7-days specific to recall, or were deficits also seen in recognition memory? For each measure (see list and descriptive statistics in **Supplementary Table 2)** a multivariable regression model was fitted where the outcome was the score (converted into % correct) and the predictors were amyloid status and whole brain atrophy rate (analogous to Model 1 above). For variables where the distributions of the scores were skewed, bootstrapping was used to produce bias-corrected and accelerated 95% CIs from 2,000 replications. All models adjusted for the same potential confounders as listed above**.**

Subjective Cognitive Decline

In all cognitively-normal participants (*n*=377; **Supplementary Fig. 1**), we tested the hypothesis that poorer performance on the ALF test would be associated with greater subjective cognitive decline.

Multivariable regression models were fitted where the outcomes were the four ALF scores (ALF-Drawing$_{total}$, ALF-Drawing$_{outline}$, ALF-Drawing$_{detail}$ and ALF-FNAME), and the predictors were firstly MyCog score (cross-sectional, administered at follow-up on the same day as the ALF assessment) and secondly 'change in MyCog score' (i.e. follow-up minus baseline score). As the distributions of the outcome variables were somewhat skewed, bootstrapping was used to produce bias-corrected and accelerated 95% CIs from 2,000 replications. All models adjusted for the following potential confounders: sex, age at ALF

assessment, childhood cognitive ability, education, socioeconomic position. For models that used change in MyCog score, we additionally adjusted for the duration of the interval between baseline and follow-up assessments.

Based on our previous finding of an association between MyCog score and trait anxiety at baseline (described above),[49] we reran the above models adjusting for follow-up trait anxiety score.

Data availability

Data from the NSHD are curated and stored by the MRC Unit for Lifelong Health and Aging at UCL. Anonymized data will be shared by request from bona fide investigators (https://skylark.ucl.ac.uk/NSHD/doku.php).

Results

Participants

Of the 429 participants with ALF scores available, 377 were classified as cognitively normal, of whom 306 had complete biomarker data (**Supplementary Fig. 1**). 95 (31%) of these were amyloid positive. Participant characteristics and descriptive statistics for ALF scores are provided in **Table 1** for the n=306 sample, subdivided by amyloid status (see **Supplementary Table 1** for a version of this table that includes all 429 participants). Note that 304 out of the 306 participants were assessed in person, with the remaining two (both amyloid-negative) assessed by video call. No significant differences were identified between amyloid-positive and amyloid-negative groups in terms of age at assessment, childhood cognitive ability, or socioeconomic position. Amyloid-positive participants were slightly less well educated and were more likely to be *APOE*-ε4 carriers.

Amyloid pathology and brain and hippocampal atrophy

Amyloid status was associated with ALF-Drawing$_{outline}$ (**Table 2**): amyloid-positive participants showed greater forgetting of the outline of the Complex Figure (90% of the outline was retained by amyloid-positives [95% CIs 85, 94] and 95% [92, 99] by amyloid-negatives

(marginal means from the regression model, $P<0.01$)). Consistent with our hypothesis, ALF-Drawing$_{outline}$ was the only Complex Figure score to show this effect; ALF-Drawing$_{total}$ and ALF-Drawing$_{detail}$ did not statistically significantly differ between amyloid-positive and amyloid-negative groups (**Table 2**). ALF-FNAME also did not differ between amyloid-positive and amyloid-negative groups (**Table 2**).

Figure 4 illustrates the trial-by-trial recall performance of amyloid-positive and amyloid-negative groups (see also **Supplementary Table 2**)**,** showing that the only trial with a statistically significant difference between the groups was the 7-day recall of the Complex Figure Drawing 'outline', where amyloid-positive participants scored lower. This poorer 7-day recall, despite unimpaired performance on 30-minute recall**,** is what gives rise to their lower ALF-Drawing$_{outline}$ score.

In analyses of trial-by-trial performance, we found no statistically significant differences between amyloid-positive and amyloid-negative groups in terms of 7-day recognition memory (Complex Figure recognition: amyloid-positive mean = 86.2% [95% CIs 80.9, 91.3], amyloid-negative 87.1% [84.4, 89.6], $P>0.05$; FNAME recognition of names and occupations: amyloid-positive 88.7% [85.9, 91.2], amyloid-negative 88.8% [87.4, 90.2] $P>0.05$).

Whole-brain and hippocampal atrophy did not have statistically significant associations with ALF scores on the Complex Figure Drawing task (adjusting for amyloid status), although results were in the expected direction of accelerated forgetting with faster atrophy rates (**Table 2**). However, there were interactions between amyloid status and atrophy rates, such that the associations between faster atrophy and accelerated forgetting were seen in those who were amyloid positive but not those who were amyloid negative (**Table 2**). In particular, statistically significant interactions were observed for ALF-Drawing$_{outline}$ (whole-brain and hippocampal atrophy rates) and ALF-Drawing$_{total}$ (whole-brain atrophy rate) (**Table 2**; **Fig. 5**). In other words, on the Complex Figure Drawing task we found evidence of a correlation between degree of ALF and rates of neurodegeneration, in the context of elevated amyloid pathology.

On the Face-Name test, there was an association between faster hippocampal atrophy and accelerated forgetting (**Table 2**; **Supplementary Fig. 2**), which did not differ according to amyloid status (i.e. no statistically significant interaction, **Table 2**). Brain atrophy showed a non-significant trend in the same direction (i.e. lower ALF-FNAME scores with faster atrophy), with a stronger association in the amyloid-positive group, although this interaction was not statistically significant (**Table 2**).

When rerunning the models with the continuous measure of amyloid pathology (SUVR), results were similar (**Supplementary Table 3**).

Of the demographic and life-course factors included in the models, only education was a statistically significant predictor of performance, with higher educational attainment associated with better ALF scores on Complex Figure Drawing (coefficients not reported). *APOE*-ε4 and white matter hyperintensity volume had no independent effects on any outcome (coefficients not reported).

Subjective Cognitive Decline

Higher cross-sectional MyCog score (i.e. greater subjective cognitive concerns) was associated with greater forgetting on ALF-Drawing$_{total}$ (coefficient = -0.45 per MyCog point [95% CIs -0.85, -0.05], P<0.05) (**Fig. 6A**) and ALF-Drawing$_{detail}$ (-0.58 [-1.16, -0.02], P<0.05). Results for ALF-Drawing$_{outline}$ were similar although non-statistically significant (-0.34 [-0.73, 0.07]). There was no evidence of an association between MyCog score and ALF on the Face-Name test (ALF-FNAME = -0.19 [-0.79, 0.35]).

Greater increase in MyCog score (i.e. increase in subjective cognitive concerns over the last ~2.4 years) was associated with greater forgetting on ALF-Drawing$_{total}$ (-0.56 per increase of one MyCog point [95% CIs -1.18, -0.03], P<0.05) (**Fig. 6B**) and ALF-Drawing$_{outline}$ (-0.52 [-1.20, -0.03], P<0.05), but not ALF-Drawing$_{detail}$ (-0.51 [-1.38, 0.24]) and ALF-FNAME (0.06 [CIs -0.67, 0.78]).

Adjusting for trait anxiety made no material difference to these results (results not shown).

Discussion

This study examined ALF in cognitively-normal ~73-year-olds using visual and verbal memory tests. Our results indicate that Complex Figure Drawing reveals ALF in individuals with amyloid pathology, accelerated rates of neurodegeneration and subjective cognitive decline. Specifically, amyloid-positive individuals showed normal recall after a standard 30-minute testing delay but forgot a greater proportion of the outline structure of the Complex Figure over 7 days. Among individuals with elevated amyloid, faster rates of whole-brain and hippocampal atrophy were associated with greater degree of ALF on the Complex Figure.

Accelerated forgetting of the Complex Figure was also associated with higher subjective cognitive decline, despite our study only including those classified as cognitively normal. This suggests that Complex Figure Drawing with 7-day delayed recall could be a useful test for identifying individuals in the preclinical stage of AD.

However, the second ALF task – the Face-Name test – did not follow the same pattern of results. Degree of forgetting on this test was not associated with either amyloid pathology or subjective cognitive decline. This discrepancy may reflect the differing psychometric properties, procedures and materials, and memory demands of the two tasks. For example, the tasks varied in number of probes of the learned information (Complex Figure: 3 recall, 1 recognition; FNAME: 5 recall, 2 recognition probes), and whilst the number of long delay periods was constant (one, at 7 days), multiple retrievals of learned information may reduce the rate of forgetting because retrieval of probed features activates other associated features within that episode.[2] We note that the standard Face-Name test (without 7-day recall) has previously been reported to be sensitive to amyloid pathology,[52,53] although this was not the case in our cohort at age 70.[32] However, we found evidence of an association between faster rates of hippocampal atrophy and greater forgetting over 7 days on this test. This is consistent with the pivotal role of the hippocampus in associative memory[54] and with evidence of hippocampal activation during face-name associative memory tasks.[55,56] To our knowledge, associations between hippocampal atrophy rates and performance on associative memory tests have not been reported before in cognitively-normal older adults. The mean hippocampal atrophy rate in our sample (-0.04 ml/year, equivalent to approximately 0.64% volume loss per year) was below the mean rate for elderly healthy controls of 1.4%/year reported in a meta-analysis,[57] suggesting that even subtle excess hippocampal atrophy may have cognitive consequences. One probable reason why our analysis was able to detect this subtle association is that the age range of our participants was so narrow (71.9-74.8 years), minimising the confounding effect of age.

Our results add to an emerging literature on ALF in the preclinical stage of AD. Our analyses suggest that previous reports of associations between *APOE*-ε4 and ALF[17,18] can be explained by amyloid pathology (which these studies did not measure), as *APOE*-ε4 had no independent effect in our study. In terms of how our results compare with evidence from the preclinical stage of autosomal dominant AD,[23–25] the evidence for ALF in that population appears to be stronger and more consistent (e.g. Weston et al found that mutation carriers showed ALF on verbal and visual memory tests, on average 7 years before expected symptom onset).[23] This

difference may be because not all amyloid-positive older adults will develop AD (whereas autosomal dominant mutations are almost fully penetrant) and the onset of symptoms may be many years away for our 73-year-old participants, based on the median age of onset of dementia of 84 years in the UK.[58] Our finding of limited evidence for an association between subjective cognitive decline and ALF is consistent with the literature, where similar associations have been reported but not consistently.[19–21]

A striking feature of performance on the Complex Figure Drawing task was how much more easily the outline of the drawing was recalled than the internal details. This could potentially be explained by the phenomenon of memory selectivity,[59] whereby human memory is adapted to work efficiently as a limited resource by remembering what is most important or most likely to enable the achievement of future goals. In our view, recalling the rough outline or skeleton of a diagram is analogous to recalling the gist of a conversation or the essence of a journal article without the actual words and details, with evidence that when recalling verbal stories, specific peripheral details are forgotten more quickly than the general gist.[26] As such, it seems to demonstrate efficient strategic operation of memory, although Complex Figure performance is likely also influenced by perceptual organisation factors including global precedence (the identification of global over local features) and principles of grouping (the tendency to perceive patterns based on proximity, similarity and connectedness).[60] In terms of why the outline may have been vulnerable to ALF in individuals with amyloid pathology, one factor of possible relevance is the organisational strategies that participants used when making their initial copy of the diagram. Anecdotally we observed that participants tended to draw the outline first, which is consistent with the literature on organisational strategies in drawing.[38] Deficits in organisational strategies of copying can mediate poorer delayed recall,[61] so it is possible that amyloid-positive participants may have been less well-organised in their copying strategies. However, if that were the case, it would be surprising that we saw no hint of an amyloid-related recall deficit after a 30-minute delay. Similarly, it is difficult to see how perceptual organisation factors could influence 7-day recall but not 30-minute recall. Instead, the divergence of performance over 7 days points us more towards differences in long-term memory storage and/or retrieval, discussed further below.

In terms of theoretical framework, little consensus has yet been reached within the field regarding the mechanisms underpinning ALF (for a review, see[10]). In line with a qualitative distinction between early and late forgetting, and under the standard model, ALF has been taken to reflect a disruption of the slow stage of memory consolidation (replacement of

hippocampal-neocortical connections with cortical-cortical connections).[62] In line with a quantitative distinction between early and later forgetting, and under Multiple Trace Theory, ALF in individuals who show normal or near normal learning and retention over short intervals has been taken to reflect subtle damage to a unitary consolidation mechanism.[63]

In line with this theoretical uncertainty, there has also been little agreement about the tests that should be used to detect ALF.[10] However the tests used in the current study (for the pragmatic reasons outlined in the Methods) fulfil the majority of criteria and quality markers set out in Elliot and colleague's review,[3] namely matching of patients and controls (in our case amyloid positive and negative individuals), use of visual and verbal material, inclusion of recall and recognition metrics, equated learning, avoidance of rehearsal (no warning given to participants of content of 7-day follow-up call) and avoidance of short term memory contribution (by virtue of delay intervals).

One reason why Elliot and colleagues[3] recommend that ALF studies should measure both recall and recognition is to allow researchers to distinguish between deficits of memory storage (impaired recall and impaired recognition) and deficits of retrieval (impaired recall but unimpaired recognition). Based on this, our results from the Complex Figure task could be argued to reflect a deficit of memory retrieval, since we found no difference between amyloid-positive and amyloid-negative groups on the 7-day recognition test. However, we think this interpretation might be too simplistic, because the subtle recall deficit observed in amyloid-positive participants only applied to the outline of the Complex Figure, not recall of the figure as a whole. The stimuli in the recognition test are each based on approximately one quadrant of the figure (i.e. they each contain bits of the outline and internal details). Therefore, the recognition test removes some of the demand to remember the overall shape and cannot be used as a direct comparison to the novel ALF-Drawing$_{outline}$ and ALF-Drawing$_{detail}$ recall scores we created. Also, the recognition test had a very small range of possible scores (0-4), which limits its sensitivity to differences between individuals.

Another clue to the processes underlying ALF in this cohort may come from the possible mechanisms by which amyloid pathology and brain atrophy could affect memory performance. Amyloid deposition leads to several changes within cell structure and function including neuronal hyperexcitability, synaptic dysfunction and cell death.[64–67] ALF in amyloid-positive participants could be mediated by any of these changes. Our results could also imply that the main impact of amyloid pathology on ALF is seen only after amyloid pathology leads to

increased atrophy. This is suggested by our finding of associations between faster rates of atrophy and greater degree of ALF, which were primarily driven by amyloid-positive individuals. This implies that ALF is due to structural changes to regions involved in memory consolidation, storage and retrieval. It is also worth noting that, in patients with temporal lobe epilepsy, the presence of ALF has been considered to result from subclinical epileptiform activity and seizures.[68] Whilst we have no evidence for seizure activity in our cohort, we are not able to rule out subclinical activity.

Our study had a number of limitations. First, our task procedure differed from some previous ALF studies in that we did not have a learning criterion (i.e. a minimum accuracy threshold for initial learning of the material, before the delayed recall trials).[3] Some previous studies have set thresholds of 60%,[69] 75%,[2,70] or 80%[17,23] for word lists or stories. To our knowledge no previous studies have applied a learning criterion to Complex Figure Drawing tasks, as it is not feasible to score the drawings instantaneously (e.g.[23,71]). Our median accuracy for the immediate recall trials of Complex Figure Drawing and Face-Name were 78% and 83% respectively (**Supplementary Table 2**), indicating that most participants learnt the material to a good level. The lack of a learning criterion could have limited our ability to detect subtle ALF in participants whose immediate recall was relatively low, but we do not think this has influenced our main results, since immediate and 30-minute recall were well-matched between amyloid-positive and amyloid-negative groups.

Second, there are limitations relating to the representativeness of Insight 46 participants, as previously discussed,[29,32] mainly that all participants are white British and tend to have slightly higher education and socioeconomic position than those not in the sub-study.[29] However, the prevalence of amyloid pathology was in line with the literature for individuals of this age.[72,73]

Third, our study lacked a measure of tau pathology, limiting our ability to draw conclusions about relationships between preclinical AD and ALF. While cognitive deficits are observed in the context of amyloid pathology alone, these correlate more closely with the presence of tau.[74,75] It will be of considerable interest to know whether the emergence of ALF in amyloid-positive individuals might be a very early sign of tau accumulation with consequent neurodegeneration. We are currently following up many of these individuals with tau-PET imaging, and will hopefully be able to address this important question in due course.

In summary, this study found associations in cognitively-normal ~73-year-olds between some aspects of performance on two ALF tests (Complex Figure Drawing and Face-Name) and

biomarkers of brain pathology (amyloid, brain atrophy rate and hippocampal atrophy rate) and subjective cognitive decline. On the Complex Figure Drawing task, a distinction was seen between forgetting of the outline of the diagram versus forgetting of the detail, with the outline generally being much better learned and remembered (suggesting memory selectivity) but also being relatively more vulnerable to ALF in individuals with amyloid pathology. Overall, our findings suggest that subtle ALF may be a detectable early memory deficit in individuals who are on a preclinical AD trajectory, and may therefore predict risk of neurodegeneration and future cognitive decline.

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Competing interests

NCF's research group has received payment for consultancy or for conducting studies from Biogen, Eli Lilly Research Laboratories, GE Healthcare, and Roche. NCF receives no personal compensation for the aforementioned activities. JMS has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly); has consulted for Roche Pharmaceuticals, Biogen, Merck, and Eli Lilly; given educational lectures sponsored by GE Healthcare, Eli Lilly, and Biogen; and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. All other authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 Accelerated Long-term Forgetting Assessment

Figure 2 'Outline' and 'detail' items in the Complex Figure from the Adult Memory and Information Processing Battery (AMIBP). (**A**) Heatmap with each item coloured according to its mean score across the immediate, 30-minute and 7-day recall trials. The heatmap colours range from red (representing the minimum mean score of 0.456) to green (representing the maximum mean score of 0.977). (**B**) Each item is numbered as per the scoring manual, with items that we have categorised as 'outline' highlighted in blue. (**C**) The bar charts show the frequency of scores awarded for each item in the full sample of Insight 46 participants (*n*=429), with the scores represented as proportions (i.e. 1 is the maximum possible score). Numbers on the x-axis refer to the item numbers as per the scoring manual (see panel (B)). Bars are ordered according to the frequency of full-mark scores i.e. starting with the best-remembered item. The blue rectangular box shows the items that participants consistently scored higher on, which we have categorised as 'outline' items, with the remaining items categorised as 'detail' items (as explained in the Methods).

Figure 3 Examples of responses to the Complex Figure Drawing test. Responses from 6 participants are shown (each participant in a different column). The original drawings were made using pencil and paper. We wrote a python script to extract the pencil lines from scanned copies of the worksheets and colour them digitally. The choice of colours is arbitrary, but the colour intensity corresponds to the score received, with paler hues indicating lower scores.

Figure 4 Means and 95% confidence intervals for recall on (A) Complex Figure Drawing, (B) Face-Name test (FNAME-12). The means and confidence intervals are predictions from multivariable regression models (see Methods) adjusted for sex, age at assessment, childhood cognitive ability, education, socioeconomic position, *APOE*-ε4 genotype, brain atrophy rate (ml/yr), white matter hyperintensity volume, and total intracranial volume. Bootstrapping was used to produce bias-corrected and accelerated confidence intervals from 2,000 replications. Asterisk indicates statistically significant difference between amyloid positive and negative groups (P<0.05) for 7-day recall of the Complex Figure outline items. Aβ = β-amyloid.

Figure 5 Associations of whole-brain and hippocampal atrophy with accelerated long-term forgetting of the Complex Figure Drawing. (A) whole-brain atrophy rate with Drawing$_{total}$, (B) whole-brain atrophy rate with Drawing$_{outline}$, (C) hippocampal atrophy rate with Drawing$_{outline}$. Note that a score of >100% is possible if participants recalled more material after 7 days than after 30 minutes. The solid line represents the line of best fit from the multivariate regression model, adjusted for sex, age at assessment, childhood cognitive ability, education, socioeconomic position, *APOE* genotype (ε4 carrier / non-carrier), amyloid status and white matter hyperintensity volume and total intracranial volume. The shaded area represents its 95% confidence intervals. Markers show the unadjusted raw data. Negative values for whole-brain and hippocampal volume change represent volume loss (atrophy). Aβ = β-amyloid.

Figure 6 Associations in cognitively-normal participants between subjective cognitive decline and accelerated long-term forgetting of the Complex Figure Drawing (Drawing$_{total}$): (A) Cross-sectional subjective cognitive concerns (B) Change in subjective cognitive concerns since baseline (~2.4 years earlier). Note that a score of >100% is possible if participants recalled more material after 7 days than after 30 minutes. In each graph, the solid line represents the line of best fit from the multivariate regression model, adjusted for sex, age at assessment, childhood cognitive ability, education, socioeconomic position, *APOE* genotype (ε4 carrier / non-carrier), amyloid status, white matter hyperintensity volume and total intracranial volume. The shaded area represents its 95% confidence intervals. Markers show the unadjusted raw data.