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When time's arrow doesn't bend: *APOE*-ε4 influences episodic memory before old age

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ABSTRACT

Episodic memory impairment is the hallmark symptom of Alzheimer's Disease (AD). However, episodic memory has also been shown to decline across the lifespan. Here, we investigated whether episodic memory is differentially affected relative to other cognitive abilities before old age, and whether being an Apolipoprotein E (*APOE)* ε4 carrier –a genetic risk factor for developing AD—exacerbates any such impairments. We used general linear models to test for performance differences within 4 composite measures of cognition - episodic memory, semantic memory, speed of processing, and fluid reasoning– as a function of age group (young, *M age* = 30.21 vs. middle-aged, *M age* = 50.84) and *APOE*-ε4 genotype status (ε4+ vs. ε4-). We replicated findings of age-related reductions in episodic memory, speed of processing, and fluid reasoning, and age-related increases in semantic memory. However, we also found that *APOE* genotype status moderated the age-related declines in episodic memory: *APOE*-ε4+ middle-aged adults exhibited impairments relative to both *APOE*-ε4- middle-aged participants, and *APOE*-ε4+ younger adults. These results suggest specific and dynamic alterations to episodic memory as a function of *APOE* allelic variation and age.

1. Introduction

Endel Tulving opened his seminal 2002 *Annual Review of Psychology* article by describing the nature of time as a straight, unidirectional arrow: "Galaxies and stars are born and they die, living creatures are young before they grow old, causes always precede effects, there is no return to yesterday". The one, remarkable exception arises because of a particular cognitive function: episodic memory. Episodic memory is a memory system that allows an individual to consciously retrieve past experienced items or episodes of life (Tulving, 1995). According to Tulving (2002), episodic memory requires a "sense of subjective time, autonoetic awareness, and self". These autobiographical, autonoetic, and highly contextualized recollections allow us to bend time's straight arrow to bring the past back into the present. A critical, and remarkable, extension of this is that we can also imagine or simulate possible futures (Tulving, 1985). Because of the role that episodic memory plays in shaping who we were, are, and will be, it is not surprising that Alzheimer's Disease (AD) is so devastating: The primary hallmark and earliest symptom of AD is episodic memory loss (McKhann et al., 2011).

While the causes of AD have not been fully elucidated, Apolipoprotein E (*APOE*)-ε4 is behind only age in imparting the greatest susceptibility for developing the disease (Raber, 2004; Strittmatter and Roses, 1996). *APOE* is a polymorphic gene, with three common alleles: ε2, ε3 and ε4 (Ghebranious et al., 2005). Being an ε4 carrier imparts an increased risk (and a markedly earlier age of onset) for AD in a dose-dependent fashion (Owen et al., 1994; Cacabelos, 2003): one copy of the ε4 allele (ε4-heterozygotic) imparts a 3-fold increased lifetime risk over non-carriers of being diagnosed with AD, while individuals homozygous for the ε4 allele are ten (Farrer et al., 1997) to sixteen (Bertram et al., 2007) times more likely to develop the disease than non-carriers. It is estimated that 91% of ε4 homozygotes will develop AD in the course of their lifetime (Corder et al., 1993).

Numerous studies have demonstrated that *APOE*-ε4 is associated with cognitive impairment in clinically-healthy as well as demented adults over the age of 60 (Hirono et al., 2003; Marra et al., 2004; Martins et al., 2005; Plassman and Breitner, 1996; Wisdom et al., 2011). A recent review by El Haj et al. (2016a) reported 14 studies that focused on episodic memory specifically, as a function of *APOE*-ε4 status, in older individuals diagnosed with AD. Of these, 11 studies reported a significant relationship between *APOE*-ε4 carriers and episodic memory decline or impairment, with a 12th study reporting the same pattern of results, but only in the early-onset AD patients.

However, normal age-related cognitive changes may begin long before so called "old age", with declines in cognitive processing,

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regional brain volume, myelin integrity, and cortical thickness reported from age 20 to 60 (Fjell et al., 2013; Liu et al., 2017; Salthouse, 2016). The model forwarded by Jack and colleagues of AD progression posits, based in part on longitudinal findings from Buchhave et al. (2012), that certain pathophysiological changes associated with AD –namely amyloid-β (Aβ) deposition as measured via cerebrospinal fluid Aβ42– can be seen 5–10 years before diagnosis (Jack et al., 2013). According to a recent review by Kanekiyo et al. (2014), *APOE*-ε4 contributes both independently, and in interaction with Aβ to drive AD pathology, and "regulates amyloid-β (Aβ) metabolism, aggregation and deposition …" in an isoform-dependent fashion: "compared to … *APOE*-ε2 or *APOE*-ε3, *APOE*-ε4 is either more likely to promote Aβ fibrillogenesis or less effective in preventing Aβ aggregation, or both" (p.8). *APOE*-ε4 has also been shown to influence tau pathogenesis, the other main pathological hallmark of AD, and to do so independently of amyloid-β pathology (Shi et al., 2017).

Despite the strong evidence linking AD, *APOE*-ε4 and episodic memory in late life (El Haj et al. (2016a,b), far fewer studies have investigated this relation, or indeed the relation between *APOE* allelic variation and any type of cognition, before old age. Of those that have, specific individual tasks, methods and approaches have been used, producing contradictory results, with some groups finding associations and other groups reporting null-effects. Lancaster et al. (2017) conducted a series of meta analyses of 36 published studies that investigated young and middle-age individuals' cognition, taxonomized into the following seven domains: global cognition, memory, executive abilities, verbal fluency, language, visuospatial processing, and processing speed. In none of their analyses did carrying an ε4 allele significantly attenuate performance. However, another, more recent review noted that nearly all of the studies to date assessing the relation between *APOE*-ε4 on cognition before old age have relied upon either individual or composite measures of traditional neuropsychological tests (O'Donoghue et al., 2018). The authors here note: "The neuropsychological measures used in most studies, whilst well-validated and quick to administer, typically lack the sensitivity to detect subtle variation in cognition and lack the specificity to measure variation in isolated cognitive processes. Neuropsychological tests therefore have limited use for investigating the direct effect of *APOE* on a cognitive phenotype in mid-adulthood samples". The use of more sensitive cognitive measurements, not designed for the purpose of diagnosing or dissociating manifest cognitive changes that occur in different neurological disorders and are typically associated with advanced age, along with the use of composite scores derived from several tests thought to tap a particular cognitive domain, may provide sufficient leverage to detect subtle cognitive changes in otherwise healthy adults before old age.

Fewer than a handful of studies have used more sensitive cognitive measures to explore cognition-*APOE* isoform associations before old age, and to our knowledge none have investigated what we, here, conjecture may be a selective impact of *APOE*-ε4 on episodic memory. Greenwood et al. (2000) investigated attentional processes in a sample of healthy, non-demented ε4 homozygotes (*M age* = 58 years) and found reduced efficacy in visuo-spatial attentional processes. Using these same tasks in a larger sample, Greenwood et al. (2005) showed that the effect is *APOE*-ε4 dose-dependent (the more ε4 alleles, the greater the deficit). Furthermore, they extended the results to a spatially-cued letter discrimination task, and showed a dose-dependent deficit there also. Korthauer et al. (2018) recently compared performance of middle-aged (*M age* = 49.9 years) carriers and non-carriers of *APOE* (along with several other AD risk alleles) on three paradigms translated from animal models that have been associated with either medial temporal lobe or prefrontal cortex function, including the Morris Water Task, the Transverse Patterning Discriminations Task and a reversal learning task. While the *APOE*-ε4 carrying participants in their study performed significantly worse, this result did not survive correction for multiple comparisons, leading the authors to conclude that these risk alleles (including minor alleles of *APOE, TOMM40, BDNF,* and *KIBRA)* "provide potential candidates for future replication studies". Zokaei et al (2017) recently examined working memory performance in a sample 40–50 year old ε4 carrying and non-carrying adults. They found enhanced memory function in the male (but not female) ε4-carriers. They attributed this to a midlife extension of "antagonistic pleiotropy" (Williams, 1957), a theory put forth to explain the perseverance of rare genetic disorders in the population under which mutation-carriers exhibit cognitive advantages in early life, but impairments in later life (Jochemsen, Muller, van der Graaf and Geerlings, 2012). However, antagonistic pleiotropy for *APOE*-ε4 carriers is more typically reported in early, and not mid-life (Bloss et al., 2010; Mondadori et al., 2007; Rusted et al., 2013; Wright et al., 2013). Contradicting these working memory findings, Greenwood et al (2014) reported that older, but not middle-aged ε4 carriers had reduced working memory performance relative to non-carriers. Thus, the few results that exist on this issue are not easily interpretable.

In the current study, younger and midlife participants performed 12 computerized cognitive tasks that have been previously shown in studies of several thousand adults across the adult lifespan to represent the key underlying cognitive demands of most tasks (Salthouse, Atkinson and Berish, 2003; Salthouse, Schroeder and Ferrer, 2004), and to factor into four latent cognitive variables: episodic memory, speed of processing, fluid reasoning and semantic memory (Habeck et al., 2016; Stern et al., 2014). Whereas episodic memory, speed of processing and fluid reasoning are thought to decline across the lifespan, semantic memory has been shown to remain stable or even increase with age (Brickman and Stern, 2009). The use of composite measures, which are arguably more sensitive with respect to the underlying core cognitive constructs of concern here than are individual tasks because they are both less affected by ceiling and floor effects of any one task, and they avoid the idiosyncrasies of a particular task, thus allows us to address questions about robust and reliable constructs, and enables us to systematically explore how *APOE*-ε4 influences patterns of cognitive change in clinically-healthy adults before old age in a novel and powerful way. Specifically, we investigated here whether *APOE*-ε4 impairs episodic memory or any other type of cognitive processes before old age, and if any such effects on cognition occur above and beyond "normal" age-related changes.

2. Methods

2.1. Participants

Data from an ongoing study investigating age-related changes to cognition and the brain across the lifespan were used for the current investigation. Participants were recruited to the study through random mass market mailings targeting individuals living within 10 miles of the Columbia University Medical Center (CUMC), which includes an area encompassing all of New York City as well as portions of Westchester and Rockland Counties in New York, and Hudson, Bergen, Essex and Union Counties in New Jersey. All participants reported that they were fluent English speakers and had at least a fourth-grade reading level. To be eligible to participate, performance was required to be within age-adjusted normal limits on a list-learning test, and participants were required to have no or minimal complaints on a functional impairment questionnaire (Roth et al., 1968). Medical, neurological, psychiatric, and neuropsychological evaluations were conducted on every participant to ensure that they had no neurological or psychiatric disease or cognitive impairment. The screening procedure included a detailed interview that excluded individuals with a self-reported history of major-or unstable medical illness, hypertension, neurological history (e.g., epilepsy, brain tumor, and stroke), history of brain trauma, history of diagnosis of an Axis I psychiatric disorder, as well as screening for dementia or Mild Cognitive Impairment. Individuals taking psychotropic medications, and those participants who scored below 135 on

the Mattis Dementia Rating Scale (Mattis, 1988), were excluded prior to participation. Written informed consent, approved by the CUMC ethics review board, was obtained from all participants.

Two hundred and seventy-three young and midlife participants (aged 20–60) had completed the cognitive tests, described in detail below, at the time data analysis began. Of these, the *APOE* genotype data from 72 younger adults and 74 middle-aged adults who had consented to provide blood samples for genetic testing were available. The evaluations, described above, as well as the blood draw for genetic testing took place in a dedicated testing room in the Department of Neurology at CUMC. A research assistant certified in phlebotomy used two 10 cc lavender top tubes to collect blood samples. Participants were not given access to their samples, nor did they receive any feedback about the results of their blood tests. The SNPs rs7412 and rs429358 in *APOE* (gene map locus 19q13.2) were genotyped with KASPar® PCR SNP genotyping system (LGC Genomics, Hoddesdon, Herts, UK). Genotype-data for these two SNPs were used to unambiguously define ε2, ε3, and ε4 alleles. The genotyping success rate was > 95%. *APOE* genotypes were transformed into a dichotomous trait based on the number of *APOE*-ε4 alleles: ε4 non-carriers ("ε4-", either ε2/ε3 or ε3/ε3), or ε4 carriers ("ε4+", either ε2/ε4, ε3/ε4 or ε4/ε4). There were no differences as a function of *APOE* status on years of education ($t(144) = -1.21$, $p = .227$), National Adult Reading Test (NART (Nelson, 1982) ($t(142) < 1$) or Wechsler Test of Adult Reading (WTAR) ($t(142) < 1$), indicating that the groups were comparable on long-standing stable traits of intelligence. There was also no gender difference between *APOE* carriers and non-carriers ($t(142) < 1$). Likewise, there was no difference as a function of Age Group on years of education ($t(144) < 1$), NART ($t(142) = -1.94$, $p = .054$) or WTAR ($t(142) < 1$. However, there was a significantly higher proportion of women in the younger group than in the middle-aged group ($t(144) = 2.58$, $p = .01$). Complete demographic information for the sample is shown in Table 1

2.2. Design

Participants performed 12 computerized cognitive tasks, described in detail below, over the course of two, 2-h functional magnetic resonance imaging (MRI) scanning sessions. One session presented three episodic memory tasks (narrative memory, word order recognition and cued recognition) and three fluid reasoning tasks (paper folding, matrix reasoning and letter sets), interspersed in a fixed order. The other session presented three semantic memory tasks (synonyms, antonyms and picture naming) and three speed of processing tasks (digit symbol, letter comparison, pattern comparison), interspersed in a fixed order. The order of the two sessions was counterbalanced across participants, with equal numbers having each order. Task stimuli were back-projected onto a screen located at the foot of the MRI bed using an LCD projector. Participants viewed the screen via a mirror system located in the head coil. Participants had vision corrected to normal using MR compatible glasses (manufactured by SafeVision, LLC. Webster Groves, MO), if needed. All cognitive tasks except picture naming required multiple-choice responses, made on a LUMItouch response system (Photon Control Company). For picture naming, participants spoke their answer out loud and their responses were recorded and later scored.

2.3. Cognitive task descriptions

Episodic Memory. A key feature of episodic memories is that they have to do with not only what happened, but when, why, where, and to whom an event occurred. Tulving (2002) notes that, until relatively recently, the majority of memory research has dealt with only the "what" aspect, for example by giving participants a list to remember and asking them to recall as many words as possible. The current set of tasks required memory not only for the "what" aspect, but also for these other contextual details that make a memory truly episodic as opposed to semantic.

Narrative Memory: This task required participants to read and then answer questions about specific details from two short stories. The first story read: "Anna Thompson of South Boston, employed as a cook in a school cafeteria, reported at the police station that she had been held up on State Street the night before and robbed of fifty-six dollars.//She had four small children, the rent was due, and they had not eaten for two days.//The police, touched by the woman's story, took up a collection for her." The second story read: "At 6:00 on Monday evening, Joe Garcia of San Francisco was watching television as he dressed to go out.//A weather bulletin interrupted the program to warn that thunderstorms would move into the area within the next 2–3 h and remain until morning. The announcer said the storm could bring hail and bring up to 4 inches of rain and cause the temperature to drop by 15°.//Joe decided to stay home. He took off his coat and sat down to watch old movies." Each story was divided into three 1 to 2 sentence sections (shown above with "//"), with each section displayed for 10 s. Participants answered 10 detailed multiple-choice questions, presented for 10 s each, about the story relating to what, where, when and why events in the story occured (e.g. "What type of work did she do?" "When did it happen?" "How much did the temperature drop?"), along with names and details about characters in the story (e.g., "How many children did she have?", "What was his last name?"), with four possible answer choices. The task was 7 min long.

Cued Recognition: In this task, six pairs of unrelated words were presented on the screen, one pair at a time, for 2 s each. Participants were instructed to remember the pairs. Following the pairs, they were given a probe word at the top of the screen and four additional word choices below. Participants were asked to choose the word that was paired with the probe word. One choice was the correct word, two choices were words from other presented pairs (lures), and the final choice was a novel word. The probe and choices were presented for 5 s. The task contained two lists of pairs, with six probe questions in each list. The task lasted a total of 3 min and 24 s.

Word Order Recognition: Participants were instructed to remember the specific temporal order in which twelve unrelated words were presented. Each word was presented on the screen for 4 s. At test, participants were given a probe word at the top of the screen, and four word choices below. Participants were instructed to select from the choices the word that had immediately followed the probe word in the

Table 1
Participant demographics.

	N	Age	(SD)	% Female	Years Education	(SD)	NART[a]	(SD)	WTAR[a]	(SD)
Young	**72**	**30.21**	**(5.34)**	**68**	**15.85**	**(2.41)**	**112.64**	**(8.46)**	**105.93**	**(15.44)**
ε4-	55	29.75	(5.73)	65	15.64	(2.19)	112.05	(8.05)	105.21	(14.98)
ε4+	17	31.71	(3.58)	76	16.53	(2.98)	114.46	(9.69)	108.18	(17.07)
Midlife	**74**	**50.84**	**(5.48)**	**47**	**15.51**	**(2.22)**	**115.43**	**(8.77)**	**107.70**	**(14.13)**
E4-	55	50.18	(5.45)	47	15.45	(2.08)	116.72	(8.29)	109.69	(13.08)
ε4+	19	52.74	(5.27)	47	15.68	(2.63)	111.69	(9.27)	101.95	(15.79)

[a] National Adult Reading Test.
[a] Wechsler Test of Adult Reading.

Table 2
Averaged Z-scores for four cognitive domains.

	Episodic Memory	(SD)	Semantic Memory	(SD)	Fluid Reasoning	(SD)	Speed of Processing	(SD)
Young	**0.38**	**(0.77)**	**−0.42**	**(0.88)**	**0.41**	**(0.86)**	**0.53**	**(0.77)**
ε4-	0.33	(0.79)	−0.46	(0.82)	0.39	(0.89)	0.51	(0.81)
ε4+	0.52	(0.69)	−0.29	(1.04)	0.47	(0.78)	0.56	(0.68)
Midlife	**0.01**	**(0.66)**	**0.12**	**(0.84)**	**−0.05**	**(0.87)**	**−0.01**	**(0.70)**
ε4-	0.13	(0.58)	0.17	(0.88)	0.06	(0.88)	0.07	(0.72)
ε4+	−0.31	(0.78)	−0.04	(0.72)	−0.34	(0.79)	−0.25	(0.59)

list. The task had two word lists, with ten questions following each list. Each probe was presented for 6 s. The total task duration was 7 min 2 s.

Semantic Memory. Tulving defined semantic memory as a memory system for "words and verbal symbols, their meanings and referents, the relations between them, and the rules, formulas, or algorithms for influencing them." (Tulving, 1972). The three tasks used in the current study indexed participants verbal knowledge, and thus are reflective of semantic memory as defined by Tulving.

Synonyms (Salthouse, 1993a,b). Participants completed 15 trials in which a capitalized probe word was presented at the top of the screen, with four numbered choices below. Participants were instructed to match the probe word to its synonym or to the word most similar in meaning as quickly and accurately as possible. Each item was presented for 13.5 s. The total task was 6 min and 26 s long, with 3 items in each of 5 blocks for a total of 15 items.

Antonyms (T. A. Salthouse, 1993a,b). This task was identical to the Synonyms task, except participants were instructed to match the probe word to its antonym.

Picture Naming (Woodcock et al., 1989): In this task, participants were presented with 40 color bitmap images of unrelated items (e.g., a chainsaw, a sand dollar, a helicopter, a unicycle) and were told to identify it by recalling its name. The task consisting of five 40 s blocks, with 8 stimuli in each block. Each stimulus was presented for 4.5 s. The task was 6 min and 16 s long.

Speed of Processing. Processing speed was assessed in the current study via three measures of perceptual speed. According to Salthouse (2000), perceptual speed tasks deal with "simple content in which everyone would be perfect if there were no time limits. Perceptual speed tasks often involve elementary comparison, search, and substitution operations …".

*Digit Symbo*l: A code table was presented on the top of the screen, consisting of the numbers 1–9, each paired with an associated symbol. Below the code table an individual number/symbol pair probe was presented. Participants were instructed to indicate whether each of 90 individual pairs was the same as that in the code table using a differential button press. Participants were instructed to respond as quickly and accurately as possible. The task was 7 min and 4 s long, consisting of 5 blocks, with 18 items in each block, presented for 2.5 s each.

Letter Comparison (Salthouse, 1993a,b): Participants were instructed to indicate whether two 3–5 letter strings, presented alongside one another, were the same or different. There were 60 total trials. The task, which contained five 42 s blocks, lasted a total of 6 min and 26 s. Each block consisted of 12 items, each presented for 3 s.

Pattern Comparison (Salthouse, 1993a,b): This task was identical to the Letter Comparison task, except participants were instructed to indicate whether two figures, consisting of varying numbers of lines connecting at different angles, presented alongside one another, were the same or different.

Fluid Reasoning. The three fluid reasoning tasks are thought to index general intelligence (Gf), or the ability to "the ability to generate, transform, and manipulate different types of novel information in real time" (Zaval et al., 2015).

Paper Folding (Ekstrom et al., 1976): Participants were shown a pictorial representation a piece of paper being folded, through which a hole was punched in the last image in the sequence. Participants had to decide which of 5 options represented the pattern of holes if the paper was unfolded. The task was 14 min and 26 s long. Each stimulus stayed on screen for between 11 and 85 s depending upon when a response was made. The minimum and maximum number of trials presented was 7 and 18, depending on each participant's response times.

Matrix Reasoning (adapted from Raven, 1962): Participants were given a matrix of abstract figures, divided into nine cells, in which the figure in the bottom right cell was missing. Below the matrix, they were given eight figure choices, and were instructed to choose which of the figures would best complete the missing cell. The task timing was identical to that of the Paper Folding task.

Letter Sets (Ekstrom et al., 1976): Participants were presented with five sets of letters, where four out of the five sets had a common rule (e.g. no vowels), with one of the sets not following this rule. Participants selected the unique set. The timing was identical to that of the Paper Folding task.

2.4. Statistical analyses

Z-scores were computed for the twelve tasks measures, based on the entire study cohort, which included participants age 18–80, with and without *APOE* genotype measures (see Table 2). The composite scores for episodic memory, fluid reasoning, and semantic memory were created using the proportion of correct trials for each participant, for each task, omitting trials on where participants did not respond. The speed score was based upon the median reaction time for correct trials. Univariate ANOVAs were conducted separately for each measure's composite score. A follow-up exploratory analysis was conducted on the raw accuracy measures from each of the 3 episodic memory tasks. For all measures, a positive score indicates better performance (the speed score was reverse scored so that a higher value indicates better performance). Statistical analyses were performed using SPSS 25 (SPSS, Chicago, Illinois). Nominally significant p values were defined as $p < .05$.

3. Results

Univariate ANOVAs were carried out for each of the four compsosite scores: episodic memory, fluid reasoning, speed of processing and semantic memory.[1] We found significant main effects of Age Group (younger vs. middle-aged) for all four cognitive domains. The middle-aged adults performed worse than the younger adults on episodic memory ($F(1, 135) = 6.865$, $p < .001$, $\eta_p^2 = 0.093$), speed of processing ($F(1, 129) = 18.127$, $p < .001$, $\eta_p^2 = 0.123$), and fluid reasoning ($F(1, 137) = 11.431$, $p = .001$, $\eta_p^2 = 0.077$), and younger adults performed worse than the middle-aged adults on semantic memory ($F(1, 139) = 6.873$, $p = .01$, $\eta_p^2 = 0.047$), replicating previous work. There were no main effects of *APOE* genetic status (ε4-vs. ε4+) in any of the models (all $Fs \leq 1$). Further, we did not find a significant interaction between *APOE*-ε4 burden and Age Group for fluid reasoning ($F(1, 137) = 2.066$, $p = .153$), speed of processing ($F(1, 129) = 1.513$,

[1] Differences in degrees of freedom are due to missing data in domain scores across participants.

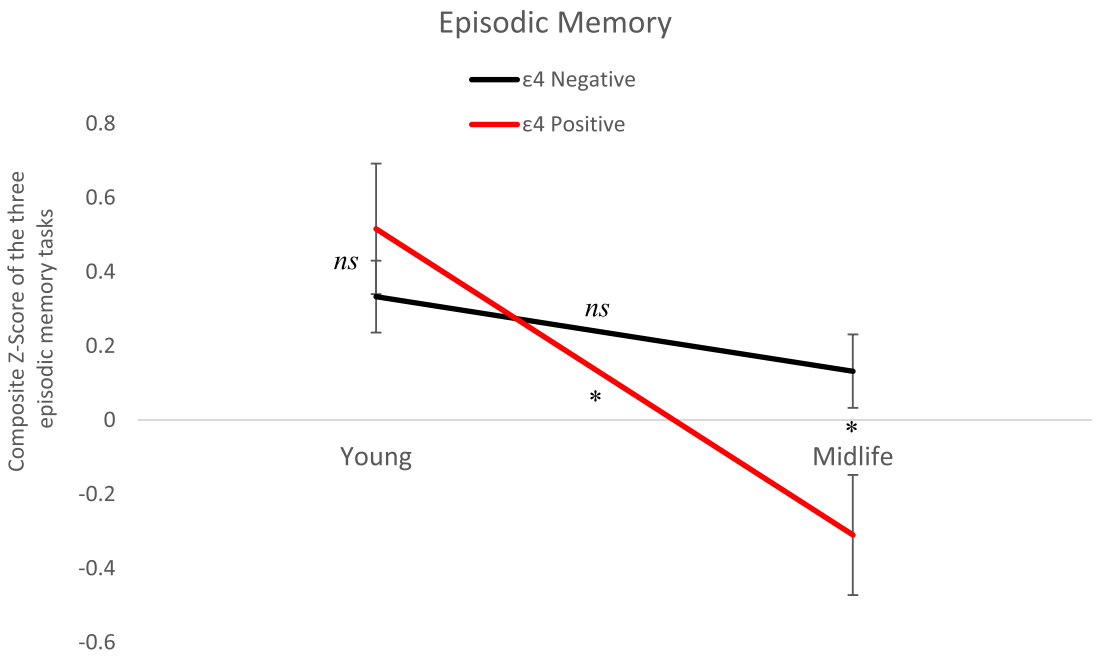


Fig. 1. The main effect of Age Group on episodic memory performance was qualified by a significant interaction between Age Group and *APOE*-ε4 genotype status. Post-hoc tests reveal no significant difference between episodic memory performance for young versus middle age ε4 negative participants, or between young ε4- versus young ε4+ participants. However, there was a significant difference in performance between midlife ε4 carrying participants and middle-aged ε4 non-carrying participants, as well as between ε4 positive younger versus ε4 positive middle-aged participants. *p < .05. *ns* = not significant. Error bars indicate standard error of the mean.

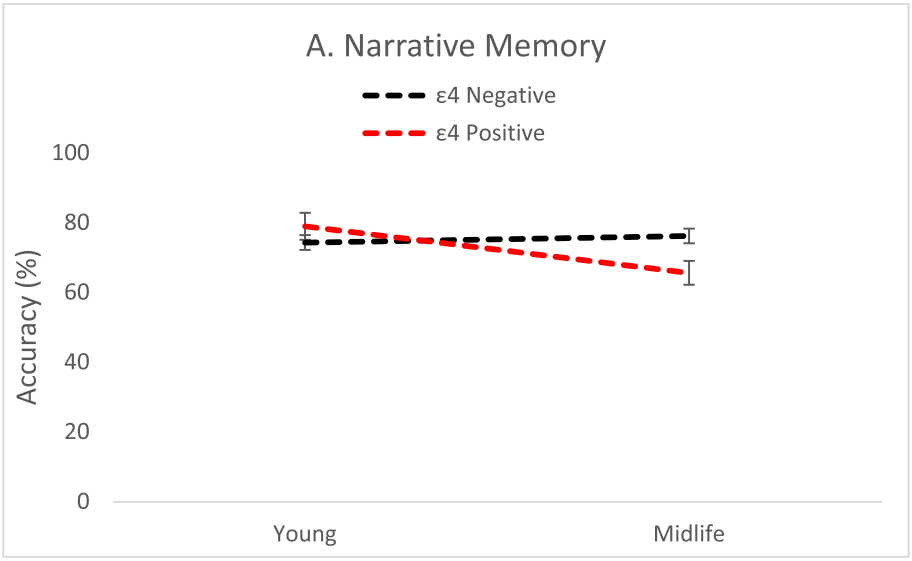
$p = .221$) or semantic memory ($F(1, 139) = 1.250$, $p = .266$).

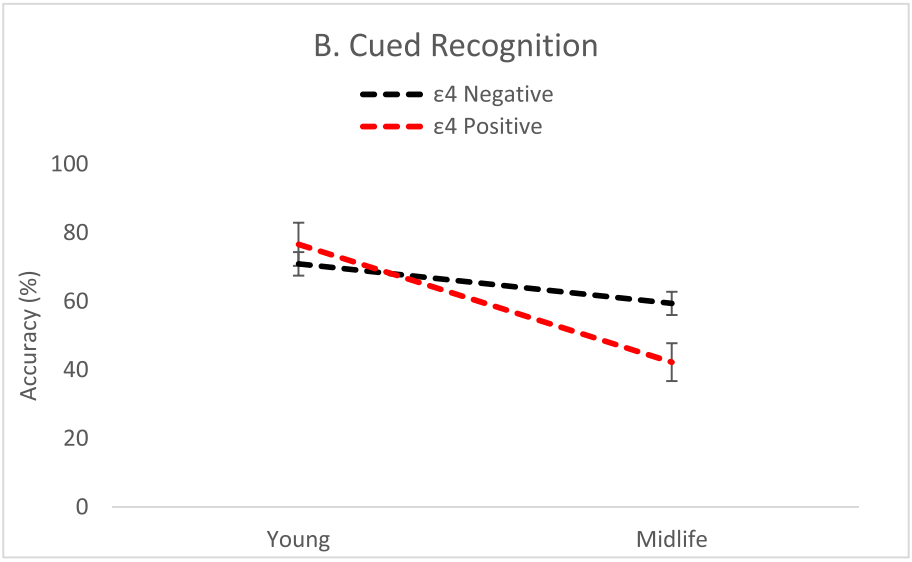
However, for episodic memory, there was a significant interaction between *APOE*-ε4 genotype and Age Group, ($F(1, 135) = 5.139$, $p = .025$, $\eta_p^2 = 0.037$). To interrogate the locus of this interaction, post-hoc t-tests were performed. The difference in episodic memory performance between *APOE* carriers and non-carriers in the younger adult group was not significant ($t(67) = -0.838$, $p = .405$). However, there was a significant difference in performance as a function of *APOE*-ε4 status in the middle-age group ($t(68) = 2.59$, $p = .012$), such that the ε4 middle-aged carriers performed worse than their ε4-non-carrying counterparts. Further, there was no difference in performance on the episodic memory measure between younger non-carriers and middle-aged non-carriers ($t(102) = 1.47$, $p = .144$). However,there was a significant difference in performance between younger and middle-aged ε4-carrying adults ($t(33) = 3.293$, $p = .002$), such that the ε4+ middle aged adults performed significantly worse ($M = -0.31$, SD = 0.78) than did their ε4+ younger counterparts ($M = 0.516$, SD = 0.62). These results are illustrated in Fig. 1.

To explore whether this effect derived from one particular task, we probed the relationship between *APOE* and Age Group within each of the three episodic memory tasks that made up the composite measure, tested above, using the raw accuracy scores as the dependent variable. As can be seen in Fig. 2 (panels A and B), for both the Narrative Memory and Cued Recognition tests, univariate ANOVAs revealed significant interactions between *APOE* and Age Group, in the same direction as the composite episodic memory score ($F(1, 123) = 6.565$, $p = .012$, $\eta_p^2 = 0.051$ and $F(1, 123) = 5.587$, $p = .02$, $\eta_p^2 = 0.043$, respectively). As with the composite measure, the differences between ε4-carrying and non-carrying younger adults in Narrative Memory and Cued Recognition was not significant ($t(59 = -1.078$, $p = .285$ and $t(49) = -0.770$, $p = .445$, respectively). However, for the middle-aged adults, accuracy was significantly higher for ε4-relative to ε4+ participants on both tasks: ($t(64) = 2.604$, $p = .011$ and $t(64) = 2.731$, $p = .008$, respectively). When splitting by carrier status, accuracy on the Narrative Memory test was not significantly different between young *APOE*-ε4 non-carriers and middle-aged *APOE*-ε4 non-carriers ($t(93) = -0.665$, $p = .508$). However, Age Group did significantly affect accuracy in the Cued Recognition task for the non-carriers: the middle-aged non-carriers performed significantly more poorly than did their non ε4-carrying younger counterparts ($t(93) = 2.275$, $p = .025$). For the *APOE*-ε4+ individuals, accuracy on both the Narrative Memory and Cued Recognition task was worse for the middle-aged adults compared to the younger adults: $t(30) = -2.305$, $p = .028$ and $t(30) = -5.005$, $p < .001$, respectively. We found no significant effect of *APOE* and Age Group on the Word Order Recognition test. As can be seen in Fig. 2 (panel C), this may be due to performance as a whole being low on this test. Thus, any effects of *APOE* may be masked by a floor effect due to the overall difficulty of this task. Overall, these results suggest that the Cued Recognition and Narrative Memory measures may be particularly sensitive to the effects of *APOE*-ε4 in midlife.

4. Discussion

Within the cognitive aging literature, it is argued that age-related cognitive decline begins long before so-called “old age” (Salthouse, 2004). Our results, however, suggest an important role for genetics that qualifies these findings. *APOE* allelic variation did not significantly moderate age related differences in fluid reasoning, processing speed or semantic memory. However, *APOE* status did moderate the typically seen age-related deficits in episodic memory. Here, differences between younger and middle-aged adults were found in ε4 carrying adults, between both middle-aged ε4 carrying participants and middle-aged ε4 non-carrying participants, and between ε4 positive younger versus ε4 positive middle-aged participants. When the episodic memory composite score was probed, such age-related differences were absent in the non ε4-carrying adults. Interestingly, exploratory analyses of the three individual tests that comprised the episodic memory composite score revealed the same pattern of results for the Narrative Memory test, but





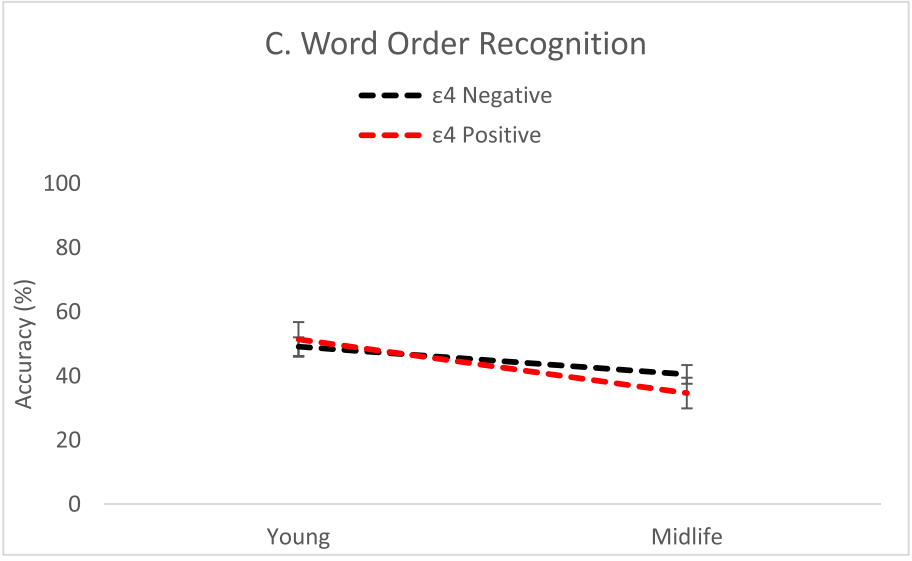


Fig. 2. Raw accuracy scores for the three episodic memory tests as a function of Age Group and *APOE* status. **A**. Narrative Memory. There was a significant interaction between *APOE* and Age Group. Post hoc tests showed no significant difference between ε4-carrying and non-carrying younger adults, but a significant difference between ε4-carrying and non-carrying midlife adults, such that the carriers performed worse. There was also no significant difference between young *APOE*-ε4 non-carriers and middle-aged *APOE*-ε4 non-carriers. However, there was a significant difference between young ε4+ and midlife ε4+ participants, such that the middle-aged participants performed worse. **B**. Cued Recognition. There was a significant interaction between *APOE* and Age Group. Post hoc tests showed no significant difference between ε4-carrying and non-carrying younger adults, but a significant difference between ε4-carrying and non-carrying midlife adults, such that the middle-aged carriers performed worse. The differences between young and middle-aged *APOE*-ε4 non-carriers, and between young and middle-aged *APOE*-ε4 carriers, were both significant. In both cases, the middle-aged participants performed worse. **C.** Word Order Recognition. The interaction between *APOE* and Age Group was not significant. Error bars indicate standard error of the mean.

an age effect for ε4-non carriers on the Cued Recognition test. Thus, for the Narrative Memory test, ε4 appears to drive age-related declines in memory, whereas for the Cued Recognition test, carrying the *APOE*-ε4 allele seems to exacerbate age-related effects, as well as potentially contribute to these supposed age effects.

Since age represents the highest risk factor for AD (Evans et al., 1989) it is possible that the finding of an episodic memory deficit in the ε4 allele carrying middle-aged group, but not in their non-carrying counterparts, may be an artefact of a higher proportion of undiagnosed or prodromal AD cases (Greenwood et al., 2005; Smith et al., 1998). Although the typical age of AD onset is well beyond the average age of our middle-aged group, AD onset has been shown to be highly influenced by *APOE* allelic variation: A large community-based study of incident dementia in cognitively healthy participants (aged > 45 years) reported both a "18–29 year difference in age at onset for Alzheimer's disease and an 18–23 year difference in age at onset dementia" for *APOE*-ε4 carriers in the high-risk tertial of a polygenetic risk score of 23 Alzheimer's disease-associated genetic variants (Lee et al., 2018). Another study reported that for non-ε4 allele carriers, the average age of diagnosis is 84.3, but for ε4/ε4 individuals, AD onset drops to 68.4 years (Corder et al., 1993).

Further, *APOE*-ε4 has been shown to interact with certain clinical risk factors to influence cognition, and has been associated with abnormal neural signatures, both early and later in life. Nishtala et al. (2015), in a longitudinal study of 50–60 years old participants, reported a significant interaction between *APOE*-ε4 and systolic blood pressure, such that blood pressure was negatively associated with the Controlled Word Association Test only in the ε4 carriers. In a group of 50–65 year old HIV^+ men, *APOE*-ε4 and elevated cholesterol were also found to be significant risk factors for cognitive decline, measured by a battery of 15 neuropsychological tests (Mukerji et al., 2016). Filippini et al. (2011) found that while non ε4-carrying middle-aged and older adults (ranging from 50 to 78 years) showed increased fMRI-measured neural activity in an encoding-based memory task compared with younger (20–35 years) participants, ε4-carrying middle-aged and older adults showed decreased activity, suggesting a failure to recruit age-related compensatory mechanisms. Dennis et al. (2010) and Filippini et al. (2009) both reported that younger *APOE*-ε4 carrying adults exhibited greater fMRI related brain activations during a memory task. Using positron-emission tomography, Reiman et al. (1996) reported reduced hippocampal volume in cognitively normal middle-aged (50–65 years) ε4 carrying adults, along with abnormally low cerebral metabolic rates for glucose in both posterior cingulate, parietal, temporal, and prefrontal regions (regions in which AD patients also show reductions in metabolism), and longitudinally measured faster rates of decline in metabolism in these regions. Based on these results, Evans et al. (2014) put forth the idea that increased brain activity seen in the younger ε4 carrying adults might cause neurophysiological changes that accelerate the later declines in brain function seen in ε4 carrying middle-aged and older adults.

Given that even neuropsychological tests have detected cognitive decline 5 (Wilson, Leurgans, Boyle and Bennett, 2011) to 10 (Amieva et al., 2008) years in advance of AD-diagnosis, and that AD onset has been shown to occur at a much earlier age in *APOE* ε4 carrying individuals, it is possible that the measures used in the current study were sensitive enough to detect subtle variation in cognition even in midlife in these individuals. The middle-aged ε4+ may thus represent a selective sampling of individuals in a preclinical phase of as-yet undetected dementia, in whom episodic memory impairments, when measured with more sensitive composite measures like the Narrative Memory and Cued Recognition tests used in the current study, are becoming apparent (Wilson, Leurgans, Boyle and Bennett, 2011).

Our results argue for a specific role for *APOE* allelic variation in episodic memory performance over and above normal age-related changes to this cognitive ability. According to Davignon et al. (1988), within a USA based sample of healthy adults aged 22–71, the relative frequency of the ε4 allele is 0.135, a number that does not change when a younger subset (age 22–44) is calculated (*M* males = 0.121, *M* females = 0.0142). Thus, given that the ε4 allele is not uncommon, it is possible that typical findings of declines in episodic memory before old age may be both exaggerated by ε4 carrying individuals within these study samples, and reflective of processes that are associated with a prodromal phase of AD, rather than normal age-related cognitive changes.

4.1. Limitations

Whereas the percentage of ε4+ individuals in our sample was larger than the hypothesized percentage in the general population, and our sample as a whole was relatively large, only ~25% of participants were *APOE*-ε4 carriers, resulting in a relatively small sample *APOE*-ε4 carrying individuals. Several drawbacks arise from this. First, the study was not powered to test for interaction effects between *APOE*-ε4 status and cognition within narrower age-bands, or to test for *APOE*-ε4 dose-dependent effects on different types of cognitive processes, and their interaction with age. Second, it is possible that the null effects reported for semantic memory, speed of processing and fluid reasoning could be due to a Type II error. Future replication studies that include larger numbers of *APOE*-ε4 carrying participants could help shed light on these possibilities and refine the findings.

4.2. Conclusion

Identifying genetic risk factors that modulate cognitive patterns of behavior is critical not only for classifying individuals most likely to develop neurodegenerative diseases like AD, but also for understanding trajectories of age-related cognitive change across the lifespan. While previously reported *APOE*-ε4 related cognitive differences in middle-aged participants are mixed—with some studies showing impairments and some studies showing no differences, our use of sensitive cognitive measures allowed us to identify differences in episodic memory as a function of age group and ε4 variation. Our results support for the idea that the ε4 allele of the *APOE* gene contributes to changes to episodic memory starting in midlife, and suggests that the general decline in episodic memory seen in many studies may be influenced by this one subgroup, insofar as the non-carriers showed little to any age-related deficit.

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