

Superior short-term memory in APOE ϵ 2 carriers across the age range

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ABSTRACT

The Apolipoprotein-E (APOE) gene is now known to be associated with individual differences in cognitive health in ageing. However, while the APOE ϵ 4 allele confers significantly increased risk of developing Alzheimer's disease (AD), the APOE ϵ 2 allele is hypothesized to be protective against the development of AD. This is in line with neuroimaging and pathological findings associated with ϵ 2 APOE allele, which go in the opposite direction to those observed in AD-related pathology. However, the precise impact of this allele on cognition remains inconclusive, with some small-cohort studies raising the possibility of an advantageous memory performance in these individuals. Here, we tested short-term memory (STM) performance in a large cohort of individuals, 300 of which were ϵ 2/ ϵ 3 carriers. Their performance was compared to 554 ϵ 3/ ϵ 3 carriers. We included participants from a wide age range spanning young, middle-aged and elderly adults. All of them performed a STM task that has previously been shown to be sensitive to subtle changes in memory in various patient and at-risk cohorts. Individuals carrying the APOE- ϵ 2 allele exhibited a significant memory advantage, regardless of STM task difficulty and across all ages. The observed memory advantage was present across the age range, suggestive of a phenotypical effect of this allele on cognition, possibly independent of any effects of this genetic allele that occur later life in these individuals.

1. Introduction

The apolipoprotein-E (APOE) gene has been linked to individual differences in risk and resilience to neurodegeneration in ageing. Three alleles make up the variants of the gene. The ϵ 3 allele is the most common variant and considered to be the population norm. The ϵ 4 allele is present in approximately 14% of the population and confers a major risk factor for developing Alzheimer's disease (AD) [1]. Accordingly, the ϵ 4 allele has been the focus of research in the past few years (e.g. 1–7). In contrast, the rarer ϵ 2 APOE allele has been hypothesized to be protective against AD pathology [8,9]. Investigations involving the ϵ 2 allele remain rare, and thus there is scant evidence pertaining to its consequences on brain or cognitive functions related to AD.

Some studies have reported that the ϵ 2 allele is associated with decreased AD-related effects on the brain, with carriers having lower hippocampal atrophy [10], or larger hippocampal volume [11,12] and

increased entorhinal cortical thickness [13,14], compared to both ϵ 3 and ϵ 4 carriers. Additionally, some investigations have concluded that the ϵ 2 allele might confer a protective effect against amyloid deposition and neurofibrillary tangle (NFT) formation [15,16]. Overall, APOE ϵ 2 allele carriers have an increased lifespan [17].

A small number of behavioural studies have focused on cognitive correlates of carrying the APOE ϵ 2 allele. The results, however, have been mixed and inconsistent. Some have reported a positive association between the ϵ 2 allele and healthy cognitive functions in advanced years [18–22], for example an increased ability to retain information in short- and long-term memories [22–25]. In one study, ϵ 2 allele carriers were also found to have superior verbal memory with increased recall scores on intermediate and long-term recall tasks compared to non-carriers [18]. Similar effects have been reported in younger ϵ 2 carriers. In fact some investigators have reported that ϵ 2 carriers demonstrated superior performance in long-term and short-term memory tasks (as measured by

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n-back tasks) as well as tests of executive function and attention across a wide age range (23–67 years) [26].

Other studies challenge the presence of any benefits of the $\epsilon 2$ allele [27,28], and some even suggest a cognitive disadvantage [29]. For example, it has been reported that compared to non-carriers, individuals with the $\epsilon 2$ allele performed significantly worse on standard memory and executive function tasks [12,30]. Moreover, in a report by Lancaster and colleagues (2016), middle-aged $\epsilon 2$ carriers had performance disadvantages on various aspects of sustained attention, with slower response times in identifying a target compared to both $\epsilon 3$ and $\epsilon 4$ carriers [31]. In line with these findings, it has been found that even though $\epsilon 2$ carriers had reduced risk of clinical dementia, compared to $\epsilon 3$ carriers, they still possessed increased plaque neuropathology [32] which in turn may impact their cognitive abilities.

The scarcity and inconsistencies in the literature may stem from a number of shortcomings. They might be due to a lack of sensitivity in commonly used neuropsychological tests, variations in the age groups tested, as well as the small number of participants within each genetic group. At this point, it is crucial to resolve inconsistencies and to strive for a better description of the influences of the *APOE* $\epsilon 2$ gene allele on cognition. Understanding whether the $\epsilon 2$ is in fact protective of cognitive decline will help advance our knowledge about the genetic and neural factors promoting cognitive resilience and ultimately improve stratification, diagnosis, and prognosis of cognitive decline in neurodegeneration. In addition, there are practical consequences for understanding cognitive decline in $\epsilon 4$ carriers. Most studies investigating $\epsilon 4$ carriers as an at-risk group for developing AD compare them to $\epsilon 2$ and $\epsilon 3$ carriers as control participants. This might result in inconsistent findings if $\epsilon 2$ and $\epsilon 3$ carriers have distinct cognitive profiles.

To overcome these shortcomings, we employed a highly sensitive task of visual short-term memory (STM) to test a large cohort of *APOE* $\epsilon 2$ carriers and non-carriers online. Our task provides a specific and quantifiable measure of the quality of the memories formed and has been shown to be more sensitive than commonly used neuropsychological measures [33]. It has also been applied to *APOE* $\epsilon 4$ carriers, revealing an interesting pattern of antagonistic pleiotropy [2,3], thereby demonstrating the sensitivity of this task to detect subtle differences in performance in otherwise healthy participants. Secondly, to determine whether putative cognitive differences were part of individuals' make-up or emerged gradually relative to non-carriers with advancing age, the large cohort included adults of various ages, spanning the young, middle-aged and elderly. Lastly, a large cohort of genotyped participants took part in online, with greater numbers of *APOE* $\epsilon 2$ carrier and non-carriers in each age-range than tested to date. The present study therefore allowed us to examine the effect of *APOE* $\epsilon 2$ allele on cognition, across the age range, and with high sensitivity.

2. Methods

Experimental procedures were reviewed and approved by the Central University Research Ethics Committee of the University of Oxford (identical to that detailed in 34).

2.1. Participants

Overall, 854 participants selected from a group of 1277 individuals recruited through the NIHR BioResources (<https://bioresource.nihr.ac.uk/>) completed the study remotely. Genetic information regarding the participants' *APOE* allelic variants was used to select the group of participants, which consisted of 300 $\epsilon 2/\epsilon 3$ carriers and 554 $\epsilon 3/\epsilon 3$ carriers (for *APOE* genotyping methods please refer to the NIHR BioResources website: <https://bioresource.nihr.ac.uk/>). Participants were specifically recruited with the aim of testing as many individuals as possible within each genotype group and age from those available in the cohort. Hence, the distribution of participants in each genotype does not represent what one would expect in the general population.

On agreeing to take part, participants received a unique identification number and a guide describing the study procedures. They were first instructed to complete a consent form, followed by a set of demographic questionnaires. Having consented, participants then completed the Oxford Memory test (OMT) on their personal tablet devices.

Table 1 presents a summary of the demographic information for the two groups (age-related changes in memory performance and the influence of the *APOE* $\epsilon 4$ was examined in a separate study 34). There was no significant difference in years of education (measured from the first year of school), gender, or handedness between the two groups.

2.2. Oxford memory test (OMT)

The Oxford Memory Test (OMT) is a flexible web-based version of a highly sensitive short-term-memory precision task we have previously successfully used to detect subtle changes in performance in healthy ageing, neurodegenerative disorders, and at-risk populations [2,35–37]. The online OMT instantiation is identical to that used in a previous study of *APOE* $\epsilon 4$ carriers [34]. The web-app platform is designed for testing in 'less strict' environments such as clinics, wards, or individuals' homes; and can be run on any tablet or touchscreen device.

A schematic of the task is presented in Fig. 1a. In each trial, participants viewed 1 or 3 coloured fractals (memory array) for 1 or 3 s respectively and had to memorise the identity and corresponding location of each fractal. The memory array was followed by a blank delay of 1 or 4 s before they were probed about their memory. At probe, participants were first presented with 2 fractals, positioned above and below the fixation cross. One was from the memory array (target) and the other was a novel fractal. Participants had to select the fractal that had been present in the previous memory array (identification) and then drag it to the remembered location (localization). To confirm their response, participants then had to press the "Done" button at screen centre. This was followed by the presentation of a blank screen with a "Next" button (Fig. 1a). When ready, participants initiated the next trial.

The stimuli were selected from a pool of 196 coloured fractals (sized to 3° of visual angle). The location of the fractals in the memory array was randomly selected with a few constraints: Fractals had a minimum distance of 4° of visual angle from each other, a minimum of 1.5° of visual angle from the edges of the screen, and a minimum of 2° of visual angle from screen centre, assuming a constant viewing distance of 40 cm.

Participants were asked to complete 2 blocks of 40 trials. Each block consisted of 10 trials per memory set-size and delay condition. Prior to the beginning of the task, participants were acquainted with the experimental design and conditions. They completed 2 trials with written instructions on each screen and a further 8 practice trials resembling the experimental trials. Practice trials were not included in the analysis. Participants were instructed to perform the task in a quiet place while placing the tablet at arm's length. Prior to the start of the task, participants were asked to report the screen dimensions within the OMT app. This information was used to normalise screen sizes across various devices.

3. Results

Mixed ANOVAs with the number of objects in the memory array (set size) and the duration of the delay period as within-subject factors and age-group and *APOE* gene-status as between-subject factors were conducted (see Table 2 for complete summary statistics). In summary, the analysis showed significant performance benefits for *APOE* $\epsilon 2$ carriers, discussed below, none of which interacted with age of participants.

For *identification times* (time participants took to select the target fractal at response), there was a significant main effect of *APOE* status ($F(1,840) = 4.75, p = 0.03, \eta^2_p = 0.006$, Fig. 1b), with faster responses by *APOE* $\epsilon 2/\epsilon 3$ carriers than non-carriers. *APOE* status, however, did not

Table 1
Demographic characteristics of $\epsilon 3/\epsilon 3$ (black) and $\epsilon 2/\epsilon 3$ carriers (light blue).

$\epsilon 3/\epsilon 3$ carriers $\epsilon 2/\epsilon 3$ carriers	Grp1 <40	Grp2 40-45	Grp3 45-50	Grp4 50-55	Grp5 55-60	Grp6 60-65	Grp7 65<
N	62 49	42 19	67 27	73 45	101 55	81 42	128 63
Mean Age (stdev)	32.8 4.9 33.5 3.7	43.2 1.5 43.9 0.8	48.3 1.4 48.3 1.6	53.1 1.3 53.2 1.5	58 1.4 58 1.4	62.8 1.3 63 1.6	70.3 3.2 69.5 3
Gender m/f	23/39 17/32	16/26 9/10	20/47 15/12	26/47 19/26	41/60 25/30	37/44 15/27	60/68 37/26
Handedness r/l	55/7 45/4	39/3 16/3	52/15 23/4	66/7 38/7	90/11 48/7	65/11 33/9	115/13 58/5
Years of Education (stdev)	15.4 4.5 15.6 4.4	15.6 3.7 15.7 3	15.3 3.5 15.6 3.5	15.1 3.9 15.6 3.3	15.3 3.9 14.5 5	14.9 3.9 15.5 3	15.6 3.9 15.7 3.5

interact with any of the other factors, i.e. age, delay interval or set size (Table 2).

For *Identification accuracy*, there was no significant main effect of *APOE* status or an interaction between *APOE* status or any of the other factors. Mean identification accuracy was high overall (mean accuracy of 99% for set size 1 and 88% for set size 3), and interacted with age of participants as well as memory delay and set size (see Table 2 for summary statistics).

Finally, there was a significant main effect of *APOE* status for *localization error* – the distance between the response location and the original location of the probed item ($F(1,840) = 5.9, p < 0.001, \eta^2_p = 0.007$), with *APOE* $\epsilon 2/\epsilon 3$ carriers localizing fractals more precisely than non-carriers. *APOE* status also interacted significantly with set size ($F(1,840) = 4.3, p = 0.038, \eta^2_p = 0.005$). This 2-way interaction was followed up by further one-way analyses per set size. For set size 1, there was no significant effect of *APOE* status ($F(1,840) = 1.85, p = 0.17$) but for set size 3, there was a significant advantage for $\epsilon 2$ carriers ($F(1,840) = 6.02, p = 0.014, \eta^2_p = 0.007$ - Fig. 1c). *APOE* status did not interact with age of participants or memory delay (Table 2).

Together, these results demonstrate that individuals with the $\epsilon 2/\epsilon 3$ genotype performed significantly better in our STM task, as measured by both faster response times and greater precision of location memory compared to the $\epsilon 3/\epsilon 3$ genotype, regardless of age.

4. Discussion

The current study provides evidence for a distinct pattern of STM performance in $\epsilon 2$ carriers compared to non-carriers. Specifically, $\epsilon 2$ carriers were faster at identifying the target item and then placed the chosen item more accurately at the remembered location. Importantly, this memory advantage was observed regardless of age of participants, with significant cognitive differences detectable even in young adults. These findings provide evidence for the influences of the *APOE* $\epsilon 2$ gene allele on cognition, which in turn can inform studies investigating cognitive biomarkers for AD in $\epsilon 4$ carriers. Traditionally, many studies have grouped the $\epsilon 2/\epsilon 3$ and $\epsilon 3/\epsilon 3$ genotypes into one “control” group to compare to the at-risk $\epsilon 4$ -carrier cohort [7,38–40]. However, as demonstrated here, due to the distinct nature of their cognitive profiles, collapsing these two groups could introduce unplanned variability. Differential inclusion of $\epsilon 2$ carriers may therefore have contributed to the inconsistencies reported in the *APOE* $\epsilon 4$ literature (e.g. 3,37–42).

Investigations on the effects of the $\epsilon 2$ allele on cognition have provided mixed results [18–29,43–45]. Our results complement and strengthen previous observations of superior memory performance in $\epsilon 2$ carriers in studies with far smaller samples [25]. For example, in an investigation of both immediate and delayed verbal memory, middle-aged and older $\epsilon 2$ carriers had better memory performance compared to non-carriers, who also experienced sharper decline in memory decay [18]. This effect remained significant even after controlling for the occurrence of cardiovascular disorders in all groups. Similarly, younger $\epsilon 2$ carriers have been shown to have advantageous effects in tasks of both short- and long-term memories previously [26]. However, it is important to note that the effect sizes in the present study are small. Therefore, even though there is a consistent influence of the *APOE* $\epsilon 2$ on performance, future attempts should identify the underlying biological mechanisms of these changes in cognition.

There are a number of possible explanations for better cognitive performance in $\epsilon 2$ carriers, though they remain speculative. First, there is evidence that $\epsilon 2$ carriers are more resistant to neurodegeneration, have more efficient clearance of amyloid from blood vessels [9,46], and are protected against neurofibrillary tangle formation [15,16]. Additionally, some studies have reported that *APOE* $\epsilon 2$ carriers have lower levels of hippocampal atrophy in old age [10]. However, such mechanisms may not fully explain the pattern of results in the current study, since the cognitive benefits of the *APOE* $\epsilon 2$ carriers were not restricted to older participants but also appeared in the younger participants. Our results suggest instead an alternative possibility, namely a phenotypic difference that is independent of side-effects of potential progression of pathology associated with age. Consistent with this view, larger hippocampal volumes have been reported in *APOE* $\epsilon 2$ carriers even in younger participants [11,12]. It will be interesting in future studies to investigate the possible link between the observed behavioural advantage and hippocampal size and functional integrity.

Our results contrast with a number of previous studies reporting no advantageous memory performance in $\epsilon 2$ carriers [12,27,28,30,31]. Many important factors may contribute to this discrepancy. To avoid the lack of power to detect genetic differences in small cohorts [25], we studied, to the best of our knowledge, one of the largest cohorts of $\epsilon 2$ carriers. Our task also brought a significantly more sensitive task of STM compared to traditional and commonly used neuropsychological measures of memory used in many of the previous studies [33]. Finally, previous investigations have each targeted different age groups, limiting

a. Oxford Memory Test

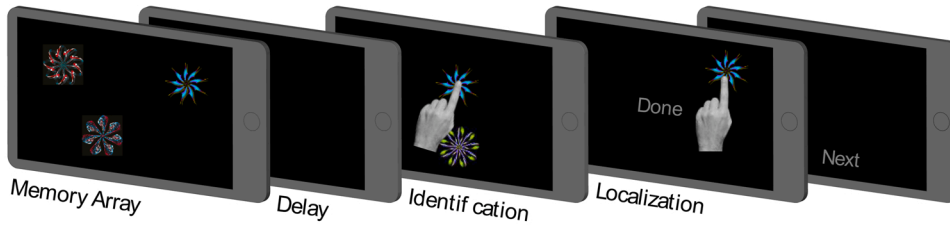
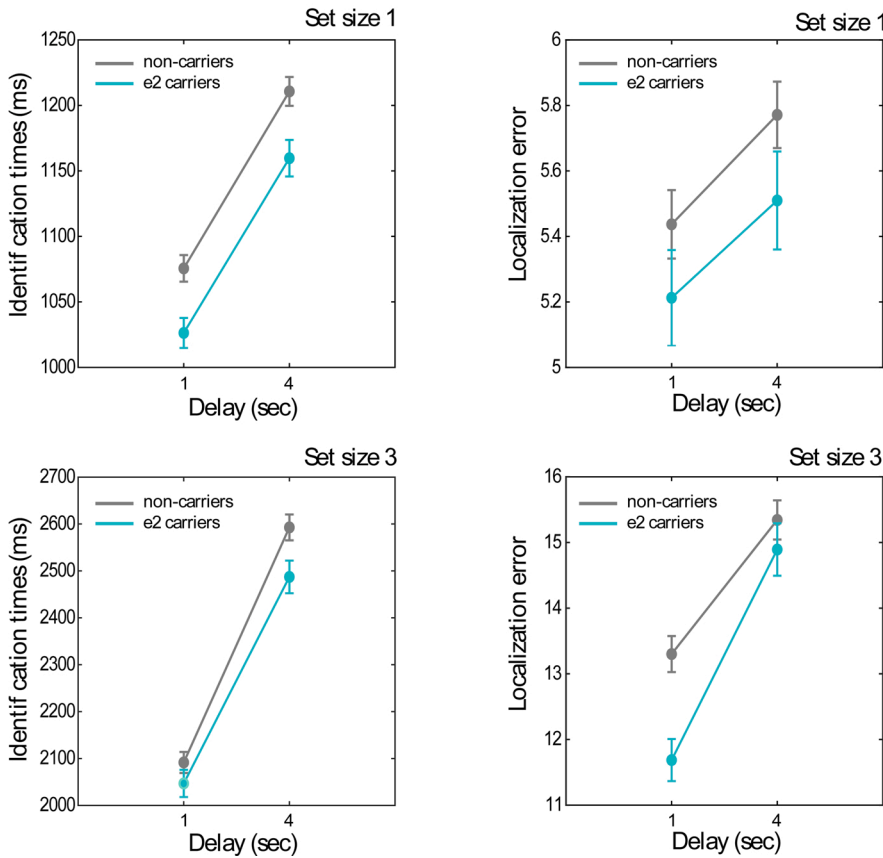


Fig. 1. Short-term memory task and performance in *APOE* $\epsilon 2/\epsilon 3$ and $\epsilon 3/\epsilon 3$ carriers. a) Schematic of the short-term-memory task delivered via the OMT app. b) Identification times – the time it took participants to select the target item at response – for memory set sizes 1 and 3. *APOE* $\epsilon 2/\epsilon 3$ carriers were significantly faster than non-carriers. c) Localization error – the distance between the reported location of the target and the true location of the item at memory array – for memory set sizes 1 and 3. Similarly, *APOE* $\epsilon 2/\epsilon 3$ carriers were significantly more precise than non-carriers.

b. Identification times

c. Localization error



the ability to generalise any findings across the age range. In this study, by using online testing, we were able to test participants across a wide age span (20 s to 70 s).

Previously we have shown that $\epsilon 4$ carriers can also demonstrate superior STM performance compared to $\epsilon 3/\epsilon 3$ carriers across the age range, using an identical task [2,3,34]. Crucially, this effect was, however, only observed for the shorter memory delays of 1 s, with higher forgetting rate compared to non-carriers in STM as well as worse LTM performance in the same individuals [2]. The advantage in very short-term memories in $\epsilon 4$ carriers was interpreted to reflect antagonistic pleiotropy effects of the *APOE* gene [47]. The overall beneficial memory performance in $\epsilon 2$ carriers, however, may be a phenotypical effect of the *APOE* $\epsilon 2$ allele on cognition arising as a secondary consequence of other biological changes associated with this allele, e.g. associated with vascular regulation [9]. Future research might profitably focus on understanding the link between physiological and cognitive changes associated with the *APOE* $\epsilon 2$ carriers. Specifically, a wider range of cognitive processes, beyond those examined here, should be

tested to provide a comprehensive cognitive landscape of *APOE* $\epsilon 2$ carriers, the relationship between processes and their link to physiological changes.

Together, the findings presented here provide evidence for beneficial effects of the *APOE* $\epsilon 2$ gene allele on memory in otherwise healthy participants, across ageing. To the best of our knowledge, this is one of the first studies to test memory in a large sample of participants, using a sensitive task, and including individuals across a large age span, overcoming possible shortcomings of previous investigations into the topic. Future research should aim to replicate these findings in the general population, limiting any possible selection biases that may have influenced the findings. Further, it would be important to identify the biological basis of such changes in cognition as a result of different variants of the *APOE* gene. Such considerations will be crucial in developing a thorough understanding of the protective vs. detrimental nature of different *APOE* alleles on neurodegeneration and brain health in general.

Table 2

Summary statistics on performance in the STM task for carriers and non-carriers of the *APOE ε2/ε3* gene allele in different age groups (significant values are highlighted in bold).

Effects	F-test	p-value	partial Eta ²
Identification Times			
Set Size	F(1,840) = 4594	<0.001	0.845
Delay	F(1,840) = 914	<0.001	0.521
Age Group	F(6,840) = 9.68	<0.001	0.065
APOE status	F(1,840) = 4.75	=0.03	0.006
Set Size x APOE status	F(1,840) = 0.136	=0.712	
Delay x APOE status	F(1,840) = 1.974	=0.16	
Set Size x Delay	F(1,840) = 339	<0.010	0.288
Delay x Age Group	F(6,840) = 1.39	=0.215	
Set Size x Age Group	F(6,840) = 3.51	=0.002	0.024
Set Size x Delay x Age Group	F(1,840) = 0.626	=0.710	
Set Size x Age Group x APOE status	F(6,840) = 1.67	=0.196	
Delay x Age Group x APOE status	F(6,840) = 0.665	=0.678	
Set Size x Delay x Age Group x APOE status	F(6,840) = 0.503	=0.806	
Identification Accuracy			
Set Size	F(1,840) = 1826	<0.001	0.68
Delay	F(1,840) = 40	<0.001	0.05
Age Group	F(6,840) = 4.9	<0.001	0.03
APOE status	F(1,840) = 0.23	=0.635	
Set Size x APOE status	F(1,840) = 0.125	=0.724	
Delay x APOE status	F(1,840) = 1.33	=0.25	
Set Size x Delay	F(1,840) = 6.73	=0.010	0.008
Delay x Age Group	F(6,840) = 1.83	=0.09	
Set Size x Age Group	F(6,840) = 5.85	<0.001	0.04
Set Size x Delay x Age Group	F(1,840) = 2.43	=0.024	0.017
Set Size x Age Group x APOE status	F(6,840) = 0.45	=0.845	
Delay x Age Group x APOE status	F(6,840) = 1.92	=0.166	
Set Size x Delay x Age Group x APOE status	F(6,840) = 0.983	=0.435	
Localization Error			
Set Size	F(1,840) = 1842	<0.001	0.68
Delay	F(1,840) = 109	<0.001	0.115
Age Group	F(6,840) = 7.71	<0.001	0.052
APOE status	F(1,840) = 5.9	=0.015	0.007
Set Size x APOE status	F(1,840) = 4.298	=0.038	0.005
Delay x APOE status	F(1,840) = 1.93	=0.31	
Set Size x Delay	F(1,840) = 66	<0.001	0.073
Delay x Age Group	F(6,840) = 1.93	=0.308	
Set Size x Age Group	F(6,840) = 4.71	<0.001	0.033
Set Size x Delay x Age Group	F(1,840) = 1.32	=0.247	0.009
Set Size x Age Group x APOE status	F(6,840) = 3.19	=0.074	
Delay x Age Group x APOE status	F(6,840) = 0.722	=0.632	
Set Size x Delay x Age Group x APOE status	F(6,840) = 1.058	=0.386	
Set Size 1			
Delay	F(1,840) = 50	<0.001	0.057
Age Group	F(6,840) = 3.5	=0.002	0.024
APOE status	F(1,840) = 1.85	=0.174	
Delay x APOE status	F(1,840) = 0.241	=0.624	
Delay x Age Group	F(6,840) = 0.406	=0.876	
Delay x Age Group x APOE status	F(6,840) = 1.12	=0.349	
Set Size 3			
Delay	F(1,840) = 89	<0.001	0.096
Age Group	F(6,840) = 7.29	<0.001	0.05
APOE status	F(1,840) = 6.02	=0.007	0.007
Delay x APOE status	F(1,840) = 2.96	=0.086	
Delay x Age Group	F(6,840) = 1.28	=0.264	
Delay x Age Group x APOE status	F(6,840) = 0.88	=0.508	

CRedit authorship contribution statement

Nahid Zokaei: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft. **Alexander G Board:** Data curation, Formal analysis, Writing - review & editing. **Ellie Slavkova:** Project administration, Data curation. **Clare E Mackay:** Supervision, Writing - review & editing. **Anna Christina Nobre:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Masud Husain:** Conceptualization, Funding acquisition, Supervision, Writing - review &

editing.

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