Prospective memory: age related change is influenced by APOE genotype

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Dr. Claire Lancaster[1]
School of Psychology, University of Sussex, Brighton, East Sussex, BN1 9QG
(+44) 1865 783493
Claire.lancaster@bdi.ox.ac.uk

Prof. Mark A. McDaniel
Department of Psychological and Brain Sciences, Washington University, St Louis
314 935-8030
Markmcdaniel@wustl.edu

Dr. Naji Tabet
Brighton and Sussex Medical School, Centre for Dementia Studies, Brighton, East Sussex, BN1 9PH
(+44) 1273 644503
N.Tabet@bsms.ac.uk

Prof. Jennifer Rusted
School of Psychology, University of Sussex, Brighton, East Sussex, BN1 9QG
(+44) 1273 678325
J.rusted@sussex.ac.uk

Corresponding author: Claire Lancaster

[1] *Current affiliation:* Big Data Institute, University of Oxford, Oxford, OX3 7FZ

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Abstract

Non-focal prospective memory (PM) is sensitive to age-related decline; an additional impairment in focal PM is characteristic of mild stage Alzheimer's disease. This research explored whether, by mid-adulthood, the distinct demands of focal and non-focal PM expose differences in carriers of an *APOE* ε4 allele, a genetic risk factor for Alzheimer's disease. Thirty-three young and 55 mid-age adults, differentiated by *APOE* genotype, completed a category-decision task with a concurrent focal or non-focal PM demand. Only mid-age ε4 carriers showed a cost of carrying a focal PM intention. In addition, mid-age ε4 carriers showed a significantly greater cost of carrying a non-focal PM intention than young ε4 carriers, supporting a profile of accelerated aging. Consistency in the profile of cost differences observed in mid-age ε4 carriers and pathological aging may indicate premature vulnerability. Future research correlating a shift in PM performance with early genotype differences in brain-based markers of decline is important.

Keywords: *APOE*, Prospective memory, Aging, Alzheimer's disease, Mid-adulthood

1. Introduction

Prospective memory (PM) refers to the timely recall of a previously formed intention whilst being engaged in ongoing cognitive activity. Importantly, what distinguishes PM from retrospective memory is that retrieval of the intention is self-initiated (McDaniel et al., 2015), and hence it relies on a somewhat different subset of cognitive processes. Each day includes numerous examples of PM, such as remembering to buy milk on the way home, and hence PM is important for maintaining independent function in older adulthood (Hering, Kliegel, Rendell, Craik, & Rose, 2018; Kliegel et al., 2016; McDaniel, Einstein, & Jacoby, 2008).

1.1. Age-related change in prospective memory

Healthy aging is associated with decline in PM performance, with the greatest change seen in situations where carrying the PM intention burdens available cognitive resources (Henry et al., 2004; Kliegel et al., 2008). In a typical laboratory paradigm, the PM task is embedded in an ongoing task designed to keep participants engaged (to approximate the real-world in which people are busily engaged in daily activities, while needing to remember to perform a PM task); the appropriate moment for executing the PM task is signalled by a particular cue that appears within the ongoing activity. The cognitive demand of PM is, in part, dependent on how central the cue initiating PM retrieval is to the ongoing task (Scullin et al., 2010). The multi-process framework (McDaniel & Einstein, 2000) argues that focal PM cues, defined as those that are processed directly as part of the ongoing task, represent reactive, relatively automatic retrieval processes. In contrast, non-focal PM cues are not processed as part of the ongoing task, and hence greater cognitive control is required to maintain the intention at the forefront of attention and actively monitor for its presence (Einstein et al., 2005; McDaniel et al., 2015; Scullin et al., 2010).

Ageing is associated with substantially greater impairment in non-focal PM retrieval compared to focal PM retrieval (Lamichhane, McDaniel, Waldum, & Braver, 2018; Mullet et al., 2013), consistent with an age-related decrease in available cognitive resource (Salthouse,

1991). Non-focal PM is dependent on frontoparietal control networks (Cona et al., 2016; Cona et al., 2015; McDaniel et al., 2013) which show early sensitivity to age-related change (Bartzokis et al., 2003; Raz, 2000; Villemagne et al., 2011), further supporting emerging deficits in non-focal PM with increasing age. Examples of non-focal retrieval in everyday life include remembering to take medication prior to eating or cancel a direct debit, with shortcomings in this cognitively demanding form of PM linked to impairment in advanced activities of daily living (e.g. healthcare, transportation use and finance), plus decreased self-reported quality of life in older adulthood (Woods et al., 2012; 2014; 2015).

Age-related neurodegenerative disease is distinguished by an additional impairment in focal PM (Blanco-Campal, Coen, Lawlor, Walsh, & Burke, 2009; Chi et al., 2014; Costa, Caltagirone, & Carlesimo, 2011; McDaniel, Shelton, & Breneiser, 2012). This may be due to a greater reliance of retrieval on 'bottom-up' attention and associative memory processes, mediated by occipital, parietal (Cona et al., 2016) and temporal lobe regions (McDaniel et al., 2013). These regions are vulnerable to the neurodegenerative processes occurring early in the progression of Alzheimer's disease (AD) (Braak & Braak, 1991), with volumetric loss in these regions (in addition to the precuneus and orbitofrontal cortex) correlated with PM impairment in response to a salient (Dermody, Hornberger, Piguet, Hodges & Irish, 2016) or focal (Gordon, Shelton, Bugg, McDaniel, & Head, 2011) cue. Naturalistic examples of focal PM, for example sealing the envelope after provision of the postal address, are impaired in individuals with very mild dementia (Huppert, Johnson, & Nickson, 2002).

1.2 *APOE* and Prospective Memory

Apolipoprotein E (*APOE*) ε4, one of the three variants of the *APOE* single nucleotide polymorphism (ε2, ε3, ε4), increases risk for late-onset AD in a gene-dose dependent manner (Corder et al. , 1993; Farrer et al., 1997). In addition, carrying at least one copy of the ε4 allele is linked to poorer cognition in older adults with no diagnosis of dementia (e.g. Jack et al., 2015; Marioni et al., 2015; Reinvang et al., 2010; for reviews see: Small et al., 2004;

Wisdom et al., 2011), with greater magnitude of effect in homozygote ε4 carriers (Caselli et al., 2009; Small et al., 2004). ε4 disadvantages, however, are not consistently reported (e.g. Bunce et al., 2014; Bunce et al., 2004; Salo et al., 2001) with variation in the sensitivity of the cognitive domain under study being one potential reason for the non-uniformity of reported effects. The multiple processes underpinning PM make this a valuable paradigm for investigating ε4 effects and possible mechanisms of 'healthy' versus pathology-driven age-related cognitive decline.

Evidence for divergent sensitivity of PM to *APOE* ε4 effects in later life is inconsistent. ε4 carriers with mild AD demonstrated impaired focal PM retrieval accuracy compared to non-ε4 peers matched by Clinical Dementia Rating score; however, an ε4 advantage was reported in healthy older controls (in comparison to an age-matched non-ε4 group) on the same paradigm (Duchek et al., 2006). In contrast, *APOE* ε4 disadvantages in focal and non-focal PM retrieval accuracy were reported in healthy older adults by Driscoll, McDaniel, & Guynn (2005), while McDaniel and colleagues (2011) reported a non-significant effect of *APOE* status in both focal and non-focal PM conditions in healthy older adults, across measures of both PM retrieval accuracy and cost of carrying an intention on ongoing task performance.

Critically, the effects of *APOE* ε4 genotype are not restricted to later life (for reviews see: Ihle et al., 2012; Lancaster et al., 2017; Rusted & Carare, 2015). To date, study of the effects of *APOE* e4 genotype on PM earlier in the lifespan has been restricted to non-focal conditions. Lancaster et al. (2016) reported that mid-age ε4 carriers showed subtle impairments in non-focal PM retrieval accuracy, alongside an increased congruency effect for errors on a Stroop-switch paradigm. Subsequent principle component analysis reported shared variance between these two cognitive indices (Lancaster et al., *in prep*). This pattern was interpreted as ε4 differences in the flexible control of multiple goals at the forefront of attention (Conway & Kane, 2001; Kane & Engle, 2003), previously linked to successful non-focal PM retrieval (Schnitzspahn et al., 2013; Zuber et al., 2016). ε4 deficits in executive attention by mid-

adulthood align with reports of early changes in frontal-lobe integrity in this group (Bartzokis et al., 2007; Jack et al., 2015). A cross-sectional comparison of mid-age (45-55 years) and young adults (18-30 years) suggested a speed-accuracy trade-off between PM accuracy and ongoing task performance in mid-age ε4 carriers, with greater non-focal PM retrieval accuracy coupled with slower ongoing task response times (RTs) (Evans et al., 2014). In this study, task-related BOLD activity in the left inferior frontal gyrus correlated with PM accuracy in ε4 carriers, interpreted as a premature use of compensatory frontal lobe activation to support cognitive performance.

1.3 Aims and hypotheses

Identifying cognitive markers of differential brain-based aging by mid-adulthood is crucial for progressing early interventions (Irwin, Sexton, Daniel, Lawlor, & Naci, 2018). This study advances existing research by exploring *APOE* ε4 genotype differences in focal and non-focal PM, utilizing the multi-process framework to help illuminate which cognitive processes are potentially more sensitive to premature age-related change in those at heightened genetic risk of cognitive decline. Understanding patterns of early cognitive differences in *APOE* ε4 carriers will further mechanistic accounts of how the variant exerts deleterious effects in later life.

The PM task (McDaniel et al., 2011) was embedded within an ongoing category decision task, and the type of PM cue (focal, non-focal) was manipulated. Both PM retrieval accuracy and ongoing task interference (Marsh et al., 2003) or cost of carrying a PM intention on ongoing task performance, are used in conjunction to index how well volunteers are completing the task. For both the 'at-risk' ε4 group and homozygous ε3 carriers (the population 'norm'), cross-sectional age-related differences in performance were used to explore the prediction that ε4 carriers show a profile of accelerated aging. In addition, in mid-adulthood, performance of ε4 carriers is directly compared with their ε3 peers to address whether this group is demonstrating disadvantages by the 5th decade.

Following Henry et al. (2004) and Kliegel et al. (2008), we anticipated that mid-age adults would find the non-focal PM condition more challenging than younger adults due to the demand this places on executive attention resources. This may be reflected in increased interference for ongoing task performance or reduced PM retrieval accuracy. The effect of age on focal PM performance was predicted to be non-significant, in agreement with the suggestion that focal PM intentions can be successfully retrieved using automatic 'stimulus-driven' processes (Harrison & Einstein, 2010; Scullin et al., 2010).

Following Lancaster et al. (2016), we predicted that mid-age ε4 carriers would show greater decline in non-focal performance compared to ε3 peers, consistent with altered executive function in this group. A deficit in focal PM performance in ε4 carriers may indicate early vulnerability in this group, consistent with the additional impairment reported in AD (Blanco-Campal et al., 2009; Costa et al., 2011; McDaniel et al. 2011). As an exploratory measure, subjective indices of task demand and motivation were included to assess if *APOE* genotype differences can be accounted for by different approaches to performing the task.

2. Methods

2.1 Participants

Participants were recruited from an existing database of young and mid-age volunteers who had previously been screened for *APOE* genotype, or via advertisement in the local community. All genotyping procedures followed UK Human Tissue Authority (HTA) guidelines, with ethical approval for the study granted by the Research Ethics committee of the School of Psychology and Life Sciences, University of Sussex. Volunteers were first asked to provide written informed consent, including acknowledgment that the results of the genotype analysis would not be made available to them. DNA was then collected with a buccal swab, using an Isohelix SK1 kit. Genotyping followed triangulated anonymization

procedures, with two anonymized codes used per sample. LCG Genomics (Hertfordshire, www.lgcgroup.com/genomics) analyzed the samples to identify *APOE* gene variant using a fluorescence-based competitive allele-specific polymerase chain reaction to determine the presence of three major *APOE* alleles (ε2, ε3, and ε4) based on two *APOE* single nucleotide polymorphisms (SNPs) (rs429358, rs7412). These SNPs could not be identified in .6% of samples collected from the database of young and mid-age volunteers. In addition, the assay (KASP™) used for SNP identification was tested on validation DNA ahead of the samples collected from research participants, with additional processing steps (e.g. the inclusion of control samples, two-step human validation, consideration of the distribution of SNPs based on the Hardy-Weinberg equation) completed to ensure high-quality genotyping.

An independent third party pseudo-randomly selected the participants from the database, maintaining a moderate bias towards homozygous ε3 (thus volunteers could not guess their genotype probabilistically, based on invitation to participate), but ensuring a proportion of ε4 carriers sufficient for between-groups *APOE* genotype comparison. No genotype information was provided directly to the researcher; genotype was added to the anonymized dataset provided by the researcher at the end of the study. For inclusion, participants had to be aged 18-30 years or 45-56 years and using English as their daily language. Exclusion criteria were: a self-reported history of neurological or psychiatric illness within the past 5 years and self-reported psychoactive medication use. The final sample consisted of 37 young volunteers (2 ε2/ε3, 1 ε2/4, 16 ε3/ε3, 12 ε3/ε4, 5 ε4/ε4, 1 unknown[2]), and 58 mid-age volunteers (3 ε2/ε2, 1 ε2/ε4, 36 ε3/ε3, 14 ε3/ε4, 4 ε4/ε4). Prior to analysis individuals with ε2/ε2 or ε2/ε3 genotypes were excluded. Volunteers with ε3/ε3 genotype, henceforth referred to as ε3 carriers, were treated as the control group, justified by this genotype being most prevalent in the population (Farrer et al., 1997). All volunteers carrying an ε4 allele (ε2/ε4, ε3/ε4, ε4/ε4) were grouped

[2] Genotype analysis unavailable for this participant

together, henceforth referred to as ε4 carriers[3]. Volunteer characteristics for the analysed dataset are shown in Table 1.

Table 1. Demographic characteristics of participants presented as mean ±SD (range) unless stated otherwise

	Age (years)	Sex (% F)	Estimated IQ	Smokers (%Y)
Young adults (18-30 yrs.)				
ε3 (*n*=16)	20.75 ±1.81 (18-25)	69	112.34 ± 6.07 (101-122)	12
ε4 (*n*=18)	21.33 ± 2.61 (18-27)	83	109.88 ± 6.14 (96-120)	21
Mid-age adults (45-56 yrs.)				
ε3 (*n*=36)	50.22 ±2.74 (45-56)	69	122.03 ± 2.76* (116-126)	3
ε4 (*n*=19)	49.74 ± 3.53 (45-56)	68	119.44 ± 3.59* (111-124)	18

* Denotes a significant genotype group difference (p>.05).

2.2 Materials

2.2.1 Demographics and baseline measures.

A short demographic questionnaire was administered establishing age, gender, occupation and general health (smoking status, medication use, blood pressure). Blood pressure and pulse rate were measured using an automatic upper-arm cuff machine. The National Adult Reading test (Nelson & Willison, 1991) was administered to provide a baseline measure of IQ.

2.2.2 Category decision PM task.

Ongoing category decision trials consisted of on-screen item and category pairings, with participants required to indicate if the lowercase word on the left (e.g. dentist) belonged to the same category as the uppercase word on the right (e.g. PROFESSION). Participants pressed a 'y' button or 'n' button, representing 'yes' and 'no' respectively to make this judgment.

[3] Volunteers with ε2/ε4 genotype were retained in the present analysis to improve sample power; an additional analysis removing these two volunteers demonstrated that the outcomes were not significantly different.

The task was divided into 3 blocks (control, focal PM and non-focal PM), counterbalanced across participants. In each block (control, focal PM and non-focal PM) there were 106 category decision-pairings (53 congruent, 53 incongruent) taken from Einstein et al. (2005). Three lists of category pairings were used across the 3 task blocks, with the order of lists counterbalanced across participants, independent of the order of PM conditions.

In the focal PM block participants were given an additional instruction to make a 'Q' keyboard press if a target word was presented as part of a category decision trials. As the ongoing task directs attention towards the meaning of the target word, semantic processing can be assumed, and the PM intention is expected to be retrieved through relatively automatic, associative memory (McDaniel et al., 2015). The focal PM target was either: tortoise, raspberry or aluminium, counterbalanced across participants. The focal PM target was always presented 3 times, embedded in the 31st, 72nd and 102nd category decision trials. In the non-focal PM condition, participants were instructed to make a 'Q' keyboard press at any point during the category decision trials if a target syllable was presented: tor, ras, min. As the ongoing task does not direct attention towards the processing of individual syllables, participants must use executive attention to monitor for the cue. Again, the non-focal PM target was counterbalanced across participants to ensure no individual received the same target for both conditions (e.g. tortoise, tor). The non-focal PM cue was presented three times (tor: tortoise, history, motorcycle; ras: raspberry, harassment, grasshopper; min: aluminium, peppermint, minister), embedded in category decision trials 31, 72 and 102. In both focal and non-focal PM blocks, the PM cue was always presented on the left of the category decision pairing in lower case font. The addition of 3 PM trials led to a total of 109 trials in these two blocks. In the control condition participants were not given an additional PM instruction, and hence were only instructed to respond to the 106 category-decision pairings.

At the start of the task, participants were instructed to make their category decision judgments as quickly and as accurately as possible. There were 12 practice trials, including 6 trials

providing feedback on response time and accuracy. Before each PM block (focal, non-focal) participants were given the PM instructions, with an additional point being that if they were unable to press the 'Q' key on the PM trial, they could make this response as soon as possible after the trial concluded. Participants were then asked to repeat these instructions back to the experimenter in their own words to ensure they had understood the task before being allowed to proceed. Between summarizing the PM instruction and beginning the PM block there was a 1-minute delay task to create a break between encoding and retrieval. Following this delay, participants were reminded of the ongoing category decision instructions but there was no mention of the PM instruction. Upon completion of each PM block, participants were told the PM cue would not appear again in the subsequent blocks.

2.2.3 The NASA task load index

Perceived workload was measured at the end of the category decision task using a pen-and-paper version of the NASA task load index. Two visual analogue scales (1- mental demand, 2- effort), used to produce a score between 0 and 100, were relevant to the current research aims.

2.3 Procedure

Volunteers took part in a single study session lasting 45 minutes, outlined in Figure 1. Mood, blood pressure and pulse were measured both before and after completing the category decision task. During the category decision task, a one-minute interval after receiving the instructions for each condition (control, focal and non-focal) was filled by a single verbal fluency trial in which volunteers were asked to generate as many words beginning with a select letter (F, A, S) as possible in 60 seconds (Strauss, Sherman, & Spreen, 2006). Participants were not reminded of the PM instruction before resuming the category-decision task. At the end of the session, participants were asked to complete the NASA task load index reflecting on all three conditions (control, focal and non-focal). Participants who were not

recruited from the pre-genotyped *APOE* database provided a buccal swab at the end of the session.

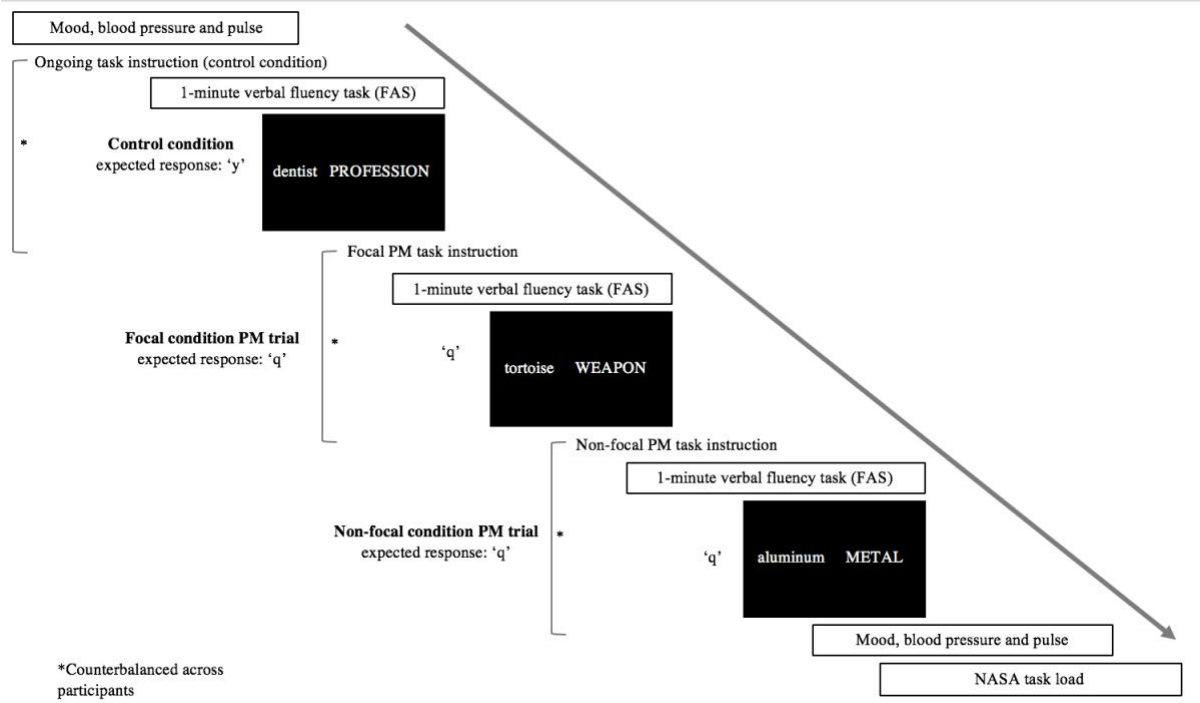


Figure 1. A timeline of the experimental procedure.

2.4 Statistical Analysis

2.4.1 Category decision PM task

Prior to analysis, category decision RTs more than 3 standard deviation (SD) away from each individual's mean were removed and performance in each group was screened for outliers. In the mid-age group, accuracy was above 85% and there were no consistent outliers across conditions for decision-making RT. In the young group one participant was removed, with their average accuracy falling below 80%, and their RTs classed as outliers in 2/3 conditions.

Group differences in category decision performance in the control condition were analyzed using a 2 (Age: Young, Mid) x 2 (Genotype: ε3, ε4) between-groups analysis of covariance (ANCOVA) for both RT and log-transformed accuracy. Estimated IQ was included as a covariate to account for the genotype differences seen in the mid-age group. In addition, a

Friedman's test was used to screen differences in category decision accuracy across conditions (control, focal PM, non-focal PM), to confirm the expectation that carrying a PM intention does not significantly impact ongoing task accuracy.

The cost of carrying a PM intention for ongoing category decision performance was indexed by differences in RT between the PM condition and the control condition. Group differences in PM interference costs were analysed using 2 (Condition: control, PM condition) x 2 (Age) x 2 (Genotype) ANCOVAs, including estimated IQ as a covariate, with separate analyses for focal and non-focal PM conditions. All groups were predicted to show a significant cost of carrying a non-focal PM intention, while PM interference cost in the focal PM condition was expected to be isolated to ε4 carriers. Following significant group differences in the focal PM condition, repeated measures *t*-tests (Bonferonni adjusted α=.013) were used to establish whether cost was significant in each group.

To test group differences in the magnitude of cost, secondary simple main effects (SME) analyses were completed including cost as a single measure (PM condition–control condition). Specifically, the effect of age in each genotype group and the difference in PM cost between mid-age e4 carriers and their e3 peers was probed in accordance with the hypotheses. Mean category decision RT in the control condition was included as an additional covariate to control for differences attributed to speed on task.

Non-parametric tests were used to assess Age and Genotype differences in PM retrieval accuracy as data violated assumptions of normality. Specifically, Mann-Whitney U-tests were used to test the hypothesis that the negative association of age on PM retrieval accuracy (focal, non-focal) would be greater in *APOE* e4 carriers compared to their e3 counterparts. In addition, differential PM retrieval accuracy (focal, non-focal) by *APOE* genotype in mid-age carriers was analyzed. A conservative α (.013) was applied.

2.4.2 NASA task load index

Prior to analysis NASA task load ratings were screened for outliers, with responses more than 3 SD from each group's mean removed. The 'Effort' and 'Mental demand' subscales were both log transformed to account for heterogeneity of variance, and then included in separate 2 (Age) x 2 (Genotype) ANOVAs.

3. Results

3.1. Volunteer Characteristics

Chi-squared tests reported no significant difference in the distribution of genders or smokers between groups (p>.05). A 2 (Age) x 2 (Genotype) between-participants ANOVA revealed significantly higher estimated IQ scores in mid-age adults compared to young adults, F(1, 83)=93.45, p<.001, η2 p=.530. In addition, ε3 carriers had significantly higher IQ scores than ε4 carriers, F(1, 83)=6.89, p=.010, η2 p=.077. [4] In both the young and the mid-age group, there was no significant genotype difference in age (p>.05), screened using independent t-tests. No participants met the criteria for hypertension (systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90); there was no significant effect of Age, Genotype or Age x Genotype interaction on baseline blood pressure (p>.05).

3.2 Category decision PM task

3.2.2 Category decision performance.

Young participants were significantly faster in the baseline category decision condition than the mid-age group, F(1, 81)=5.95, p=.017, η2 p=.068, but neither the main effect of genotype nor the Genotype x Age interaction were significant (p >.05). Baseline category decision accuracy was significantly higher in the mid-age group (M=.96) compared to the young group

[4] IQ did not account for significant variance (p>.05) across indices of category decision PM task performance and hence will not be discussed in further detail.

(*M*=.92), *F*(1, 81)=14.165, *p*<.001, η2 p=.149, however, there was no significant effect of genotype, nor any Genotype x Age interaction (*p*>.05). The inclusion of a PM intention (focal or non-focal) did not significantly impact category decision accuracy (*p*>.05). Hence all further considerations of category decision performance will be restricted to RTs. Table 2 shows mean accuracy for each group for each condition.

Table 2. Mean accuracy on the category decision task shown by age and genotype group

	Young adults (18-30 yrs.)		**Mid-age adults (45-56 yrs.)**	
	ε3	**ε4**	**ε3**	**ε4**
Control	.93 (.02)	.91 (.04)	.96 (.02)	.96 (.03)
Focal	.92 (.03)	.92 (.05)	.96 (.02)	.96 (.02)
Non-focal	.92 (.04)	.93 (.03)	.96 (.03)	.95 (.02)

Notes: Values represent mean (SD)

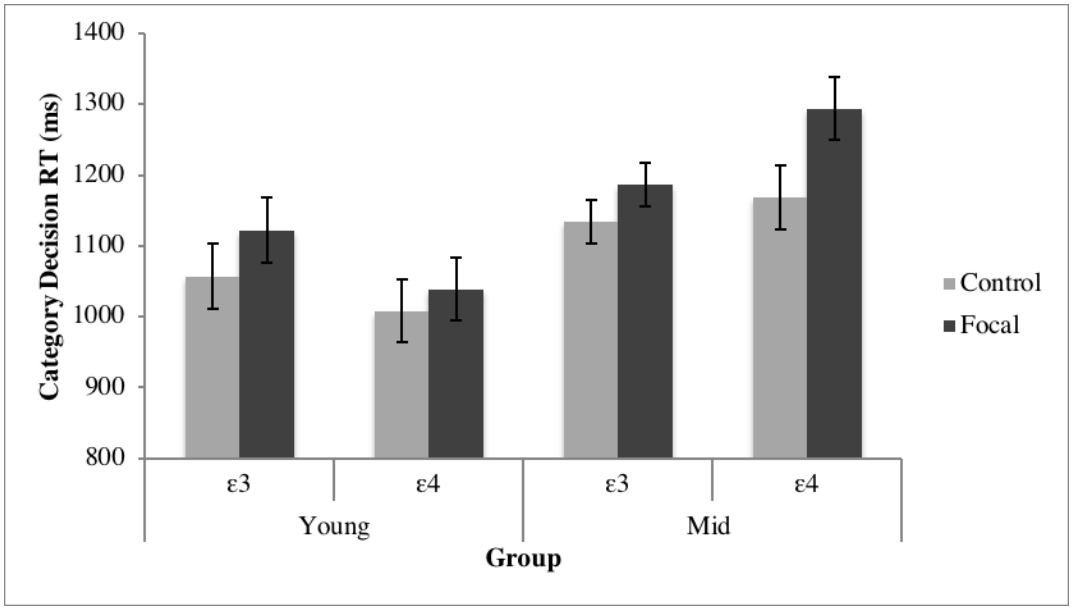
3.2.3 Ongoing task interference: RT cost

3.2.3.1 Focal condition.

Across participants there was no significant difference in category decision RTs in the focal PM condition (M=1154 ms, SE=22 ms) compared to the control condition (M=1089 ms, SD=23 ms) *F*(1,80)=.786, *p*=.378, η2 p=.010. Mid-age volunteers (M=1207, SE=30) were significantly slower than young volunteers (M=1036ms, SE=42ms), *F*(1,80)=8.30, *p*=.005, η2 p=094. Importantly, there was a significant Condition x Age x Genotype interaction, *F*(1,80)=4.25, *p*=.042, η2 p=.050.

After accounting for a significant effect of category decision RT in the control condition, (*F*(1, 80)=7.05, *p*=.010, η2p=.081, β=-.17), mid-age ε4 carriers demonstrated a significantly greater cost than both young ε4 carriers (*p*=.002), and mid-age ε3 carriers (*p*=.024). Focal PM cost was equivalent between age-groups for ε3 carriers (*p*=.585). In addition, only mid-age ε4 carriers showed a significant cost of carrying a focal PM intention (*p*=.001) (Figure 2).

Figure 2. *Mean category decision RT shown for the control and focal condition.*



3.2.3.2 Non-focal condition

Category decision RTs were significantly longer in the non-focal PM condition (M=1495ms, SD= 409 ms) than the control condition (M=1107 ms, SD = 196 ms), $F(1,83)=142.99$, $p<.001$, $\eta 2$ p=.633. Across conditions mid-age volunteers (M=1394ms, SE=38ms) were significantly slower than young volunteers (M=1189ms, SE=46ms), $F(1,83)=13.73$, $p<.001$, $\eta 2$ p=.142. There was a significant Condition x Age x Genotype interaction, $F(1,83)=5.27$, $p=.024$, $\eta 2$ p=.060.

After accounting for a significant effect of category decision RT in the control condition, ($F(1, 80)=6.04$, $p=.016$, $\eta 2p=.070$, $\beta=.41$), SME analyses revealed a greater non-focal PM cost in mid-age ε4 carriers compared to young ε4 carriers ($p=.027$). There was a non-significant age-difference in the ε3 group ($p=.828$). In mid-age volunteers there were no significant genotype differences in non-focal PM cost ($p=.142$) (Figure 3).

Figure 3. *Mean category decision RT shown for the control and non-focal condition.*

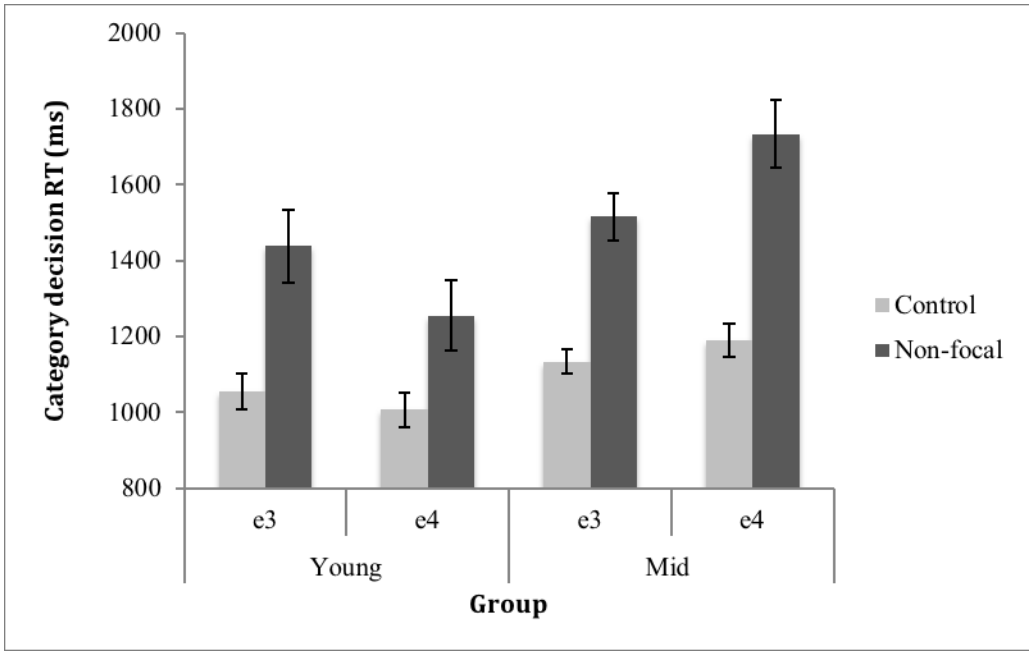


Table 3. Mean RT and PM cost shown for category decision performance

		Young adults (18-30 yrs.)		Mid-age adults (45-56 yrs.)	
		ε3	**ε4**	**ε3**	**ε4**
Control	**RT**	1055 (129)	1008(142)	1134 (206)	1168 (208)
Focal	**RT**	1122 (163)	1039 (109)	1187 (219)	1294 (186)
	Cost	67 (77)	32 (72)	53 (120)	123 (136)
Non-Focal	**RT**	1439 (267)	1255 (218)	1516 (381)	1735 (555)
	Cost	383 (255)	247 (209)	382 (263)	544 (404)

Table 4. The mean (SD) proportion of correct PM responses across conditions (Focal; Non-focal)

		Focal	**Non-focal**
Young adults	**ε3**	.98 (.08)	.67 (.35)
(18-30 yrs.)	**ε4**	.82 (.34)	.65 (.36)
Mid-age adults	**ε3**	.94 (.21)	.70 (.35)
(45-56 yrs.)	**ε4**	.98 (.08)	.74 (.35)

3.2.1 PM accuracy

The effect of Age on PM retrieval accuracy was non-significant for both focal and non-focal retrieval cues, irrespective of genotype group (p>.013). In addition, there were no significant mid-age genotype difference in focal or non-focal PM accuracy (p>.013). The mean

proportion of focal and non-focal PM cues correctly retrieved for each volunteer group can be seen in Table 4.

3.3 NASA task load index

Table 5 shows the non-transformed ratings of subjective task load. There were no significant group differences in perceived effort during the category decision task, indexed using the NASA (p>.05). There was, however, a main effect of Genotype on subjective task demand, $F(1, 80)=5.97$, p=.017, η2 p=.069, driven by ε4 carriers (M=54.2) reporting greater mental demand than the ε3 group (M=47.5). The main effect of Age and the Age x Genotype interaction were non-significant for ratings of mental demand (p>.05).

Table 5. The mean (SD) NASA task load ratings shown by group

		Mental Demand	**Effort**
Young adults	**ε3**	31.6 (10.6)	40.7 (13.8)
(18-30 yrs.)	**ε4**	43.9 (19.3)	54.2 (27.6)
Mid-age adults	**ε3**	41.5 (24.2)	46.7 (27.2)
(45-56 yrs.)	**ε4**	54.4 (22.5)	48.6 (23.15)

4. Discussion

The *APOE* ε4 genetic variant confers a risk for increased cognitive decline, both in association with AD and in older adults with no diagnosis of dementia. The present study asked whether *APOE* ε4 carriers show a distinct profile of early age-related change in focal and non-focal PM performance. Here, both PM retrieval accuracy and the cost of carrying a PM intention were interrogated as indices of PM performance. In addition, the research included subjective indices of mental demand and effort.

Irrespective of cue focality, the current findings report no *APOE*-genotype differences in PM retrieval accuracy. Task interference (the cost of carrying a PM intention on ongoing task performance), however, did indicate detrimental effects of *APOE* ε4: carrying a focal PM intention selectively slowed ongoing task performance in mid-age ε4 volunteers. For both focal and non-focal PM intentions, reports of greater PM interference in mid-age as compared

to early adulthood was limited to carriers of the ε4 allele. In addition, ε4 carriers reported greater subjective mental demand of the category decision PM paradigm, irrespective of age.

Based on previous research (Lancaster et al., 2016), we anticipated genotype differences in the accuracy of non-focal PM retrieval. In this study, however, ε4 carriers demonstrated equivalent PM retrieval accuracy for both focal and non-focal cues but registered a higher cost in maintaining the PM intention. Past research reported increased frontal BOLD response during non-focal PM retrieval in mid-age ε4 carriers suggestive of the employment of early compensatory strategies (Evans et al., 2014). Hence, comparable PM retrieval in this mid-age ε4 carriers may be supported by greater allocation of cognitive resource, evidenced by slowing of ongoing task performance.

Only mid-age ε4 carriers showed a significant cost of carrying a focal PM intention, with slowed ongoing category decision-making compared to their age equivalent ε3 peers and to young ε4 carriers. Differential performance in the focal PM condition, coupled with the suggestion of differences in non-focal PM, draws a parallel between mid-age *APOE* ε4 carriers and the broad deficit reported across focal and non-focal PM in the very early stages of pathological memory decline (Duchek et al., 2006; McDaniel et al., 2011). Of note, however, the differences reported in mid-age ε4 carriers manifest as cost rather than prospective memory retrieval deficits. Because focal PM retrieval is hypothesized to rely on spontaneous memory processes, the presence of a focal PM costs may indicate compromised associative processing and supporting brain regions (Atienza et al., 2011; McDaniel et al., 2013; Cona et al., 2016) in mid-age *APOE* ε4 carriers. As ε4 genotype differences in the presence of AD pathology have been reported from the mid 5th decade (Lautner et al., 2017; Morris et al., 2010; Mishra et al., 2018), it is possible the ε4 differences reported here reflect undetected, preclinical disease. Indeed, the presence of focal PM costs in this group suggests mid-age ε4 carriers are shifting towards a monitoring strategy (characteristic of non-focal PM) to retrieve intentions. An alternative, but not mutually exclusive, account is that ε4

carriers alter the strategy they used to complete the focal PM task based on a metacognitive awareness of their cognitive abilities (Phillips et al., 2008; Schnitzspahn et al., 2011), a factor in paradoxical age-related advantages in naturalistic prospective memory (Henry et al., 2004; Phillips et al., 2008; Schnitzspahn et al., 2011). Future research using subjective measures of anticipated task demand and predicted performance may help adjudicate between these alternatives.

Consistent with a profile of accelerated aging, mid-age ε4 carriers showed a greater age-related increase in ongoing task cost (relative to young ε4 carriers) than did mid-age ε3 carriers (relative to young ε3 carriers) for both focal and non-focal PM intentions. Specifically, non-focal prospective interference costs are suggested to differ as a result of how individuals adjust the distribution of executive resources to the ongoing task based on their ability to cope with the demands of the PM (Boywitt & Rummel, 2012; Marsh et al., 2005). In support, increased variability of ongoing task RTs following the introduction of a non-focal PM correlates with successful PM retrieval (Loft et al., 2014), reflecting the necessary monitoring processes implemented to support retrieval. Hence, a trend of increased age-related change in non-focal PM costs may reflect compromised maintenance of the PM intention in ε4 carriers by mid-adulthood. This is consistent with earlier conclusions of ε4 deficits in the ability to actively support multiple goals at the forefront of attention by mid-adulthood, based on performance on a card-sort measure of PM and a Stroop-switch paradigm (Lancaster et al, 2016).

Alternative accounts of prospective interference costs, however, are worth considering. It may be that the age-related increase in PM interference costs observed in ε4 carriers reflects increased ongoing response hesitancy, in the face of a more complicated decision making task (i.e. both a category-decision and a PM decision) (Heathcote et al., 2015; Horn et al., 2013; Strickland et al., 2017). Mid-age ε4 carriers may be adopting a more conservative task strategy to support PM retrieval, driving the observed performance differences. In the current

study, however, there were no group differences in reported subjective effort during the completion of the PM task, which might be anticipated had there been greater checking for a PM cue on a trial-by-trial basis.

Finally, the absence of age-effects on PM retrieval accuracy is consistent with a previous study reporting comparable levels of PM accuracy in older (*M*=66.3 years), and mid-age *(M*=42.5 years) adults compared to young adults on an event-based PM task (Einstein et al., 1995, Experiment 3). The current study builds on these findings by including ongoing task interference as an additional metric, suggesting that early age-related change in PM performance may manifest as cost. This apparent accelerated decline in the ability to actively support multiple goals in ε4 carriers may disadvantage everyday function; for example, maintaining prospective intentions at the cost of ongoing attentional resource impacts driving (Lemercier et al., 2014) and multi-tasking performance in lab-based simulations of real-world behaviours (Schmitter-Edgecombe et al., 2013). This supports the importance of considering PM interference costs as a marker of functional impairment. A second conclusion of the earlier paper (Einstein et al., 1995), that age-associated change in PM retrieval accuracy depends on the degree of self-initiation required, could be an interesting manipulation for future research exploring *APOE* genotype effects on PM.

Several limitations of the present study must be acknowledged. First, the number of participants within each group (Genotype x Age) was relatively small and were unequal, hence statistical analysis may be underpowered for detecting small effect sizes (Rusticus & Lovato, 2014). Sample size further limited our consideration of *APOE* gene dose, with greater differences in attention and general processing reported in homozygote ε4 carriers by mid-adulthood (Blair et al., 2005; Greenwood, Lambert, Sunderland, Parasuraman, 2005), but not consistently (Trachtenberg et al., 2012). In addition, the current sample was not asked to complete a validated neuropsychological screen; at this sensitive stage of the lifespan there may be a number of confounding factors influencing the results including the presence of

emerging cognitive impairment.

A more general limitation of studying PM in a laboratory setting is the difficulty establishing automatic, associative retrieval processes in a situation where individuals may be motivated to maximally perform on task. Whilst steps were taken to discourage monitoring for focal cues (Anderson, McDaniel, & Einstein, 2017), the presence of ε4 differences in the automatic retrieval of a PM intention should be further established, for example using functional brain imaging. Future research can test the ecological validity of these findings by considering how *APOE* ε4 differences in lab-based tests of PM translate to complaints of prospective memory in daily life. In addition, the relatively limited number of binary PM retrieval opportunities in the current paradigm, whilst closer to the real-life demands of PM, limits the reliability and sensitivity of this as a measure of self-initiated retrieval (Uttl, 2008).

4.1 Conclusions

Mid-age individuals carrying at least one copy of the *APOE* ε4 genetic risk variant for AD showed greater costs of maintaining a concurrent PM intention relative to their young adult counterparts. They did not, however, show select impairment in PM retrieval accuracy by mid-adulthood. This mid-age deficit in cost of carrying a PM intention was observed for focal and non-focal PM cues, and selectively disadvantaged ongoing performance of ε4 carriers. Differential performance across the distinct subset of cognitive processes supporting both focal and non-focal PM is comparable to the broad pattern of deficits observed in individuals diagnosed with mild AD, and hence may represent early vulnerability in both MTL and frontal-based neural systems in carriers of this 'at-risk' allele. In conclusion, this research confirms subtle differences in the early aging trajectory of ε4 carriers, perhaps indicative of a vulnerability likeable to the preclinical stages of AD. Further research is needed to interrogate the mechanisms of early change in ε4 carriers, focusing on the vulnerability of neural systems to change across the lifespan, the effect of strategies on PM task performance and how this manifests in everyday life.

Disclosure Statement

The authors have no conflicts of interest to report.

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