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Dissociable effects of *APOE*-ε4 and β-amyloid pathology on visual working memory

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J.M.S., S.J.C., M.R. and N.C.F conceptualized and led the Insight 46 study. Y.P. and M.H. designed the visual working memory experiment. K.L., I.P., and S.N.J. collected the data for the visual working memory test. T.D.P, C.A.L., A.K., S.E.K. and S.M.B. collected clinical and neuroimaging data. H.M.S and A.W. were responsible for study co-ordination and data management. K.L., S.M.D.H., J.M.S. and S.J.C conceived the manuscript. J.G. and M.H. developed the 2D-mixture model. K.L. analysed the data and drafted the initial manuscript. J.M.N. provided statistical support. D.M.C., I.B.M., C.H.S. and W.C. generated neuroimaging outcomes. K.L., S.M.D.H., J.G., M.H., J.M.S. and S.J.C. aided in manuscript preparation and interpretation. All authors revised and approved the manuscript.

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Introductory Paragraph

Although *APOE*-ε4 carriers are at significantly higher risk of developing Alzheimer's disease than non-carriers[1], controversial evidence suggests that *APOE*-ε4 might confer some advantages, explaining the survival of this gene (antagonistic pleiotropy)[2,3]. In a population-based cohort born in one week in 1946 (assessed aged 69-71), we assessed differential effects of *APOE*-ε4 and β-amyloid pathology (quantified using ^{18}F-Florbetapir-PET) on visual working memory (object-location binding). In 398 cognitively normal participants, *APOE*-ε4 and β-amyloid had opposing effects on object identification, predicting better and poorer recall respectively. ε4-carriers also recalled locations more precisely, with a greater advantage at higher β-amyloid burden. These results provide evidence of superior visual working memory in ε4-carriers, showing that some benefits of this genotype are demonstrable in older age, even in the preclinical stages of Alzheimer's disease.

The human apolipoprotein E (*APOE*) gene has three main alleles – ε2, ε3 and ε4 – with ε3 being the most common. *APOE*-ε4 is the strongest genetic risk factor for sporadic Alzheimer's disease, increasing risk in a dose-dependent manner (3-4-fold for ε4-heterozygotes;12-16-fold for ε4-homozygotes[1,2]), and resulting in earlier dementia onset[1]. The role of apoE in Alzheimer's disease pathogenesis is not fully understood, but ε4 is associated with reduced clearance and hence accumulation of β-amyloid[1,4]. β-amyloid pathology is detectable up to 2-3 decades before symptoms emerge[5,6], is associated with subtle cognitive deficits in cognitively unimpaired older adults[7], and is necessary but not sufficient for a diagnosis of Alzheimer's dementia[8].

However, a diverse range of survival advantages have been reported in ε4-carriers including increased fertility[2,9,10], resistance to infections[2], decreased perinatal and infant mortality[2], and some slight cognitive advantages[2,3,11–17]. *APOE*-ε4 may be an example of antagonistic pleiotropy – a leading evolutionary explanation for aging and non-communicable disease[9,18] – whereby a gene has both beneficial and detrimental effects, with the detrimental effects generally manifesting later in life when the forces of natural selection are weaker[18]. This hypothesis may explain why *APOE*-ε4 (the ancestral allele) persists in human populations rather than being replaced by the ε3 and ε2 alleles which evolved later[2,19,20]; however, evidence for its putative cognitive benefits remains mixed and controversial[3,13,21].

One cognitive measure where ε4-carriers have shown superior performance is the "What was where?" visual working memory test[22]: ε4-carriers have been reported to recall object locations more accurately than non-carriers after delays of a few seconds[23–25]. These studies did however not evaluate the possible influence of preclinical Alzheimer's disease pathology. One notable feature of this task is its analogue measure of location memory (in contrast to traditional 'correct or incorrect' measures), which allows fine-grained assessment of the precision or quality of memory representations[26,27].

We aimed to assess the relative influence of *APOE*-ε4 and β-amyloid pathology on the "What was where?" task in a large population-based sample of adults from Insight 46, a sub-study of the MRC National Survey of Health and Development (the British 1946 Birth Cohort)[28] – the world's longest continuously-running birth cohort [28,29]. Participants

were aged ~70 years – an age when rates of dementia are low but a significant proportion (~15-25%) have biomarker evidence of preclinical Alzheimer's disease[30,31]. Based on the literature, we hypothesised that *APOE*-ε4 would be associated with slightly more accurate recall of object locations, but that β-amyloid pathology would be associated with subtly poorer performance across the task. As these two predicted effects are in opposition for ε4-carriers with elevated amyloid burden, we aimed to explore interactions between *APOE*-ε4 and β-amyloid on visual working memory. We also aimed to test whether this task is sensitive to differences in hippocampal volume and white matter hyperintensity volume (WMHV, a marker of cerebral small vessel disease that is common in older people and is associated with cognitive decline, particularly in executive function[32]).

Results

Participants underwent *APOE* genotyping, amyloid-PET/MRI neuroimaging, and neuropsychological assessment including the "What was where?" visual working memory task (Methods; Figure 1b; Figure 1c). 486 participants completed the task: 398 were cognitively normal with complete biomarker data (Figure 1a) of whom 120 (30%) were *APOE*-ε4 carriers. Participant characteristics are provided in Supplementary Table 1, along with descriptive statistics for the primary outcome measures. (Performance on established tests of memory are presented in Supplementary material (1. ii)). The prevalence of amyloid-positivity among ε4-carriers and non-ε4-carriers was 37.5% and 9.7% respectively (X^2 = 43.7, $p < 0.0001$), consistent with the literature[30].

In cognitively normal participants with complete biomarker data, multivariable regression models were fitted (Methods) to investigate associations between task performance and *APOE*-ε4 (carrier or non-carrier), amyloid status (positive or negative), hippocampal volume, and WMHV. The models also included the task condition factors of memory load (low or high) and delay interval (short or long), as well as adjusting for head size and demographic and life-course factors, previously shown to predict cognitive performance throughout adulthood in this cohort (Methods). Where between-individual factors were significantly associated with performance, we tested for interactions with delay, to investigate whether or not group differences were due to better retention over time. We also tested for interactions between *APOE*-ε4 and amyloid status, to investigate whether effects of *APOE*-ε4 differed between amyloid-positive and -negative groups.

Results of the regression models are given in Table 1. (See Supplementary material (1. iv) for results relating to demographic and life-course factors.) As expected, identification and localisation memory were poorer in the high-load than low-load condition, and localisation was also poorer after long compared to short delay (Table 1). However, in contrast to previous studies[22,23,33], delay had no statistically significant effect on the proportion of identification or misbinding errors (Table 1).

Identification

On average, amyloid-positive participants were 19% *more likely* to make identification errors than amyloid-negative participants (p=0.029; adjusted error rate [95% CIs]: amyloid-positive 0.20 [0.17 – 0.22]; amyloid-negative 0.17 [0.16 – 0.18]) (Table 1; Figure 2a).

Independently, *APOE*-ε4 carriers were 14% *less likely* to make identification errors (p=0.026; ε4-carriers 0.16 [0.15 – 0.17]; non-ε4-carriers 0.18 [0.17 – 0.19]) (Table 1; Figure 2a). These group differences in error rates are very small in magnitude: error rates of 0.16 and 0.18 equate to 3.8 and 4.3 errors respectively. There was no evidence of a statistically significant interaction between amyloid status and *APOE*-ε4 for identification errors (*OR* = 0.88 [0.63 – 1.15], p=0.29). (Similar dissociable effects of amyloid status and *APOE*-ε4 were observed on a verbal story recall task – Supplementary material (1. ii)).

The association between *APOE*-ε4 and identification was consistent across long and short delays (*OR* for interaction between *APOE*-ε4 and delay = 0.97 [0.77 – 1.22], p=0.79), as was the association between amyloid-positivity and identification (*OR* = 0.83 [0.62 – 1.09], p=0.18). When assessed as a continuous variable (Standardised Uptake Value Ratio (SUVR)), the association between amyloid burden and identification error was not statistically significant, although was in the expected direction (*OR* = 1.05 [95% CIs 0.96 – 1.15] per 0.1 SUVR increment, p=0.26).

Hippocampal volume and WMHV did not show statistically significant associations with identification (Table 1).

Localisation

APOE-ε4 carriers performed better with respect to spatial memory, on average positioning objects 7% closer to the true location than non-ε4-carriers (p=0.007) (Table 1; Figure 2b). Supplementary material (3.), shows that ε4-carriers had smaller mean localisation error on 19/24 trials.

There was no evidence of a statistically significant difference in localisation error between the amyloid groups (Table 1; Figure 2b), nor an association between continuous amyloid burden and localisation error (coefficient = 1.00 [0.97 – 1.04] per 0.1 SUVR increment, p=0.90). Regarding an interaction between amyloid status and *APOE*-ε4, the localisation memory advantage associated with *APOE*-ε4 was greater among amyloid-positive than amyloid-negative participants, but this interaction was not statistically significant (interaction coefficient = 0.88 [0.76 – 1.01], p=0.072) (Figure 2b). A similar but statistically significant interaction was observed when considering continuous amyloid burden, such that the advantage for ε4-carriers was greater at higher SUVRs (interaction coefficient = 0.93 [0.87 – 1.00] per 0.1 SUVR increment, p=0.043) (Figure 3). Post-hoc analyses indicated that this interaction was due to the coefficients for SUVR going in opposite directions within ε4-carriers and non-carriers (i.e. smaller localisation error with increasing SUVR among ε4-carriers, versus greater localisation error with increasing SUVR among non-ε4-carriers), although neither of these effects were statistically significant (coefficient within ε4-carriers = 0.97 [0.93 – 1.01] per 0.1 SUVR increment, p=0.15; coefficient within non-ε4-carriers = 1.04 [0.99 – 1.10], p=0.15). .

The beneficial effect of *APOE*-ε4 on localisation was consistent across the long and short delays (interaction coefficient = 1.03 [0.97 – 1.09], p=0.37). Additional analyses confirmed that this effect was seen even when considering trials on which the incorrect object was selected (Supplementary material (1. viii)).

Despite finding sex differences in localisation memory (Supplementary material (1. iv)), and a previous study reporting an interaction between sex and *APOE*-ε4 on localisation memory[23], we found no evidence for an interaction between sex and *APOE*-ε4 (interaction coefficient = 0.99 [0.89 – 1.09], p=0.45).

Hippocampal volume and WMHV did not show statistically significant associations with localisation (Table 1).

Misbinding

APOE-ε4, amyloid status, hippocampal volume, WMHV (Table 1) and amyloid burden (*OR* = 0.97 [95% CIs 0.86 – 1.09], p=0.60) were not associated with misbinding errors. See Supplementary material (1. v) for comments on object-location misbinding in relation to previous literature.

2D-mixture model for sources of localisation error

To clarify and extend the results reported above, we used a 2D-mixture model approach that isolates the contributions of three sources of localisation error: misbinding, guessing and imprecision[25,34] (Methods). Its main advantage is the ability to account for random guesses which can potentially have a large effect on the traditional localisation error and misbinding measures. The results for the imprecision parameter agreed with the traditional localisation error metric:

- ε4-carriers performed better than non-carriers, with significantly lower imprecision (adjusted mean [95% CIs]: ε4-carriers = 99 pixels [95 – 103]; non-ε4-carriers = 105 [102 – 108]) (Table 1).
- The reduced imprecision associated with *APOE*-ε4 was greater among amyloid-positive than amyloid-negative participants, although this was not statistically significant (*interaction coefficient* = -11 pixels [-23 – 2], p=0.090).
- Imprecision was significantly worse for the long delay (adjusted mean [95% CIs]: long delay 110 pixels [107 – 113]; short delay 97 [95 – 100]) (Table 1).

This confirms that the differences in localisation error cannot be explained by random guessing, but do indeed reflect differences in precision of location memory.

Discussion

This study shows for the first time that superior performance on a computerised visual working memory task is detectable in *APOE*-ε4 carriers at age ~70 years, even in the presence of β-amyloid pathology indicative of preclinical Alzheimer's disease. ε4-carriers had better recall for object identities, and recalled locations more precisely, while β-amyloid pathology was independently associated with poorer recall for object identities; our analyses suggest that there was an interaction between *APOE*-ε4 and β-amyloid burden for localisation. The results support the hypothesis of antagonistic pleiotropy but also highlight the possibility that beneficial effects of *APOE*-ε4 on specific aspects of cognition may persist into older age[3]. To what extent such a cognitive advantage may explain the survival of the ε4 allele in human populations is an intriguing question.

The superior performance of *APOE*-ε4 carriers did not significantly differ according to the length of the delay between encoding and recall (1-second or 4-seconds). This guides us away from attributing the effect to better retention of memory representations over time, instead pointing towards differences in attention and precision of encoding[25]. This is also supported by the patterns of performance we observed on other memory tests in this cohort, with an advantage for ε4-carriers on a verbal memory test with strong attentional and working memory demands, but not on memory tests requiring learning and retention of material over multiple trials (Supplementary material (1. ii)). This interpretation is consistent with one mechanism proposed for ε4-associated cognitive advantage, i.e. that ε4-carriers show increased task-related activation in frontal and parietal regions and corresponding better performance on tasks requiring attention, short-term memory and top-down cognitive control; such effects have been observed across the life-course[3,11,12,15,16,23,24,35], including in children with Down's Syndrome[17]. Therefore, our result may be explained by the attention and frontal/executive demands of this task (with the localisation measure being particularly sensitive due to its continuous nature), rather than visuospatial or memory aspects *per se*. At older ages, increased frontal activation in ε4-carriers has been proposed to reflect compensatory recruitment, since frontal regions are relatively spared from Alzheimer's disease-related neurodegeneration[3,11,36]. Our finding that the localisation advantage for *APOE*-ε4 carriers appeared relatively greater as amyloid burden increased is consistent with this hypothesis of compensation.

There is currently no consensus on ε4-associated cognitive benefits, and which domains and functions they may apply to[2,3,13,21]. Associations between *APOE*-ε4 and poorer cognition are generally not observed until past middle age[37–39], when they are presumed to reflect the emergence of preclinical pathologies. Additive detrimental effects of *APOE*-ε4 and β-amyloid have been observed in older age, with accelerated cognitive decline and disease progression in ε4-carriers[1,40,41], possibly due to additional pathological effects of *APOE*-ε4 (e.g. on synaptic loss, neuroinflammation and cerebrovascular disease[1,4]). The complex interplay of *APOE*-ε4 with different pathologies in the ageing brain remains difficult to unravel; our analysis accounted for white matter hyperintensity volume and hippocampal volume (neither of which were associated with task performance), providing evidence that the effects of *APOE*-ε4 and β-amyloid on visual working memory are independent of these factors.

One limitation is the relatively small number of trials (24) compared to the 100-trial version used previously[23,24,33,42], although a previous study concluded that a shorter version would be sufficient as group differences were more apparent towards the beginning of the task[42]. Performance on the primary outcomes was broadly similar to the longer version, with no floor or ceiling effects, and our results suggest that this short version (~8 minutes duration, practical for inclusion in a busy assessment schedule) is sufficient for detecting subtle differences between individuals. Having said that, there is no published data on the test-retest reliability of measures extracted from this task, so future studies examining this point are warranted. One particular strength of our analysis was the availability of life-course data in this cohort, which allowed us to control for factors such as childhood cognitive ability, thus reducing unexplained variability in working memory performance (higher childhood

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cognitive ability was associated with better recall for object identities and object-location binding– see Supplementary material (1. iv)).

Strengths and limitations relating to the representativeness of Insight 46 participants have been previously discussed[43,44], the main limitations being that all participants are white and the sample is inevitably biased towards those who were willing and able to travel to the research centre[45], which may have resulted in underrepresentation of individuals with cognitive decline or neuropsychiatric symptoms that can be present in preclinical Alzheimer's disease. As previously reported, participants tended to be more highly educated and in better health than their peers not recruited to this sub-study, and participants who completed the brain scan were less likely to be obese and to have mental health problems than those with missing neuroimaging data[45]. As education, obesity and depression are associated with increased dementia risk[46], this raises the possibility that individuals (including *APOE*-ε4 carriers) destined to develop Alzheimer's disease or other forms of late life cognitive impairment may be underrepresented in our analyses. The very small number of ε4-homozygotes (consistent with population prevalence) precluded investigation of dose-dependent effects of *APOE*-ε4 (see Supplementary material (1. iii) for descriptive statistics). As we conducted a large number of statistical tests with multiple outcome measures, these results require verification in replication studies. Future data collections will include measures of tau pathology, enhancing our ability to draw conclusions about relationships between preclinical Alzheimer's disease and alterations in visual working memory.

In summary, we provide evidence of superior visual working memory in *APOE*-ε4 carriers at age ~70, even in the presence of subtle cognitive deficits associated with preclinical Alzheimer's disease. This is consistent with the antagonistic pleiotropy hypothesis and suggests that beneficial effects of *APOE*-ε4 on specific cognitive functions may persist into older age.

Methods

Participants in the Insight 46 study – a sub-study of the MRC National Survey of Health and Development (NSHD, the British 1946 Birth Cohort)[28] – were assessed at University College London between May 2015 and January 2018. Recruitment procedures, assessment protocols, and recruitment flow-charts have been published[28,43,45,47]. In brief, assessments included neuropsychological tests, clinical examination, combined MRI / β-amyloid PET neuroimaging, and other biomarker and genetic measures. All assessments were typically completed on one day, although 62 participants had to have their scans rescheduled for a later date (median interval= 49 days). The neuropsychological battery comprised standard paper-and-pencil tests and more novel computerized tasks[28,43,44,48], none of which had been administered previously within the NSHD. The study was approved by the Queen Square Research Ethics Committee - London (REC reference 14/LO/1173). All participants provided written informed consent.

Stimuli and Procedure

The stimuli and procedure of the 'What was where?' task have been described in detail [22,33,42,49]. This type of working memory recall precision task has shown convergent validity with traditional measures of working memory span in older adults, and greater sensitivity than these traditional measures to subtle changes in working memory in patients with Parkinson's disease[27]. The participant was seated in front of a 23" DELL Optiplex 9030 all-in-one touchscreen computer. The dimensions of the screen were 1920 x 1080 pixels and the approximate distance from the subject's eyes to the centre of the screen was 58 cm.

The procedure for the "What was where?" task is presented in Figure 1b. In each trial, one or three objects were displayed on the screen in random locations, presented on a black background. Participants were asked to look at the objects and to try to remember their identities and locations. The maximum height and width of the objects was 120 pixels. See Supplementary material (3.) for images of stimuli.

1-object trials are referred to as 'low load' and 3-object trials as 'high load'. The low load trials were displayed for 1 second; high load trials were displayed for 3 seconds to allow time for encoding. This was followed by a blank screen for either a short or long delay (1 or 4 seconds), and then a test array appeared in which two objects were displayed along the vertical meridian. One of these objects had appeared in the memory array on the previous screen (the target) and the other was a foil/distractor. Participants were instructed to touch the object that they remembered seeing and drag it to the location where they think it was originally presented (Figure 1b). There was no time limit for reporting the location – the tester pressed the space bar to initiate the next trial when the participant was ready.

Previous studies using the "What was where?" task have administered at least 100 trials[22–24,33,42,49], but for Insight 46 a shortened version was used containing 24 trials: 4 low load and 20 high load (2 x low load with short delay; 2 x low load with long delay; 10 x high load with short delay; 10 x high load with long delay). The experiment was preceded by 4 practice trials – one of each of the load x delay combinations – and the tester ensured that the participant understood the task before continuing.

All objects including the foils were drawn from a pool of 60 fractals that were used across the experiment (rendered using http://sprott.physics.wisc.edu/fractals.htm).

The locations of the objects were generated in a pseudo-randomised manner by a MATLAB script (MathWorks, Inc) imposing the following restrictions necessary to allow analysis of localisation error, a key outcome of this task: objects were always at least 280 pixels away from each other to avoid crowding and to ensure that there was a clear zone of 140 pixels around each object (necessary for the calculation of misbinding errors (see below)); and objects were at least 200 pixels from the centre of the screen and 120 pixels from the edges. The 24 trials were the same for all participants (i.e. the same objects were presented in the same locations) but were presented in a random order so the load and delay conditions were interspersed throughout. Using a random order avoids the results being confounded by either practice effects (familiarity with the procedure could cause performance to improve throughout the task) or interference effects on (as objects appear more than once during the

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task, the foil in the test array could be recognised from a previous trial, which could increase the likelihood of errors in object identification throughout the task).

Outcome Variables

Primary outcomes—Primary outcomes are illustrated in Figure 1c. For each trial, an object **identification error** was recorded if the participant selected the incorrect object from the 2-choice array.

Memory for object location was defined in terms of **localisation error** – the distance between the location reported by the participant and the closest of the three original locations from the memory array. This definition takes account of the fact that, in high load trials, participants may mislocalise the target to the location of a different (unprobed) object from the memory array (i.e. they make a misbinding error – see definition below). Previous studies have also calculated **gross localisation error**, which is the distance between the location reported by the participant and the true location of the target in the original memory array. In the case of a misbinding error, the gross localisation error could be very large, so it is a less pure measure of localisation precision. We calculated gross localisation error for comparison with previous studies, but it was not used as an outcome measure for statistical analyses.

A **misbinding error** occurs when a participant correctly identifies the target object but swaps its location with the location of another object. If the target is positioned within 140 pixels of the location of a different object from the memory array, this is counted as a misbinding error. This threshold was used to ensure that a location could not be attributed to more than one object, as objects were always at least 280 pixels apart. Note that in the low load condition it is not possible to make a misbinding error as there is only one object in the memory array.

As in previous papers, localisation and misbinding errors were only analysed for trials in which the correct object was identified from the 2-choice array[22,33,42,49].

2D-mixture model outcomes—We additionally analysed performance on the “What was where?” task using a 2D-mixture model approach that isolates the contributions of three sources of localisation error: misbinding, guessing and imprecision[25,34]. In contrast to the traditional localisation metric, which only considers the magnitude of localisation errors, the 2D-mixture model approach considers two dimensions of error: failure to remember the target location (i.e. a misbinding error or a random guess), and imprecision in localisation (which applies to both target and misbinding responses). It has shown convergent validity with the traditional metrics and is more accurate at recovering the parameters of simulated data[34]. As the 2D-mixture model gave similar results to the traditional outcomes, for simplicity we chose to focus this report on the traditional outcomes, with the 2D-mixture model results presented as confirmation that inter-individual differences in localisation error and misbinding cannot be explained by random guessing. Code for the 2D-mixture model is freely available in the MemToolbox2D package for MATLAB[50]. The model is described in detail[34], but in brief, a response density equation is defined as follows:

$$P(\hat{\theta}) = \alpha\psi_{\sigma}(\hat{\theta} - \theta) + \beta\frac{1}{m}\Sigma_{i}^{m}\psi_{\sigma}\left(\hat{\theta} - \varphi_{i}\right) + \gamma\frac{1}{A} \quad \text{Equation 1}$$

θand ψ are vectors indicating locations on the screen, where $P(\hat{\theta})$ is the probability of finding a response location $\hat{\theta}$, θ is the location of the target φ_i is the location of the target, stimulus i, m is the number of non-target stimuli, A is the area of the screen, and ψ_σ is a bivariate Gaussian distribution with standard deviation σ and zero covariance. The parameters α, β and γ represent the proportion of target responding, misbinding and guessing respectively. As α, β and γ must sum to 1, α is not included as a free parameter in the fitting, so the three free parameters are β (misbinding), γ (guessing) and σ (imprecision), estimated using maximum likelihood methods. Thus, the model isolates and quantifies three different sources of error. Any spatial units can be used; we used pixels. The model assumes that guesses are uniformly distributed across the entire screen; see Supplementary material (1. ix) for exploration of alternatives to this assumption and information about goodness of fit.

In order to visualise the performance of the model on the raw data, we outputted the probability that each individual response location was 1) target; 2) guess; 3) misbind to the first distractor; 4) misbind to the second distractor. These probabilities were normalised for each trial so that they summed to 1, and then each response was classified into whichever category had the highest probability. The third and fourth categories were then combined as both represent misbinding. These classifications are illustrated for the complete raw data in Supplementary material (3.).

Data Cleaning—Six participants had one trial where the software did not record whether they selected the correct or incorrect object, likely caused by the participant touching the screen exactly midway between the two objects. These six trials were excluded.

Life-course and clinical variables—Childhood cognitive ability was measured at age 8 (or ages 11 or 15 if earlier data were missing) as a standardised z-score based on tests of verbal and non-verbal ability, as previously described[43].

Educational attainment was represented as the highest qualification achieved by age 26, grouped into three categories: no qualification; vocational or O-levels and equivalents; A-levels or degree and equivalents.

Socioeconomic position was derived from participants' own occupation at age 53, or earlier if this was missing, coded according to the UK Registrar General's Standard Occupational Classification and classified as manual or non-manual.

Participants were classified as having a neurological or major psychiatric condition (including dementia and mild cognitive impairment) as previously described[43] (see Figure 1a for specific diagnoses). Participants not meeting these criteria are herein referred to as cognitively normal and represent a sample free from possible confounding neurological or psychiatric comorbidities. This does not imply that all participants with a neurological or major psychiatric condition necessarily had a measurable cognitive impairment.

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Biomarker measures—As previously described[28,47,51], β-amyloid-PET and multi-modal MRI data were collected simultaneously during a 60-minute scanning session on a single Biograph mMR 3T PET/MRI scanner (Siemens Healthcare, Erlangen), with intravenous injection of 370 MBq of 18F-Florbetapir (Amyvid). β-amyloid deposition was quantified using the Standardised Uptake Value Ratio (SUVR) calculated from cortical regions of interest with a reference region of eroded subcortical white matter. A cut-point for amyloid-positivity was determined using a mixture model to define two Gaussians, and taking the 99th percentile of the lower (amyloid-negative) Gaussian at SUVR >0.6104[43,47,51].

Global white matter hyperintensity volume (WMHV) was generated using an automated segmentation algorithm followed by visual quality control[47,52]. Hippocampal volume was generated using the Similarity and Truth Estimation for Propagated Segmentations (STEPS) automated segmentation method with appropriate manual editing[53]. Total intracranial volume (TIV) was generated using statistical parametric mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm)[54].

APOE genotype was determined[28] and classified as ε4-carrier or non-ε4-carrier. The number of homozygous ε4-carriers (n = 11, 3% of the sample) was too small to consider them as a separate group, but descriptive statistics on their performance are provided in Supplementary material (1. iii).

Statistical Analyses

Analyses were conducted using Stata 15 (StataCorp, College Station, TX). Statistical significance was set at the conventional threshold of $p<0.05$.

To investigate associations between performance on the “What was where?” task and biomarkers of brain pathologies, analyses only included participants classified as cognitively normal, and for whom complete biomarker data were available (n = 398; Figure 1a). The rationale for excluding participants with neurological or major psychiatric conditions was that these conditions can have varied impacts on cognitive performance which may confound the associations between the key predictors of interest (preclinical amyloid pathology and *APOE*-ε4) and visual working memory, and the numbers involved are not sufficient to provide power to detect meaningful differences between specific conditions. Multivariable regression models were fitted (details below), with predictors of amyloid status (positive *vs*. negative), hippocampal volume, WMHV, *APOE*-ε4 (carrier *vs*. non-carrier) and delay (short *vs*. long). An additional predictor of load (low *vs*. high) was included for all outcomes except those which relate to misbinding, since misbinding cannot occur in the low-load condition. Total intracranial volume (TIV) was included as a covariate to adjust for the correlation between brain volumes and head size, and we additionally adjusted for sex, age at assessment, and the following life-course factors that have previously been shown to predict cognitive performance throughout adulthood in this cohort[43,44,55,56]: childhood cognitive ability, education and socioeconomic position. Adjusting for these factors reduces the unexplained variance in cognitive performance between individuals, which can increase the sensitivity of our analyses to detect subtle effects of APOE-ε4 and brain pathologies[43]. Analyses were additionally rerun replacing dichotomised amyloid status with continuous SUVR. We did not apply a correction for multiple comparisons,

following recommendations in the statistical literature[57,58], as this was a hypothesis-driven study motivated by previous literature.

Where between-individual factors were significantly associated with performance, we tested for interactions with delay (short *vs.* long), to investigate whether or not group differences were due to better retention over time. We also tested for interactions between *APOE*-ε4 and amyloid (dichotomous amyloid status, and continuous SUVR) to investigate whether effects of *APOE*-ε4 differed according to burden of amyloid pathology.

Primary outcomes—Analyses were conducted using trial-by-trial data, rather than using summary scores (e.g. mean localisation error) to avoid losing information.

Identification errors (correct *vs.* incorrect) and **misbinding errors** (yes *vs.* no), were analysed using generalised estimating equations (GEE) logistic regression models with an independent correlation structure and robust standard errors to allow for the correlation between repeated measures of the same participant. Results are expressed as odds ratios for ease of interpretation.

Localisation error was analysed using GEE models, assuming a normal distribution for the dependent variable and an identity link (as with standard linear regression), but including an exchangeable correlation structure and robust standard errors. Localisation errors were first log-transformed as the distributions were positively skewed. Model assumptions were tested by examination of residual plots; no departures from assumptions were noted.

2D-mixure model outcomes—To generate the outcome scores for analysis, the mixture model (see above) was fitted twice for each participant: once using their responses to short-delay trials (low and high load combined), and once using their responses to long-delay trials (low and high load combined). As for the traditional localisation metrics, the model only included responses for trials in which the correct object was identified from the 2-choice array. This generated a value for the misbinding, guessing and imprecision parameters for each participant in the short and long delay conditions. It was not possible to separate the responses by load, as the number of low-load trials was too small for reliable estimation of the imprecision parameter (as this is a standard deviation metric). The low-load trials do not influence the estimation of the misbinding parameter, since they do not contain distractors.

The imprecision parameter was analysed using the same model structure as localisation error (see above), as it was approximately normally distributed. The guessing and misbinding parameters were analysed using the same model structure as identification errors (see above), since they represent proportions of responses classified as guesses and misbinds respectively. See Supplementary material (1. ix) for examination of goodness of fit and Supplementary material (3.) for visual illustration of the performance of the model.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

All data from the National Survey of Health and Development are curated and stored by the Lifelong Health and Aging Unit at UCL. Anonymized data will be shared by request from qualified investigators (https://skylark.ucl.ac.uk/NSHD/doku.php).

Code Availability

Code for the 2D-mixture model (MATLAB) is freely available at https://doi.org/10.5281/zenodo.3752705. Code for statistical analyses conducted in Stata is provided in Supplementary material (2.).

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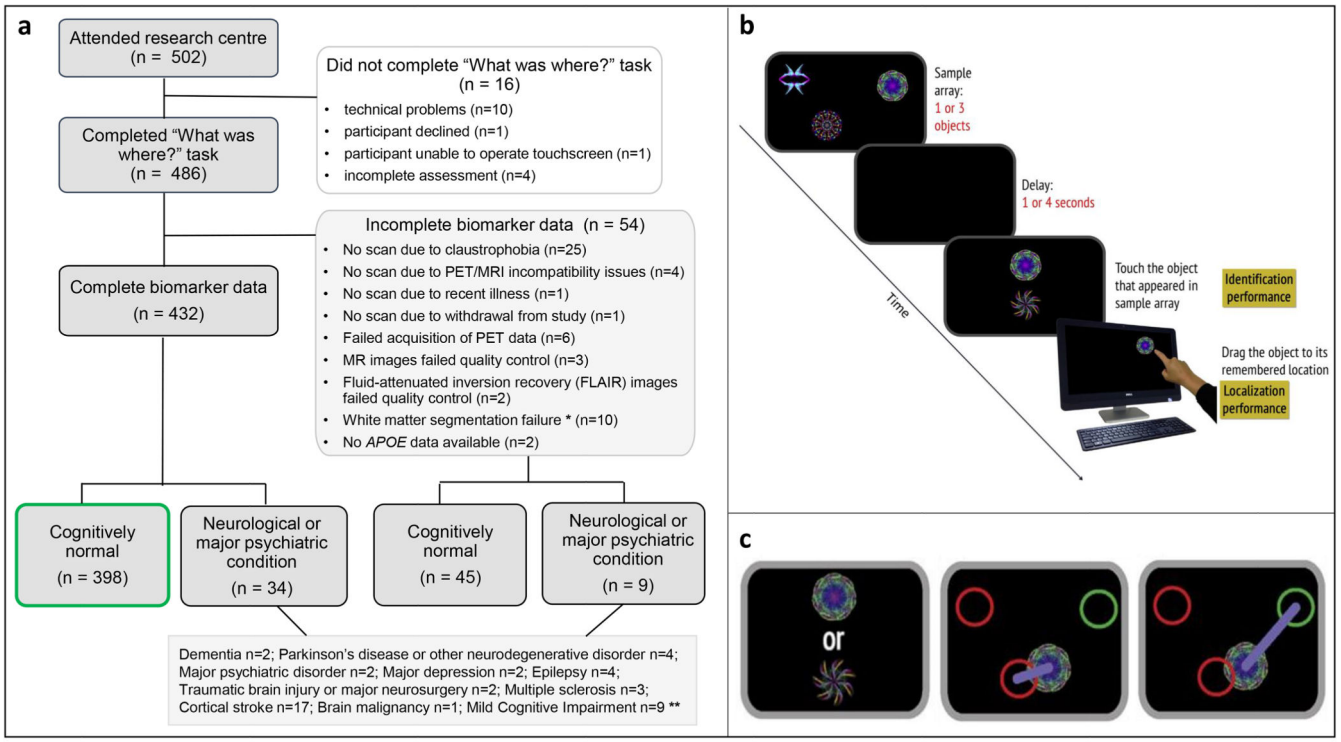

Figure 1. Study design: (a) flow-chart of data acquisition and reasons for missing data; (b) presentation of the "What was where?" task; (c) illustration of outcome measures

The 398 cognitively normal participants with complete biomarker data formed the main analysis sample; see Methods and [42] for more details on the definitions of neurological and major psychiatric disorders. ***** In most cases, this was due to erroneous segmentation of vascular abnormalities such as stroke or demyelination. **These numbers add up to 46 because some participants had more than one condition. (b) and (c) are reprinted from Liang et al. (2016) under the terms of the Creative Commons Attribution License (CC BY) https://creativecommons.org/licenses/by/4.0/. In the middle and right-hand images of (c), green circles indicate the original location of the target object, red circles indicate the original locations of non-target objects, and blue lines indicate measured localisation error. Object identification (c left-hand panel): the participant is required to select the object that they remember seeing. Localisation error (c middle panel) is measured from the location reported by the participant to the location of the closest object; if the reported location is within 140 pixels of the location of a non-target object, this is considered to be a misbinding error. Gross localisation error (c right-hand panel) is measured from the location reported by the participant to the original location of the target object.

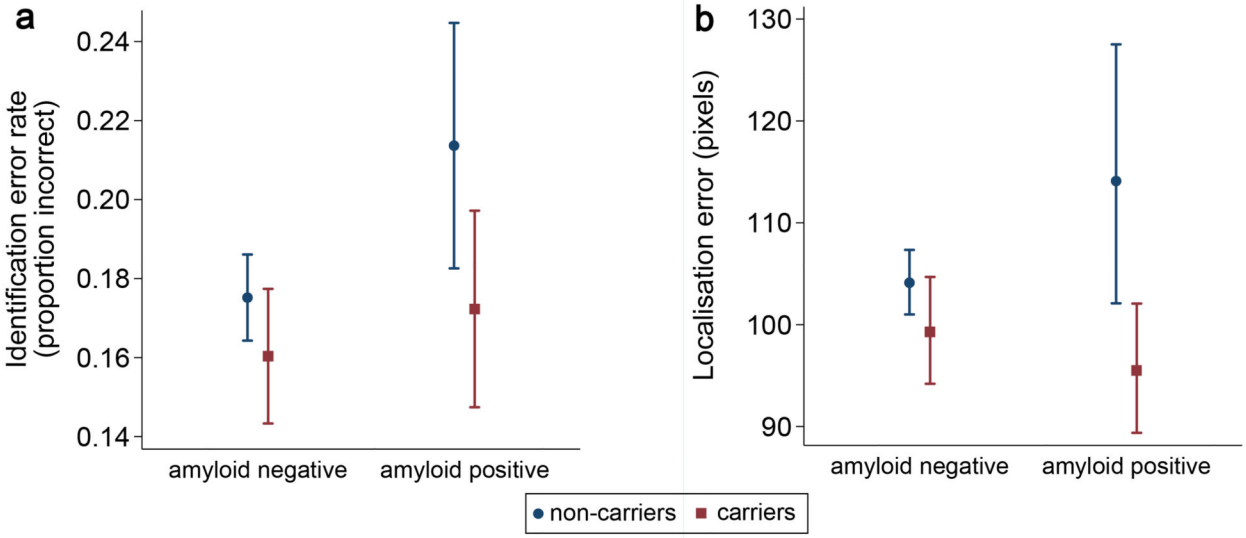

Figure 2. Performance on the "What was where?" task in cognitively normal participants (n = 398), by amyloid status and *APOE*-ε4 (carriers *vs*. non-carriers): (a) Identification error rate; (b) Localisation error

Figure (a) shows the main effects of amyloid status and *APOE*-ε4 on identification error rate. Figure (b) shows the main effect of *APOE*-ε4 on localisation error. Markers show adjusted means from the multivariable regression models, adjusted for delay (long *vs*. short), load (low *vs*. high), sex, age at assessment, childhood cognitive ability, education, socioeconomic position, white matter hyperintensity volume, hippocampal volume and total intracranial volume. Error bars show 95% confidence intervals. Note that the plotted values are essentially unchanged if the model does not include adjustment for white matter hyperintensity volume, hippocampal volume and total intracranial volume. In Figure (b), data were log-transformed for analysis but the means and confidence intervals presented here have been back-transformed for ease of interpretation. For numbers of participants in each group, see Supplementary Table 1.

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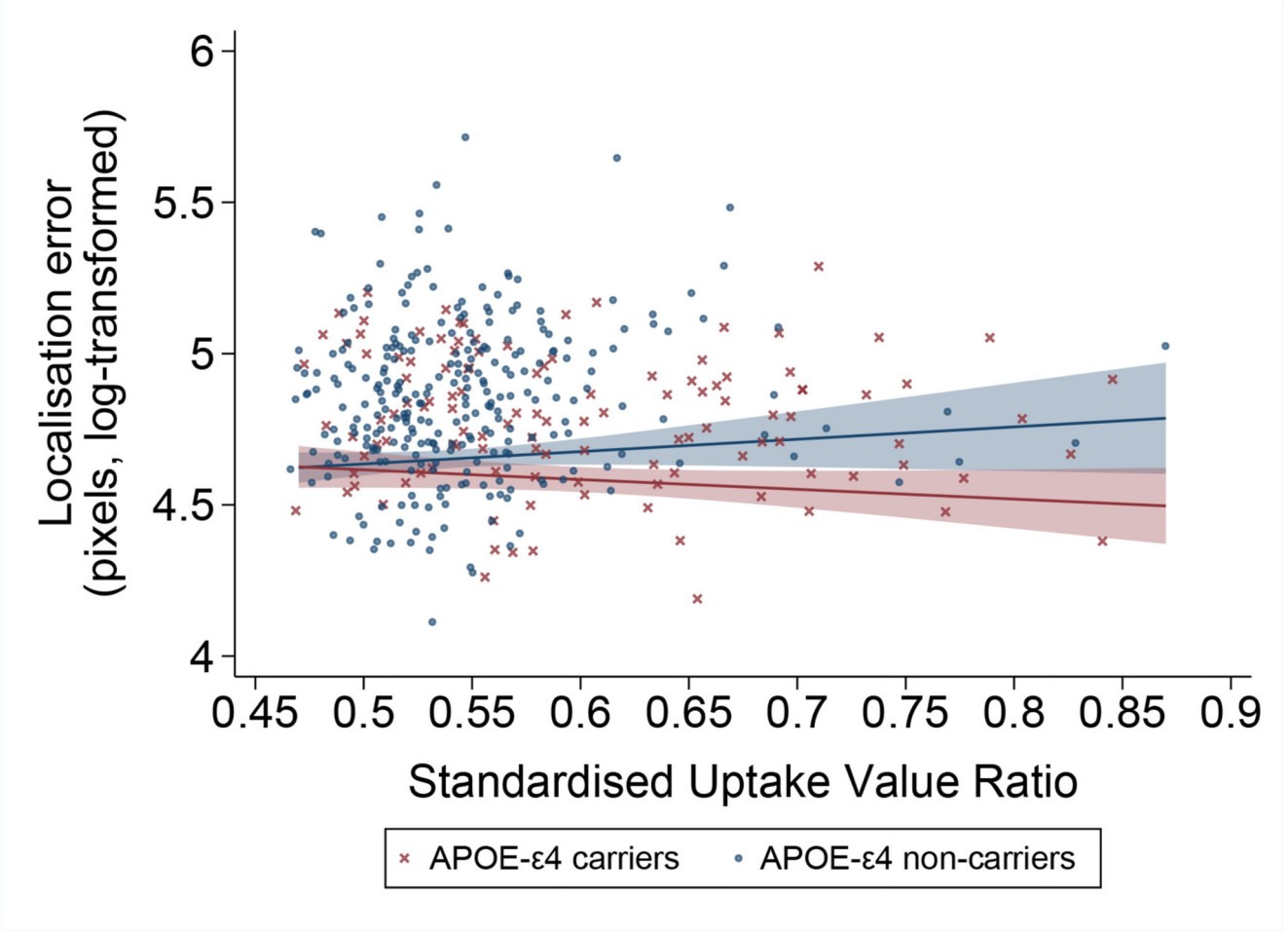

Figure 3. Association between β-amyloid burden (quantified using Standardised Uptake Value Ratio) and localisation error on the "What was where?" task, for *APOE*-ε4 carriers (n = 120) and non-carriers (n = 278)

Solid lines represent marginal means from the multivariable regression model (see methods) and shaded areas represent 95% confidence intervals, with ε4-carriers shown in red and non-carriers shown in blue. Models were adjusted for load (low *vs.* high), delay (short *vs.* long), sex, age, education, socioeconomic position, white matter hyperintensity volume, hippocampal volume, and total intracranial volume, and no adjustments were made for multiple comparisons. Markers show each participant's mean localisation error across the experiment as a whole. This illustrates the interaction between *APOE*-ε4 and β-amyloid burden (p=0.043).

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Table 1

Associations between biomarkers and "What was where?" outcomes in cognitively normal participants (n = 398)

Predictor	Primary outcome measures			2D-mixture model outcomes		
	Identification errors: *OR* for incorrect response (95% CIs)	**Localisation error coef. (95% CIs) [a]**	**Misbinding errors: *OR* for error (95% CIs)**	**Imprecision parameter (pixels): coef. (95% CIs)**	**Misbinding parameter: *OR* (95% CIs) [b]**	**Guessing parameter: *OR* (95% CIs) [c]**
β-amyloid status (negative as reference)	**1.19** * (1.02, 1.38) $p = 0.029$	1.02 (0.95, 1.10) $p = 0.58$	0.94 (0.77, 1.15) $p = 0.55$	3 (-4, 9) $p = 0.42$	0.96 (0.78, 1.20) $p = 0.74$	1.03 (0.57, 1.88) $p = 0.92$
White matter hyperintensity volume (per 10 ml)	0.98 (0.89, 1.09) $p = 0.77$	0.99 (0.95, 1.03) $p = 0.67$	0.97 (0.88, 1.08) $p = 0.63$	0 (-4, 5) $p = 0.84$	0.98 (0.86, 1.11) $p = 0.73$	0.89 (0.64, 1.25) $p = 0.50$
Hippocampal volume (per ml)	0.98 (0.88, 1.09) $p = 0.69$	0.98 (0.95, 1.02) $p = 0.41$	1.05 (0.93, 1.19) $p = 0.41$	-3 (-6, 1) $p = 0.19$	1.05 (0.92, 1.20) $p = 0.49$	0.93 (0.66, 1.30) $p = 0.65$
APOE-ε4 (non-carriers as reference)	**0.86** * (0.75, 0.98) $p = 0.026$	**0.93** ** (0.88, 0.98) $p = 0.007$	1.01 (0.87, 1.17) $p = 0.94$	**-6** * (-11, -1) $p = 0.027$	0.96 (0.82, 1.13) $p = 0.63$	0.75 (0.45, 1.26) $p = 0.28$
High load (low load as reference)	**4.42** ** (3.52, 5.56) $p < 0.001$	**1.48** ** (1.42, 1.54) $p < 0.001$	N/A	N/A	N/A	N/A
Long delay (short delay as reference)	1.05 (0.95, 1.17) $p = 0.32$	1.11** (1.08, 1.14) $p < 0.001$	0.98 (0.87, 1.10) $p = 0.73$	**13** ** (9, 16) $p < 0.001$	0.91 (0.81, 1.03) $p = 0.13$	0.93 (0.66, 1.30) $p = 0.66$

*significant at $p < 0.05$; **significant at $p < 0.01$. These results are from the multivariable regression models (see methods); therefore, each association is independent of all others. No adjustments were made for multiple comparisons. In addition to the predictors listed, models also adjusted for sex, age at assessment, childhood cognitive ability, education, socioeconomic position, and total intracranial volume– for details on the associations of these demographic and life-course factors with visual working memory performance, see Supplementary material (1. iv) and Supplementary Table 4.

[a] As the localisation error data were log-transformed, the coefficients are quoted in exponentiated form for ease of interpretation; for example, a coefficient of 1.10 would mean that the predictor was associated with 10% greater localisation error, and a coefficient of 0.90 would mean that the predictor was associated with 10% smaller localisation error.

[b] *OR* > 1 indicates that the predictor is associated with a higher proportion of misbinds.

[c] *OR* > 1 indicates that the predictor is associated with a higher proportion of guesses.

[d] See Methods for definition of categories. CI = confidence interval; coef. = coefficient; *OR* = odds ratio.