Memory precision of object-location binding is unimpaired in *APOE* ε4-carriers with spatial navigation deficits

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Abstract

Research suggests that tests of memory fidelity, feature binding and spatial navigation are promising for early detection of subtle behavioural changes related to Alzheimer's disease (AD). In the absence of longitudinal data, one way of testing the early detection potential of cognitive tasks is through the comparison of individuals at different genetic risk for AD. Most studies have done so using samples aged 70 years or older. Here, we tested whether memory fidelity of long-term object-location binding may be a sensitive marker even among cognitively healthy individuals in their mid-60s by comparing participants at low and higher risk based on presence of the ε4-allele of the apolipoprotein gene (n=26 ε3ε3 and n=20 ε3ε4 carriers). We used a continuous report paradigm in a visual memory task that required participants to recreate the spatial position of objects in a scene. We employed mixture modelling to estimate the two distinct memory processes that underpin the trial-by-trial variation in localisation errors: retrieval success which indexes the proportion of trials where participants recalled any information about an object's position and the precision with which participants retrieved this information. Prior work has shown that these memory paradigms that separate retrieval success from precision are capable of detecting subtle differences in mnemonic fidelity even when retrieval success could not. Nonetheless, a Bayesian analysis found good evidence that ε3ε4 carriers did not remember fewer object locations ($F(1, 42)=.450$, $p=.506$, $BF_{01}=3.02$), nor was their precision for the spatial position of objects reduced compared to ε3ε3 carriers ($F(1, 42)=.12$, $p=.726$, $BF_{01}=3.19$). Importantly, ε3ε4-carriers from the same sample have previously been reported to exhibit wayfinding deficits in a spatial navigation task (Coughlan et al. 2019, *PNAS*, 116(19)). The sensitivity of memory fidelity tasks may therefore not extend to individuals with one ε4-allele in their early to mid-60s. These results provide further support to prior proposals that spatial navigation may be a sensitive marker for the earliest AD-dependent cognitive changes, even before episodic memory. More research in preclinical AD is needed to confirm this hypothesis by direct comparison of memory fidelity and spatial navigation tasks.

Keywords: Alzheimer's disease, APOE, early detection, memory, spatial navigation

Introduction

Alzheimer's disease (AD) has a long preclinical phase during which pathological neural changes occur without overt, detrimental effects on behaviour.[1–4] This long preclinical phase offers the possibility of interventions that may target further pathological changes and prevent irreversible cell death.[5,6] Cognitive tests are the most cost-effective and simple way to screen for cognitive impairment related to dementia, yet standard neuropsychological tests typically fail to detect these subtle preclinical symptoms of AD pathology.[7,8] In the absence of longitudinal data, carriers of the major genetic risk factor for late-onset Alzheimer's disease are a good model to test the diagnostic sensitivity of cognitive tests.[7,9–11] Heterozygotes who carry one ε4-allele of the apolipoprotein (*APOE*) gene are three times more likely to develop AD compared to the "wildtype" ε3ε3 carriers, while those with two alleles (homozygotes) have a 15-fold higher likelihood.[12] People with an ε4-allele tend to exhibit AD pathology and other biomarkers at an earlier age,[13] and show a faster rate of cognitive decline than other genotypes.[14,15]

Current efforts in early detection research deem tests of feature binding, mnemonic discrimination and spatial navigation as particularly promising markers of incipient cognitive decline as they all crucially depend on the integrity of regions affected in the earliest stages of AD.[1,16–19] For example, posterior parietal areas are among the first to exhibit amyloid beta pathology,[1,16] while the transentorhinal region, the transition zone between lateral and medial aspects of the entorhinal cortex (ERC), is the earliest site of tau neurofibrillary tangles, which then spread to the hippocampus.[17–19] Memory for high fidelity representations crucially relies on hippocampus, ERC, perirhinal cortex and posterior parietal regions. The ERC supports high fidelity representations of objects, spatial features of objects and the environment,[20–26] which are bound by the hippocampus into holistic episodes[27–31] that can be faithfully reinstated upon retrieval with the concerted action of the recollection network.[32,33] Importantly, tau spreads from transentorhinal to parietal regions of the recollection network that are crucial for memory fidelity,[21] and the communication of these brain regions is already altered in preclinical AD and genetic-risk carriers.[34–36] Based on these preclinical changes, tasks that tap into the functional integrity of AD vulnerable brain regions may prove clinically meaningful, which has prompted researchers to investigate the utility of mnemonic fidelity tests in preclinical and prodromal dementia cases.

In studies across the AD continuum, a number of tests of memory fidelity and relational binding is in use: the mnemonic similarity task, which requires the discrimination between previously studied target items and highly similar lures;[22] memory binding tasks to test for intact associations between the identity of an object and its features (e.g. location, colour);[23] and continuous report paradigms in which feature binding is not assessed by categorical responding but requires participants to precisely recreate studied object features.[24,25] Older adults, individuals with mild cognitive impairment (MCI) and preclinical individuals with positive AD biomarkers exhibit significant deficits in differentiating novel stimuli from previously studied targets under conditions of high feature overlap.[22,27–34,37,38] Similarly, MCI and AD patients, and individuals without apparent cognitive deficits but very high AD risk based on genotype or biomarkers of AD pathology, also perform significantly worse in tests of feature binding, showing a marked decline in representational fidelity.[39–5960]

Despite evidence of reduced memory fidelity in aging and prodromal AD, its sensitivity as a marker of preclinical genetic vulnerability in otherwise cognitively normal adults has rarely been tested. Moreover, mean ages in these studies are typically around 70 or older.[61,62] Although prior studies have shown that AD pathology begins to accrue in midlife,[63] most studies of memory fidelity do not include middle-aged individuals (exceptions are [32,64]). Here we include both middle-aged and older adults to determine whether memory fidelity

differs by *APOE* status (ε3ε3 vs ε4-carriers). We focus on a version of a feature binding task that uses study-test delays that preclude the use of working memory. Studies on short-term feature binding suggest these metrics may be sensitive to cognitive decline in familial and prodromal AD cases.[45,59,60] However, carriers of the *APOE* ε4-allele may have an advantage in short study-test delays but may be predisposed to accelerated rate of forgetting thereafter.[52,60] A longer study-test delay may be able to index such faster forgetting.

We capitalise on current evidence for subtle deficits in preclinical AD by using a memory precision task with demands on memory binding, fidelity of mnemonic representations and visuospatial construction, all abilities that are particularly affected by AD pathology even from preclinical stages onwards.[6,31,65] Moreover, we use a computational modelling approach to isolate the probability of recalling any task-relevant content and the precision of the retrieved memory representations.[24,66] This is in contrast to previous studies that rely on categorical definitions of correctly vs. incorrectly recalled information. Our precision metric therefore adds a potentially more sensitive qualitative dimension to the memory assessment by indexing the trial-by-trial variability in memory fidelity, which may be capable of identifying even subtle differences between individuals that categorical responding may fail to unmask.[50,67]

Only one study has tested the fidelity of relational binding with longer memory retention intervals using continuous report paradigms in an *APOE* genotyped cohort.[52] Zokaei and colleagues show a reduction in the fidelity of object-location binding for preclinical ε4 homozygote older adults, but no such effect for ε3ε4 heterozygotes when using the mean error between target location and response as a performance metric. The presence of an effect of the ε4-allele on the fidelity of long-term object-memory binding is promising as it suggests that this task is potentially sensitive to preclinical AD-related changes even in individuals in their 60s. There may be ways in which such object-location tasks could be made more sensitive, such that performance could index even subtler changes in memory, such as those that might exist in a medium risk group such as ε4-heterozygotes. Other studies typically use mean target-response distance to index memory fidelity,[5268] yet this metric includes both successfully retrieved and forgotten locations, thereby resulting in a potentially strong influence of guess trials on performance. It is therefore possible that performance reductions might be observed not just in ε4 homozygotes but also heterozygotes for object-location binding when using a more specific index of precision that controls for accessibility of any information from memory. Another option may be to increase the number of objects tested per study display. Increasing the amount of interfering information may place further demands on transentorhinal and hippocampal processes,[69–71] and may result in a higher number of misbinding errors among individuals with poorer mnemonic representations, such as in cases with preclinical or prodromal AD.[59,68] Here, we use both approaches to investigate whether continuous report paradigms can be made even more sensitive than previously achieved.

We examine the utility of a novel test of memory fidelity of relational binding that engages regions vulnerable to early AD, supplemented with a mixture modelling approach that specifically indexes precision, to test the effect of the ε4-allele on the precision of object-location binding beyond short-term memory retention. We compare model-derived metrics with those used in prior studies with continuous report paradigms such as those by Zokaei et al.[52] to determine if the separation of precision and retrieval success may be able to tease apart subtle differences in memory abilities between *APOE* genotypes.[50] We also increase the degree of interference between exemplars for a given study episode to place more demands on high fidelity representations and pattern separation. Moreover, we apply our test to a sample that has previously been characterised in terms of spatial navigation abilities.[9] An added benefit of our study is therefore to test whether a fidelity metric for spatial memory

will be similarly sensitive to AD risk as spatial navigation measures. To our knowledge no other study to date provides data on the effect of the ε4-allele on spatial memory fidelity and spatial navigation in the same preclinical sample.

Methods and methods

Participants

The study was carried out at the University of East Anglia, Norwich with ethical approval from the Faculty of Medicine and Health Sciences Ethics Committee at UEA (Reference FMH/2016/2017-11). Participants provided written informed consent before participation. Exclusion criteria included psychiatric or neurological disease, substance dependence disorder and clinical depression and/or anxiety. Individuals with medicated cholesterol or blood pressure were included in the study, but medication intake was recorded to ensure no medical differences between genetic groups. The sample presented here was previously described by Coughlan and colleagues.[9] The sample size was based on that of prior studies that investigated the effect of the ε4-allele on spatial navigation.[72]

Forty-nine participants completed the spatial precision memory task. We included n=26 individuals with the ε3ε3 genotype aged 53 to 74 (M=63.38, SD=5.99; 13 females) and n=20 individuals with the ε3ε4 genotype aged 54 to 80 (M=64.80, SD=6.83; 5 females) for our main analysis. Three volunteers with the ε4ε4 genotype aged 63 or 64 years also completed the test battery (M=63.33, SD=.58; 1 female). Given the small number of ε4 homozygotes and the differences between ε3ε4 and ε4ε4 carriers in general, in this study our main analysis focused on a comparison of ε3ε3 carriers and ε4 heterozygotes to avoid the admixture of different genotypes. In a sensitivity analysis, we determined whether the addition of the high risk ε4 homozygotes influenced the results.

The genotype groups did not differ significantly in terms of age or scores on the Addenbrookes Cognitive Examination (ACE) regardless of whether the total score or the memory subscore was used (all t<1, p>.4). In all analyses, we controlled for age and sex. Sample demographics and standard neuropsychological scores are shown in Table 1.

Table 1. Demographics and standard neuropsychological test scores by *APOE* genotype group.

	ε3ε3 (*n*=26) *Mean* (*SD*)	**ε3ε4** (*n*=20) *Mean* (*SD*)	**ε4ε4** (*n*=3) *Mean* (*SD*)
Age	63.4 (6.07)	64.8 (6.83)	63.3 (.58)
Sex			
Female	13 (50%)	5 (25%)	1 (33%)
Male	13 (50%)	15 (75%)	2 (67%)
Education	14.25 (2.31)	13.80 (2.26)	14.67 (.58)
ACE Total	93.9 (4.91)	94.6 (2.42)	93.0 (3.61)
ACE Memory	25.0 (1.50)	25.1 (1.00)	24.7 (1.53)
ROCF immediate	33.3 (2.59)	31.8 (2.69)	32.0 (2.65)
ROCF delayed	21.4 (5.73)	21.9 (4.67)	22.2 (9.78)

Note: ACE: Addenbrookes Cognitive Examination; ROCF: Rey-Osterrieth Complex Figure. Delayed copy was three minutes after presentation.

Precision memory task

Details for the precision memory task can be found in the Supplementary Material. Briefly, participants were asked to remember the identity and locations of objects in a scene. Each encoding display consisted of a trial-unique background image with three objects pseudorandomly arranged around an invisible circle centred at the midpoint of the image. Object positions were constrained to maintain a minimum of 62.04° between objects to avoid spatial overlap.

Participants undertook five practice trials before beginning the actual task. They were told that memorising the details of object and their locations during the study phase was crucial to support good performance in the test phase. Participants received feedback during training and only moved on to the main task after a minimum of five practice displays and after the experimenter had verified good comprehension of the task. The main task comprised five study-test blocks. In each of the five blocks, participants first viewed five displays during the study phase. After encoding, an interference task required participants to count backwards from a random number between 50 and 100 for 12 seconds to prevent active rehearsal of memorised displays. Each test trial began with an identification question where participants were asked to determine which of two presented objects had previously been shown. If they chose correctly, the associated background image appeared, and participants were asked to move the object around the screen to recreate its studied location as precisely as possible.

In total, participants viewed 25 displays and completed 75 test trials, each containing an identification and a localisation question.

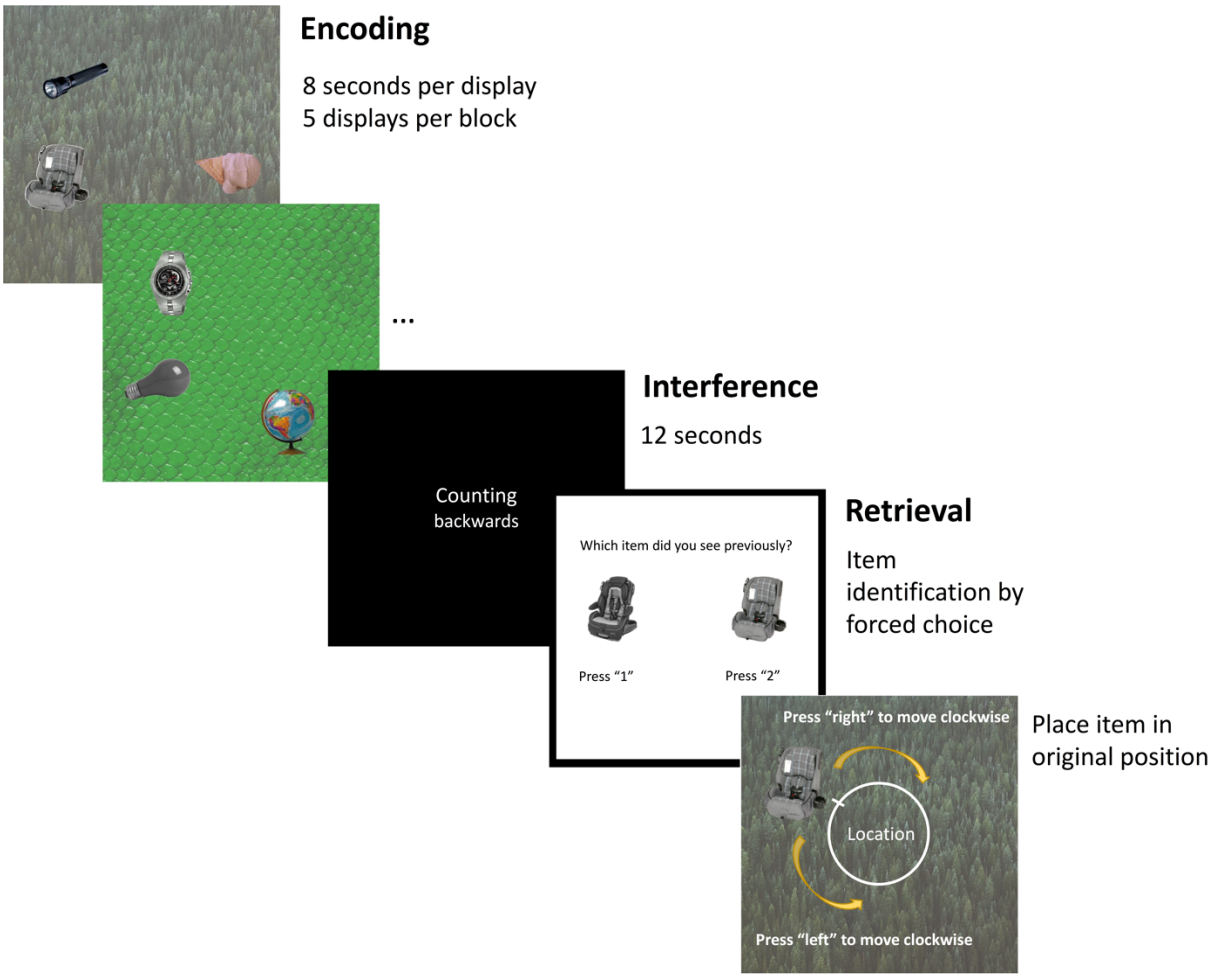

Figure 1. Schematic of the precision memory task.

APOE genotyping

DNA was collected using a Darcon tip buccal swab (LE11 5RG; Fisher Scientific). Buccal swabs were refrigerated at 2–4 °C until DNA was extracted using the QIAGEN QIAamp DNA Mini Kit (M15 6SH; QIAGEN). DNA was quantified by analyzing 2-µL aliquots of each extraction on a QUBIT 3.0 fluorometer (LE11 5RG; Fisher Scientific). DNA extractions were confirmed by the presence of a DNA concentration of 1.5 µg or higher per 100 µg of AE buffer as indicated on the QUBIT reading. PCR amplification and plate read analysis was performed using Applied Biosystems 7500 Fast Real-Time PCR System (TN23 4FD; Thermo Fisher Scientific). TaqMan Genotyping Master Mix was mixed with two single-nucleotide polymorphisms of *APOE* (rs429358 at codon 112 and rs7412 at codon 158). These two single-nucleotide polymorphisms determine the genotype of *APOE*2, E3, and E4 (2007; Applied Biosystems).

Mixture modelling

Models fitted to the data and distribution of responses across all participants by genotype are shown in Fig. 2A, 2B. We fit probabilistic mixture models to the location placement errors expressed as the degrees separating the response from the target. This is a

well-established method to probe memory fidelity that has been widely used by both our work and others across short-term and long-term memory studies.[24,66,73–75] The approach aims to determine the distribution of trial responses in order to examine which retrieval mechanisms best explain the observed responses: i) correctly recalled locations, ii) random guesses or iii) a misbinding error in which the location of the target item is confused with that of another object also presented on the same display. Guess trials can be modelled using a uniform distribution. The proportion of trials within the uniform distribution represents the guess rate *pU* and 1-*pU* therefore expresses retrieval success *pT*. Correctly remembered items can be modelled by a circular Gaussian (von Mises) distribution centred at the target location with its standard deviation reflecting the precision with which locations are recalled. Larger standard deviations (*SD*) correspond to lower fidelity of the recalled responses. Finally, misbinding errors can be modelled by von Mises distributions centred around the two distractor items.

To maximise comparability with the only other study on the effect of the *APOE* genotype on location memory precision, we also used Bayesian modelling implemented with the MemToolbox in MATLAB 2016a (code available at: http://visionlab.github.io/ MemToolbox/).[73 75] Of note, that study employed a short- rather than a long-term memory task. We fit three models to the error data collapsed across all participants by *APOE* genotype group to test whether the same model components could explain responding in each group. The models contained the following components (Fig. 2A): Model 1 (von Mises distribution only) assumes that no guessing occurred; Model 2 (uniform + von Mises distribution) assumes that responses reflect a mixture of guessed trials and correctly recalled locations with response-to-target distance varying across trials; Model 3 (uniform + von Mises + von Mises for non-targets) extends Model 2 by additionally assuming that some incorrect responses were due to object-location misbinding. For more details on modelling and comparison with an alternative model fitting procedure based on work by Bays and colleagues[24,25,50] refer to the Supplementary Material.

This approach allowed us to test if the *APOE* ε4-allele affects the probability of correctly retrieving information from memory and/or the fidelity (i.e. the precision with which this information is recalled). Mixture modelling is superior to other approaches that distinguish between retrieval success and fidelity of retrieved information because the estimation of the uniform distribution accounts for guess responses placed near the target item.

A model selection procedure using Deviance Information Criterion favoured Model 2 which describes the standard mixture model with a uniform distribution for guessed responses and a von Mises distribution for the precision of correctly recalled responses as the best model. All further analyses are conducted using Model 2. Details on model selection and model metrics for the final model are shown in the Supplementary Material.

Finally, we calculated retrieval success and precision for each subject. When using individual subjects for model fitting, fewer trials are available for parameter estimation. Moreover, the estimation procedure may produce more robust and precise estimates for some subjects compared to others. To improve robustness of estimates for precision and retrieval success, we calculated a cut-off for guessing from the mixture modelling approach across the full sample following the examples of prior studies (for details see Supplementary

Material).[24,50] Localisation errors exceeding 63° response-to-target distance were deemed as failure to retrieve an object's location. Consequently, for each subject we calculated retrieval success as the proportion of trials with errors ≤63°. A measure of imprecision was derived from the standard deviation across all responses with localisation errors ≤63°.

Statistical analysis: Testing APOE group differences in retrieval success and memory precision.

We employed a combination of frequentist (two-tailed tests with a statistical significance level of $p<.05$) and Bayesian methods to test for APOE genotype effects.

Group differences based on permutations. We first tested for differences in guessing (*g*) and imprecision (*SD*) estimates for the standard mixture models fit to all responses across subjects in the ε3ε3-carrier and ε3ε4-carrier group, respectively. To obtain a *p*-value, true group differences were compared to the distribution of standardised differences obtained from random group assignments over 1000 permutations (sample 1 with n=26 to match the number of participants in the ε3ε3 group; sample 2 with n=20, as in the ε3ε4 group). This approach has the advantage of operating on more robust model parameters due to reduced noise resulting from larger number of trials available for mixture modelling.

Group differences while controlling for age and sex. Next, we carried out analyses on individual subject data while controlling for nuisance variables using a linear model with sex and age as covariates and APOE genotype as between-subjects factor of interest. Dependent variables were the proportion of correctly identified items, and the measures of retrieval success and precision based on a 63° cut-off for guessing (see Supplementary Material). We also calculated the Bayes Factor for the contrast of the model with covariates (age, sex) and the full model with covariates and ε4-status as between-subjects factor of interest using the R package *BayesFactor* (https://CRAN.R-project.org/package=BayesFactor). For the model comparison, the numerator was the control model with covariates, and the denominator was the model of interest (including both covariates and APOE genotype) such that a factor >1 was indicative of more support for the null as opposed to the alternative hypothesis. A Bayes Factor of >3 was deemed as strong evidence in support of the null hypothesis.[50,76,77]

Sensitivity analyses. Although our modelling approach suggested that misbinding errors did not account for a significant proportion of location memory responses across all participants, this does not take into account potential differences in misbinding frequency between participants. We therefore conducted a control analysis termed 'nearest neighbour analysis' as used in prior work.[52,78] This analysis allowed us to test whether there was a difference in the nature of incorrect responses between genetic groups by taking into account the occurrence of misbinding errors. A significant *APOE* effect on the distance to the nearest neighbour would suggest that error responses in the two groups are not caused by the same mechanisms. The group with significantly smaller nearest neighbour difference is likely to commit more misbinding errors.

In order to make our results more comparable with prior studies that used a similar object-location binding paradigm without mixture modelling to separate retrieval success from precision,[52,79] we also calculated the mean absolute error between targets and responses (see Supplementary Material). This would allow us to determine whether a modelling approach to separate retrieval success and memory precision may be more sensitive to detect

APOE ε4 effects on memory. To compare performance of the ε4ε4 carriers to that of the ε3ε3 group, we calculated their performance in terms of *Z*-scores based on the mean and standard deviation of test scores in the ε3ε3 group.

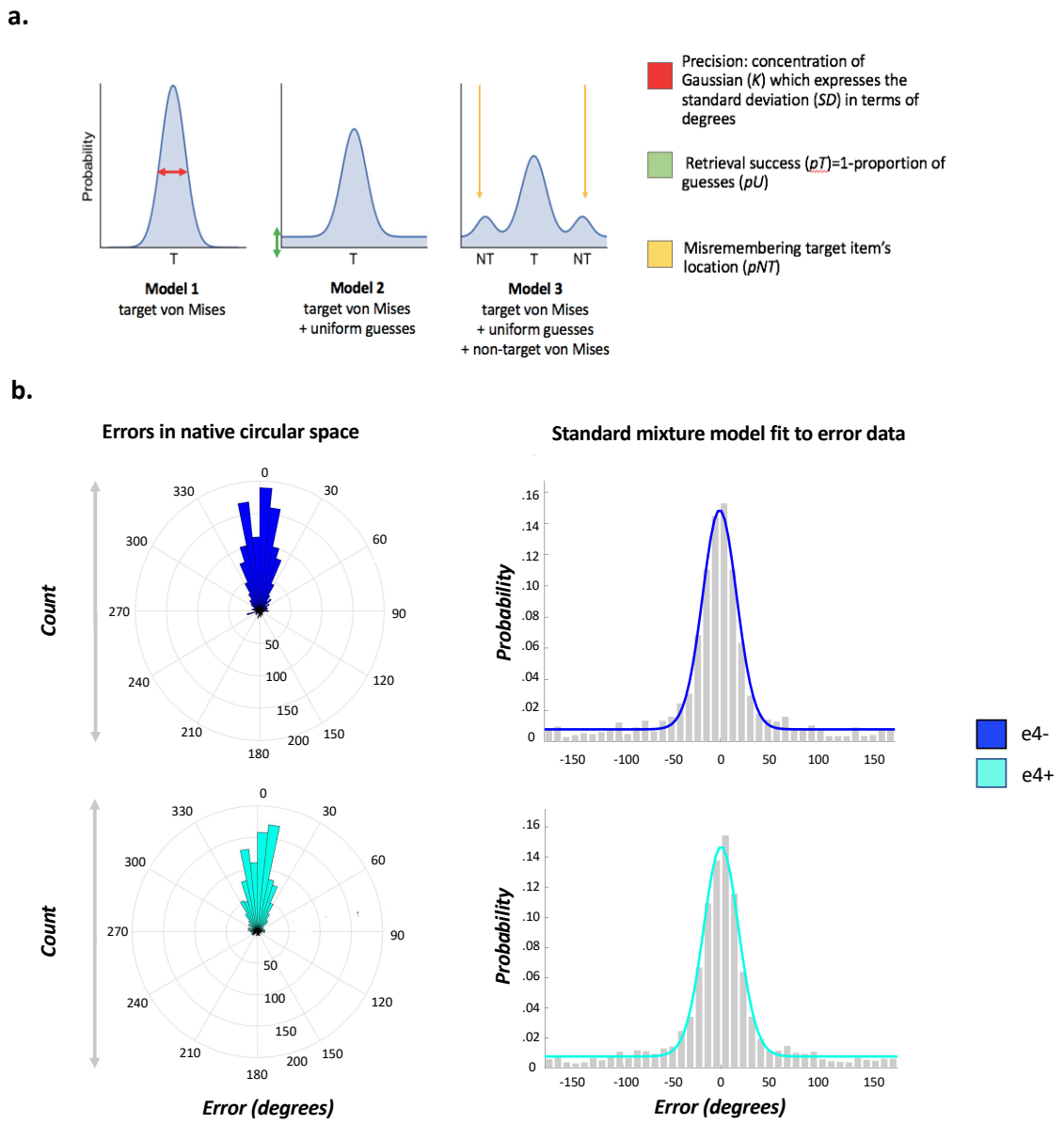

Figure 2. Tested models and results from the mixture modelling approach.

(a) Proposed models to capture location memory performance. In Model 1, all object locations are assumed to be correctly recalled without any guess responses (probability of guessing: *pU*=0). The mean distance of responses from the target can be represented by the width of the von Mises (circular Gaussian) distribution, expressing the precision of memory recall (expressed as the standard deviation (*SD*) of the von Mises distribution where higher values reflect less precision; for a more intuitive interpretation where higher values reflect better performance, the *SD* value can be converted to the von Mises distribution concentration parameter *K*; see Supplementary Material). Model 2 assumes a mixture of guessed and correctly remembered responses, where the proportion of responses that fall within the uniform distribution is denoted by the parameter *pU* that captures the proportion of guessed responses. For a more intuitive understanding where higher values reflect

higher performance this parameter can also be expressed as retrieval success denoted by *pT*, the proportion of trials within the von Mises distribution, i.e. trials in which the target location was correctly recalled. Model 3 assumes that responses reflect a combination of guessing, correctly remembered responses with variable degree of precision, and swaps of target and distractor locations, represented as von Mises distributions centered at the locations of distractor objects. **(b) Distribution of location errors by ε4-status in native circular space (left hand side) and the Standard Mixture Model (von Mises + uniform) fit to responses.** Model 2 was identified as the best fitting model in a model comparison procedure detailed in the Supplementary Material.

Results

Effects of genotype on memory performance.

A summary of the memory performance metrics as a function of *APOE* group is shown in Table 2. Fig. 3 shows the comparison of retrieval success and precision estimates as a function of ε4-status.

Group differences based on memory metrics derived from modelling across subjects by APOE group. The results of the permutation analysis are shown in Fig. 3A. The error distributions derived from across subjects in each *APOE* group exhibited considerable overlap. The distribution of permutation-based group differences derived from random assignments to groups confirmed that the differences in guessing and imprecision between the *APOE* groups were not significant (*guessing*: z=.31, p=.704=; *imprecision*: z=-.59, p=.555).

Group differences based on memory metrics derived for each subject. We investigated the effect of *APOE* genotype on object identification, retrieval success for location and precision for correctly retrieved items at the individual subject level (Fig. 3C). The linear models controlling for age and sex found no significant effect of *APOE* on identification of objects ($F(1, 42)$=1.14, p=.292, BF_{01}=2.17), retrieval success for object locations ($F(1, 42)$=.450, p=.506, BF_{01}=3.02) or the precision of recreating locations of correctly retrieved items ($F(1, 42)$=.12, p=.726, BF_{01}=3.19).

To facilitate comparison with a previous study on *APOE* genotype effects on localisation performance in a continuous report paradigm we also compared mean absolute angular disparity between targets and responses across all trials.[52] There were no significant differences between *APOE* ε4-status groups ($F(1, 42)$=1.14, p=.292, BF_{01}=1.99).

Control analysis accounting for misbinding errors. In line with the results from the overall group comparisons based on permutations, there were no significant differences in the occurrence of swap errors. The Bayes Factor further provided good evidence in support of the absence of an *APOE* ε4 effect ($F(1, 42)$=.83, p=.367; BF_{01}=2.54).

Sensitivity analysis: effect of inclusion of ε4 homozygotes
Even with the addition of the high risk ε4 homozygotes the comparison between ε4-carriers and non-carriers showed no effect of AD genetic risk on object identification ($F(3, 45)$=.25,

p=.861, BF_{01}=3.16), retrieval success (F(3, 45)=1.36 p=.268, BF_{01}=3.33), precision of object location memory (F(3, 45)=.87, p=.462, BF_{01}=3.35), mean absolute localisation error (F(3, 45)=1.43, p=.246, BF_{01}=3.36) or the occurrence of swap errors (F(3, 45)=1.45, p=.242; BF_{01}=3.09). Looking at the performance of each ε4ε4 carrier individually, none of the *Z*-scores of the ε4ε4 carriers computed on the basis of the ε3ε3 group were larger than ±1.65 in any of item identification, retrieval success or precision, indicating no significant reductions in any of the participants at the highest genetic risk.

Table 2. Summary of memory performance across subjects by *APOE* genotype.

Metric	**ε3ε3** (*n*=26)	**ε3ε4** (*n*=23)	**All ε4 carriers** (*n*=26)
Identification accuracy	.83 (.06)	.81 (.08)	.83 (.08)
Location retrieved success	.80 (.13)	.80 (.16)	.81 (.15)
Localisation Precision	22.4 (5.31)	22.1 (3.97)	22.16 (4.09)
Mean target-response distance	35.5 (16.1)	35.1 (16.2)	34.10 (15.7)
Mean distance to nearest item	20.7 (5.60)	21.0 (5.00)	20.67 (4.84)
Model-derived estimates calculated across all subjects per group			
pU [95% CI]	.31 [.28; .34]	.29 [.26; .33]	.30 [.28; .33]
SD [95% CI]	17.90 [16.82; 19.32]	18.84 [17.54; 20.49]	18.35 [17.43; 19.30]

Note: Retrieval success and precision were calculated based on a model derived cut-off score for guessing at a response-to-target distance of 63° (see Supplementary Material for details). *CI:* credibility interval of the posterior distribution derived from the Bayesian estimation procedure.

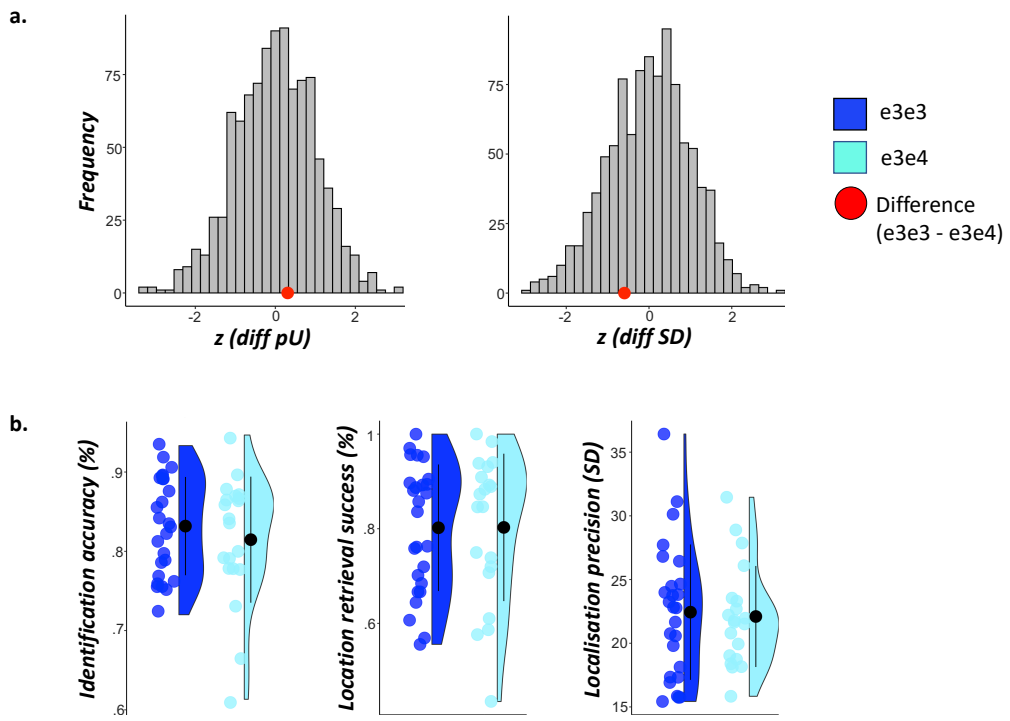

Figure 3. Precision memory performance by *APOE* genotype.

(a) Distribution of standardised group differences derived from 1000 permutations where *n*=26 subjects were randomly assigned to one sample and *n*=20 subjects to another (to match the actual group sizes in our sample). Retrieval success and precision were obtained using mixture modelling on all trials across subjects for the ε3ε44 and the ε3ε4 group, respectively. The red dots represent the standardised true differences in model metrics calculated by subtracting the scores of the ε3ε4 from those of the ε3ε3 group (for *guessing*: *z*=.31; for *SD*: *z*=-.5). (b) Mean and standard deviation of identification accuracy, retrieval success and precision for each *APOE* group. Retrieval success refers to the proportion of trials falling within 63° of the target object. Precision reflects the standard deviation in response-to-target distance for all trials within 63° of the target object.

Discussion

In this study we aimed to determine whether the precision of long-term memory for object-location bindings is affected in healthy middle- and older-aged *APOE* ε4-carriers who do not exhibit impairments on standard neuropsychological tests. We used a continuous report paradigm in which participants were asked to recreate object locations as precisely as possible[24] and employed Bayesian mixture modelling to separate memory retrieval success from the precision of retrieved locations.[66,73] We hypothesised that the precision task may be capable of identifying subtle changes in memory fidelity in preclinical *APOE* ε4-carriers. Prior evidence suggests that such tasks have potential for early detection of AD-related cognitive changes because 1) the task involves relational binding of objects and locations, which is impaired in prodromal AD and taps into the integrity of the entorhinal cortex and hippocampus,[34,68,80–82] 2) a continuous metric may be a more sensitive index than categorical measures of retrieval,[50,67] and 3) memory fidelity relies on communication between hippocampus and cortical regions, which exhibit altered connectivity in the early course of AD.[1,16,24,83–90] Previously, preclinical ε4 homozygotes at high risk of AD were impaired on a similar memory fidelity task, while heterozygotes were not.[52] Here, we aimed to increase sensitivity of such continuous report paradigms by increasing the to-be-recalled information per test display and by separating memory precision from retrieval success. We then tested if these adjustments may be capable of picking up subtle differences between controls and a genetic risk group, even if the risk group was comprised of individuals with moderate genetic risk of AD (ε4 heterozygotes), who represent 47% of the general population.[91]

However, we found robust evidence for the absence of an effect of the ε4-allele on object-location long-term memory performance in preclinical middle-aged and older adults, regardless of whether the risk groups included only ε4 heterozygotes or additionally added the ε4 homozygotes. Carriers of the ε4 allele did not recall fewer locations of objects, nor was the precision of their retrieved object-location associations affected. E4-carriers also did not commit more misbinding errors of item identity and location. To our knowledge, this is the first study comparing cognitively healthy *APOE* genotype groups, using a mixture modelling approach to separate retrieval success from retrieval precision, with study-test delays that prevented the involvement of short-term memory. Intriguingly, despite this absence of spatial memory deficits, the ε4-carriers in this sample did exhibit altered wayfinding trajectories in real-time while navigating a virtual environment in the SeaHero Quest game, as previously shown by Coughlan and colleagues.[9]

Few studies have previously investigated memory fidelity in individuals at higher risk for AD during preclinical stages of the disease. Preclinical individuals with higher AD risk based on biomarkers or the *APOE* genotype have been reported to show poorer performance in mnemonic discrimination (combined group of heterozygotes and homozygotes) and continuous report tasks of feature binding in long-term memory (homozygotes).[31,59,92] Specifically, they exhibit a greater tendency to falsely label as old novel lures that are similar to studied stimuli.[31,62,92] They also have higher rates of misbinding and larger placement errors.[52] In the case of continuous report tasks it was shown that individuals with the highest genetic risk for late-onset AD (ε4 homozygotes) and familial AD do indeed have poorer representational quality for object-location binding, as measured using the mean error between target and response.[52,59] This metric encompasses both the success of retrieving any information from memory and the precision with which this information is recalled. In this study, we therefore tested whether the mixture modelling approach we applied might render this task more sensitive by isolating precision from retrieval success, and potentially identifying subtle reductions even in a genetic risk cohort consisting mainly of ε4 heterozygotes as in the present study. However, our data show that this was not the case, with Bayes factors providing good evidence for the null hypothesis that ε4-carriers are unimpaired on object recall or object localisation precision.

Given that *APOE* ε4 homozygotes and those with autosomal dominant AD show pathological markers at an earlier age than ε3ε4 carriers,[12,93,94] it is possible that impairments in the fidelity of object-location binding may be more apparent in preclinical ε4ε4 and early-onset AD cases, compared to the ε3ε4 carriers investigated in this study whose mean age was significantly below that of most other studies testing the use of memory fidelity tasks for early detection.[61,62,64,95] Our sensitivity analysis showed that the null effect was still confirmed after inclusion of a smaller group of ε4 homozygotes in the AD risk group.

Similar to results for continuous report paradigms, mnemonic similarity tasks have also found reduced memory fidelity in ε4-carriers.[61,62] These studies included participants who were on average five years older than those in our sample (mean ages of 70 vs. 65 years), which may have been a reason for the differences between their findings and ours. Notably, their ε4-carriers had deficits on the standard neuropsychological assessments, while no differences in such tasks were found in our sample. Those two studies[61,62] could therefore not establish the relative sensitivity of standard and memory fidelity tasks for early preclinical AD signs, although they do suggest that fidelity metrics may be a promising early detection tool in prodromal MCI.

Another strategy to test the sensitivity of early detection tasks is to classify cognitively normal preclinical older adults based on tau and amyloid AD biomarker status. To date, this has been done to test for the sensitivity of mnemonic discrimination tests, which shown a correlation between both tau and amyloid beta loads with mnemonic discrimination performance.[31,32,64,96,97] Again, mean ages in these samples (70+) tend to be significantly older than the participants in the present study (~65), although in one study the association between tau levels and object mnemonic discrimination could still be observed in individuals aged below 70 years.[31] Interestingly, the association of AD biomarker concentration and mnemonic discrimination deficits remained even after accounting for *APOE* status.[32] Unfortunately no such biomarker data exist for memory precision binding tasks.

Nevertheless, findings suggest that risk classification based on biomarkers, as opposed to ε4-genotype, may be a better strategy to test the sensitivity of memory precision for early detection of AD in preclinical samples without cognitive signs on standard tests.[98]

Currently, it is difficult to compare the sensitivity of precision binding and mnemonic similarity tasks to early AD-related decline given the considerable difference in mean ages of study samples and the different approaches to index preclinical AD cases. Future studies are needed to better understand the relationship between continuous and categorical metrics of memory fidelity as measured using our precision task and mnemonic discrimination tests, respectively. Based on moderate correlations between test scores, mnemonic similarity judgments and object-location binding may involve similar but also somewhat dissociable mechanisms.[99] Pattern separation likely contributes to good performance in both tasks.[99–101] Both mnemonic similarity and precision rely on the integrity of, and effective communication between, perirhinal cortex, ERC and hippocampus, particularly subregions CA3 and dentate gyrus.[28,84,102–105] Functional MRI data suggest that the precision task further engages posterior parietal cortex regions upon retrieval to allow for the faithful reinstatement and visuospatial reconstruction of object features[24,84] and that hippocampal activity at encoding scales with precision.[20] Importantly, MTL-parietal connectivity tracks memory precision, which is of note given that these connections may already be altered in the early stages of AD, and even among relatively young ε4-carriers.[83,84,106–108]

Despite the absence of a precision memory deficit in the present sample, Coughlan and colleagues recently described suboptimal navigation patterns in these same ε3ε4 carriers (a subset of whom were enrolled in this study).[9] This subtle navigational deficit was attributed to a bias toward navigating close to environmental boundaries. This very specific impairment is thought to be a result of early tau pathology in the ERC thought to alter the integrity of grid cell representations, which are essential for updating self-motion during navigation.[9,72,109–111] This interpretation is in line with recent evidence suggesting that preclinical ε4-carriers only exhibit spatial navigation deficits in the absence of nearby landmarks or environmental boundaries that normally correct for accumulating temporal error in the grid-cell code.[110,112]

Although grid cells are most famously involved in spatial navigation, they also support visual memory.[113] Research suggests that both visual and navigational processes are supported by the entorhinal cortex via common mechanisms that include the formation of spatial or visual maps via grid cells.[114,115] Specifically, grid cells code for spatial locations in a visual scene much in the same way in which they code for space during exploration of a 3D environment.[113,114] Based on these findings it has been proposed that grid cells support both spatial navigation and relational memory.[115] It may therefore be surprising that we did not find any effect in our relational memory precision task, while impairments were observed in the navigation task by Coughlan et al.[9] However, the border bias is a very specific behaviour in ε4-carriers that appears when arenas have larger open spaces where anchoring spatial maps to nearby landmarks cannot be used as a corrective strategy.[9,72,110] Therefore, it has no direct equivalent in 2D visual scene memory in our precision task. This may explain why there is an effect of the ε4-allele on virtual reality spatial navigation but not in object-location memory precision in our sample. A preference for environmental borders may indeed be the very first

sign of AD risk dependent behavioural changes, whereas impairment in relational memory may arise at a later stage.[62,92,116]

Despite our relatively small sample size, our power analysis suggested that our study had moderate power to detect a difference in precision memory between ε3ε3 and ε3ε4 carriers similar in magnitude to that of the spatial navigation test in the same individuals (Supplementary Material).[9] Even though power was moderate, our Bayesian analysis provided good evidence in favour of a null effect, suggesting that the absence of a genotype effect was not due to an inadequate sample size. If a genotype effect on object-location precision does indeed exist in this sample, it is likely to be rather small and may be less meaningful for early detection efforts. This small effect may in part be due to the high heterogeneity of ε3ε4 carriers, given that only a subgroup will move on to actually develop AD.[12] It would be informative to follow up the present sample longitudinally to test whether any differences in memory precision are apparent in the current data when comparing participants who do or do not subsequently exhibit cognitive decline associated with AD. Additionally, as discussed above, a promising strategy to test the sensitivity of the precision task in preclinical cases in future studies may be to use biomarkers for classifying individuals into risk groups. This would not only allow studies to determine the sensitivity of memory fidelity metrics but to also assess the specificity of these tasks to AD-related cognitive decline. This is particularly important given the high heterogeneity of ε4-carriers and MCI patients. To date there is still a lack of studies on memory fidelity that stratify MCI patient groups based on AD biomarkers.[40,45,46]

To our knowledge this is the first study to employ a modelling approach to separate episodic memory retrieval success and precision and test the sensitivity of mnemonic fidelity metrics to preclinical AD risk as measured in a contrast of ε3ε3 and ε3ε4 carriers. Prior work in high risk AD individuals (familial, ε3ε4/ε4ε4, tau and amyloid positive cases) has suggested that object-location memory fidelity may be a sensitive marker for preclinical AD cases and that this effect can be detected in samples aged 70 and older.[32,52,59 62,92] We provide robust evidence that this may not be the case for middle-aged ε3ε4 carriers who were, on average, five years younger than individuals in prior studies. The sensitivity of memory fidelity tasks may therefore not extend to ε4 heterozygotes in their early to mid-60s. Despite no APOE genotype effect on object-location memory precision, prior evidence has shown that ε3ε4 carriers from the same sample do exhibit subtle behavioural deficits in spatial navigation.[9] These results provide further support to prior proposals that spatial navigation may be a sensitive marker for the earliest AD-dependent cognitive changes, even before episodic memory.[72,117] More research in preclinical AD is needed to confirm this hypothesis by direct comparisons of memory fidelity and spatial navigation tasks.

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