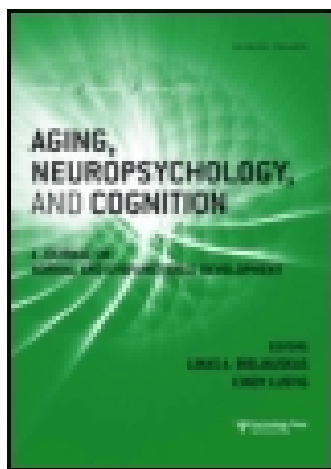


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## ***APOE* $\epsilon 4$ genotype predicts memory for everyday activities**

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The *apolipoprotein E (ApOE)*  $\epsilon 4$  allele is associated with neuropathological buildup of amyloid in the brain, and with lower performance on some laboratory measures of memory in some populations. In two studies, we tested whether *ApOE* genotype affects memory for everyday activities. In Study 1, participants aged 20–79 years old ( $n = 188$ ) watched movies of actors engaged in daily activities and completed memory tests for the activities in the movies. In Study 2, cognitively healthy and demented older adults ( $n = 97$ ) watched and remembered similar movies, and also underwent structural MRI scanning. All participants provided saliva samples for genetic analysis. In both samples we found that, in older adults, *ApOE*  $\epsilon 4$  carriers demonstrated worse everyday memory performance than did  $\epsilon 4$  noncarriers. In Study 2, *ApOE*  $\epsilon 4$  carriers had smaller medial temporal lobes (MTL) volumes, and MTL volume mediated the relationship between *ApOE* genotype and everyday memory performance. These everyday memory tasks measure genetically determined cognitive decline that can occur prior to a clinical diagnosis of dementia. Further, these tasks are easily administered and may be a useful clinical tool in identifying  $\epsilon 4$  carriers who may be at risk for MTL atrophy and further cognitive decline that is a common characteristic of the earliest stages of Alzheimer's disease.

**Keywords:** everyday memory; *APOE*; episodic memory; aging; Alzheimer's disease

### ***APOE* $\epsilon 4$ predicts memory for everyday activities**

*APOE* is a gene located on chromosome 19 that encodes apolipoprotein E (Mahley & Rall, Jr, 2000). This protein aids in the transportation of cholesterol and lipids throughout the body, thus influencing the risk for many cardiovascular diseases. The *APOE* gene has three main alleles ( $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ ); the  $\epsilon 4$  allele is associated with increased risk for developing late-onset Alzheimer's disease (AD; e.g., Corder et al., 1993; Poirier et al., 1993). Given the link between *APOE*  $\epsilon 4$  and AD and given the episodic memory deficits associated with AD, researchers have been interested in the relationship between *APOE*  $\epsilon 4$  status and performance on measures of episodic memory.

Using laboratory measures of episodic memory can help clinicians identify who may be at risk for developing AD and when they will begin to show cognitive decline. However, the stimuli often used in laboratory episodic memory tests (i.e., memory for pictures and word lists) are not representative of the sort of information individuals need to remember on a daily basis – what they read in the last chapter of a novel, what they just saw on television, or what they had for dinner last night. Cognitively healthy and demented older adults often cite memory for everyday activities as their biggest concern (Gilewski, Zelinski, & Schaie,

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1990; Jorm & Jacomb, 1989). Problems that older adults commonly report are going to the store and then forgetting what they wanted to buy or repeatedly telling someone the same story (see Memory Functioning Questionnaire; Gilewski et al., 1990).

Although laboratory measures of episodic memory may not capture these concerns, prospective memory tasks are a valuable complement to episodic memory tasks. Prospective memory is one's ability to remember to perform an action in the future such as remembering to get a gallon of milk on the way home from work or remembering to go to your dentist appointment on Tuesday at 10:00 a.m. Previous research has evaluated the relationship between *APOE*  $\epsilon 4$  and prospective memory, but results generally show no effect of *APOE*  $\epsilon 4$  on older adults' prospective memory performance (e.g., Duchek, Balota, & Cortese, 2006; McDaniel, Shelton, Breneiser, Moynan, & Balota, 2011). However, it is important to note that these studies used laboratory-based stimuli (e.g., item-category pairings) that were still less representative of older adults' everyday memory concerns.

Given that the link between *APOE*  $\epsilon 4$  and memory for everyday activities has not been examined, the current study evaluated whether  $\epsilon 4$  carrier status affects performance on tests of *everyday memory*.<sup>1</sup> Everyday memory involves remembering information from events that happen in daily life, and this information is usually complex and highly structured.

One method for assessing everyday memory in the laboratory is to show individuals short movies of actors performing everyday activities such as preparing breakfast or doing laundry, and then test their memory for the activity in the movies (e.g., Lichtenstein & Brewer, 1980; Magliano, Dijkstra, & Zwaan, 1996; Wells & Penrod, 2011). The encoding and retrieval of this type of information involves the interaction of episodic, semantic, and working memory systems (Zacks, Speer, Swallow, Braver, & Reynolds, 2007).

For example, when trying to remember what happened in a specific movie showing a person doing laundry, performance relies on episodic memory of previous experiences with doing laundry. These previous experiences aid in the comprehension of the perceptual input by helping one to predict what will happen in the near future and to organize the activity into more manageable chunks of activity (Zacks et al., 2007). In much the same way, semantic knowledge helps to encode and retrieve information about the movie; knowledge that clothes need to be washed in the washing machine before they are put into the dryer will help to perceive and remember the sequence of events in a particular laundry doing episode. Finally, everyday activities contain a wealth of perceptual information that grossly exceeds the capacity of working memory. Thus, working memory must be updated at various points in the movie as one watches an activity unfold. The points at which working memory is updated during movie viewing affect how well the activity is later remembered (Bailey et al., 2013; Kurby & Zacks, 2011; Sargent et al., 2013; Zacks, Speer, Vettel, & Jacoby, 2006). Activity is better organized in long-term memory when working memory is updated at an event boundary (e.g., when the actor finishes putting clothes in the washer and begins adding detergent) rather than when it is updated in the middle of an event (e.g., while the actor is loading clothes into the washer). Thus, more effective updating of working memory should lead to better memory for the activity.

Because memory for everyday activities relies heavily on these different memory systems, everyday memory performance should be related to performance on measures of these factors. In fact, a large-scale individual differences study by Sargent et al. (2013) evaluated the relationships amongst several episodic (e.g., associative learning, word list recall), semantic (e.g., WAIS information subtest, synonym and antonym vocabulary), working memory (e.g., reading span, operation span, symmetry span), and everyday memory (e.g., recall of everyday activities) tasks across the life span. Everyday memory was strongly correlated with individual differences in episodic, semantic, and working

memory, but importantly, multiple everyday memory measures formed a latent construct that was statistically unique from these other cognitive constructs (Sargent et al., 2013).

Although no study has examined whether *APOE*  $\epsilon 4$  carrier status influences everyday memory, a number of studies of memory for verbal and pictorial materials have shown that  $\epsilon 4$  carrier status affects episodic memory in older adults (e.g., Adamson et al., 2010; Baxter, Caselli, Johnson, Reiman, & Osborne, 2003; Bondi et al., 1995; Caselli et al., 2009; Nilsson et al., 2006; Packard et al., 2007; Pike et al., 2011; Wisdom, Callahan, & Hawkins, 2011). *APOE* genotype interacts with age such that the effect of the  $\epsilon 4$  allele is more detrimental in older adults, and is often absent (Filippini et al., 2009) or even beneficial in younger adults (Alexander et al., 2007; Mondadori et al., 2007; Rusted et al., 2013). Schultz et al. (2008) found that  $\epsilon 4$  carrier status does predict episodic memory performance for adults in their 50s; however, this result was specific to verbal – not visuospatial – memory performance. Although most research has focused on *APOE* and episodic memory, links have been found between *APOE* and working memory (e.g., Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010), semantic memory (Boyle, Buchman, Wilson, Kelly, & Bennett, 2010) and general cognitive ability (Deary et al., 2002).

Given that *APOE*  $\epsilon 4$  carrier status is related to performance on episodic, semantic, and working memory tasks, we were interested in whether it is related to performance on everyday memory tasks. Specifically, we evaluated whether *APOE*  $\epsilon 4$  carrier status predicts memory for everyday activities and whether this relationship is present in younger adults, healthy older adults, and older adults with early stage AD. We tested these hypotheses in two studies. In the first study, participants included cognitively healthy adults aged 20–79 years; in the second study, they included cognitively healthy and mildly demented older adults.

In addition to *APOE*, we also examined *brain-derived neurotrophic factor (BDNF)* and *KIBRA* (also known as *WWCI* gene that encodes the kidney and brain expressed protein) as genetic predictors of episodic and everyday memory. The methionine (*Met*) allele of the *BDNF* Val66 Met polymorphism has been linked to decreased long-term potentiation in the hippocampus as well as poorer episodic memory in healthy individuals (e.g., Egan et al., 2003; Hariri et al., 2003; Kambeitz et al., 2012; Raz, Rodrigue, Kennedy, & Land, 2009; but see Laukka et al., 2012). Further, carriers of the *KIBRA* *T* allele demonstrate better episodic memory performance (Almeida et al., 2008; Milnik et al., 2012; Papassotiropoulos et al., 2006; Schaper, Kolsch, Popp, Wagner, & Jessen, 2008; but see Need et al., 2008), whereas there is conflicting evidence as to whether *T* carriers (Rodríguez-Rodríguez et al., 2009) or *non-T* carriers (Comeveaux et al., 2010) are at a greater risk for developing AD (for a review, see Schneider et al., 2010). However, across both current studies we did not find strong evidence that either was associated with the laboratory episodic or everyday memory performance, so we will describe those results only briefly.

## Study 1

In the first study, we asked whether *APOE*  $\epsilon 4$  status affects everyday memory performance across the life span. Previous research suggests that the effects of *APOE*  $\epsilon 4$  status on laboratory memory may manifest later in life (e.g., Bondi et al., 1995; Nilsson et al., 2006; Pike et al., 2011; Wisdom et al., 2011). We tested whether its effects on everyday memory were present across the life span or whether the effects were present only in older adults.

## **Method**

### ***Participants***

Two hundred thirty-three cognitively healthy adults (117 women, ages 20–79 years) were recruited from the general St. Louis community through the Volunteers for Health participant pool at Washington University School of Medicine. All participants took part in a related cognition and aging study (Sargent et al., 2013) in which they completed a battery of psychometric measures and answered a series of demographic, educational, and health-related questions. Participants were screened for dementia and other neurological disorders once they were in the laboratory. Participants completed both the Short Blessed dementia screen (Katzman et al., 1983) and the AD8 (Galvin et al., 2005). We administered two dementia screenings to increase reliability and to provide additional information in the event a participant was identified as having “questionable impairment” on one of the screening tests. Participants received \$10 per hour as compensation for their time and effort.

### ***Materials***

#### *Everyday memory measures*

To test everyday memory, participants viewed four movies of actors engaging in everyday activities. A practice movie involved a male actor building a ship out of Legos (155 s duration). The three experimental movies involved a female actor preparing breakfast (329 s), a male actor decorating for a party (376 s), and a male actor potting plants (354 s). Following each movie, participants then completed three everyday memory measures: recall, recognition, and order memory. For recall, participants were given 7 min to write, in as much detail as possible, what had occurred in the movie they had just viewed. To score free recall responses, a research team member first created a list of the basic actions performed in each movie, using criteria described by Schwartz (1991, termed “A-1” units). Units were fine-grained parts of an activity (e.g., she walked to the sink, turned on the water, put soap on her hands, etc.). Two research team members then scored responses based on the number of correctly recalled actions from each movie (inter-rater reliability,  $\kappa = 0.84, p < .0001, CI [0.78, 0.90]$ ). For recognition and order memory, we used testing procedures as described in Zacks et al. (2006). The forced-choice recognition task consisted of participants being shown two still frames: a target still frame from the movie just viewed and a lure still frame from an alternate take of the same movie. Participants were instructed to select the still frame that had come from the movie they had recently viewed. Each movie had 20 trials, and recognition memory was scored as the number of correctly identified target still frames from each movie. Lastly, to test order memory, participants were given 12 randomly ordered still frames from each movie, printed on 10 cm × 15 cm index cards, and were asked to arrange the still frames in the correct temporal order each had occurred in the recently viewed movie. Order memory was scored as an error measure, which was the mean absolute deviation from the correct position, i.e., lower scores meant better performance.

#### *Laboratory episodic memory measures*

Episodic memory was measured using both the immediate and delayed recall portions of the Selective Reminding Test (Buschke, 1973), the Wechsler Memory Scale-III (WMS-III) Verbal Paired Associates Test (Wechsler, 1997), and the Word List Recall Test from the Victoria Longitudinal Study (Small, Dixon, Hultsch, & Hertzog, 1999). In the WMS-III Verbal Paired Associates task, participants were asked to memorize eight word pairs and then

asked to recall the second word from each pair when given the first word. After a 30-min delay, participants were again asked to perform the task but only for one trial. The number of correctly recalled word pairs from the first three trials and from the trial after the delay, were the immediate and delayed recall scores, respectively. In the word list recall, participants studied two lists of 30 words in two trials. On each trial, following a 2-min study period, participants were given 5 min to recall as many words as possible from the studied list. Performance was based on the average number of correctly recalled words across both trials. In the Selective Reminding task, participants were asked to memorize 16 objects and were given each object's associated category. Following a successful practice recall for all 16 objects, participants were then asked to immediately recall as many of the 16 objects as possible in three separate trials. If a participant was unable to recall all 16 objects, the experimenter provided the category cue(s) for the missing object(s). The same task was repeated 30 min later for delayed recall. The number of correctly recalled items, without providing category cues, was recorded for both immediate and delayed recall portions.

**Genotyping.** Saliva of the participants was collected in Oragene collection kits ([www.dnagenotek.com](http://www.dnagenotek.com)) and the DNA was extracted from the saliva samples using the manufacturer's protocol. The single-nucleotide polymorphisms, which define the *APOE*  $\epsilon 2/\epsilon 3/\epsilon 4$  isoforms, rs7412 and rs429358, and rs17070145 in *KIBRA*, were genotyped using the TaqMan® genotyping technology. The Val66 Met (rs6265) polymorphism in *BDNF* was genotyped using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using the following primers: F:5'-ACTCTGGAGAGCGTGAAT-3' and R: 5'-ATACTGTACACACGCTC-3'. The PCR products were digested with NlaIII. (The VAL allele remains intact.)

### **Procedure**

Psychometric testing occurred in two 150-min sessions separated by no more than one week from each other. As part of the first session, participants consented to participate and then watched three movies of everyday activities. Following each movie, participants completed the recall, recognition, and order memory tasks. At the end of the first session, participants were given the AD8 dementia screen to complete at home and were scheduled to return within one week for the second session. During the second session, participants completed all three measures of laboratory episodic memory. Participants also completed the Short Blessed dementia screen and provided information regarding their health before the end of the second session. The institutional review board at Washington University St. Louis approved this study. Further details are provided in Sargent et al. (2013).

### **Data Preparation**

Forty-five participants were excluded for being unable to meet the experimental session scheduling requirements ( $n = 8$ ), failing to meet criteria on both dementia screens (Short Blessed scores  $> 5$  and AD8 scores  $> 2$ ;  $n = 9$ ), failing to follow instructions ( $n = 6$ ), missing genetic data ( $n = 20$ ), or experimenter error ( $n = 2$ ). For the remaining 188 participants, we regressed each variable onto age, and then screened the residuals for values over 3.5 standard deviations from the total sample mean (univariate outliers); we replaced 21 values that met this criterion using the expectation maximization procedure in SPSS 19.0. We also replaced 10 missing values (<1% of the data) – 4 everyday memory recall values, 2 everyday recognition values, and 4 Selective Reminding values – using the same procedure. The variables were approximately normally distributed ( $|\text{skewness}| < 2.0$ ,  $|\text{kurtosis}| < 2.0$ ).

Table 1. Frequency of *APOE*  $\epsilon 4$  carriers and noncarriers for Study 1 and Study 2.

Sample	<i>APOE</i> $\epsilon 4$ carriers	<i>APOE</i> $\epsilon 4$ noncarriers
Study 1		
Young adults	27	66
Older adults	30	65
Sample size	57	131
Study 2		
CDR 0	12	28
CDR 0.5	14	24
CDR 1	11	8
Sample size	37	60

Note: The young adult group included participants aged 20–49, whereas the older adult group included participants aged 50–79.

## Results and discussion

Although age was evaluated as a continuous variable for most of the statistical analyses, the frequencies of genotypes, demographics, and descriptive statistics for the memory measures were calculated separately within the younger and older age group. The young adult group included participants aged 20–49 ( $n = 93$ ), whereas the older adult group included participants aged 50–79 ( $n = 95$ ). All genotypes were in Hardy–Weinberg equilibrium,  $p < .05$ . The number of  $\epsilon 4$  carriers and noncarriers in the young and older adults is presented in Table 1 (for the frequency of each genotype within young and older adults, see Table S1 in the Supplementary Materials). Given the small sample size within each allele type, for all analyses we compared two groups:  $\epsilon 4$  carriers (i.e., 2–4,<sup>2</sup> 3–4, and 4–4) and noncarriers (i.e., 2–2, 2–3, and 3–3). There were 57  $\epsilon 4$  carriers and 131  $\epsilon 4$ -noncarriers. See Table 2 for the demographic information (i.e., age, gender, and education) for individuals in each group.

### *Effect of the APOE $\epsilon 4$ allele on laboratory episodic memory and everyday memory*

Young and older adults' performance on the laboratory episodic and everyday memory tasks is reported in Table 3. Composite scores were created because the laboratory

Table 2. Demographics for participants in Study 1 and Study 2 for each of the *APOE* genotypes.

Sample	<i>APOE</i> $\epsilon 4$ carriers		<i>APOE</i> $\epsilon 4$ noncarriers			
	Young	Older	Young	Older		
Study 1						
Age	35.8 (8.9)	64.9 (8.1)	33.9 (8.9)	63.8 (8.6)		
Number of females	13	13	35	33		
Education	14.8 (2.7)	14.6 (2.6)	15.6 (2.4)	14.6 (2.7)		
Study 2						
	<i>APOE</i> $\epsilon 4$ carriers			<i>APOE</i> $\epsilon 4$ noncarriers		
CDR group	0	0.5	1	0	0.5	1
Age	73.2 (5.6)	76.5 (6.5)	77.6 (3.1)	75.3 (6.0)	78.8 (5.2)	77.6 (10.6)
Number of females	8	5	3	17	9	2

Notes: The young adult group included participants aged 20–49, whereas the older adult group included participants aged 50–79. Education = mean years of education; standard deviations are reported in parentheses.



Table 3. Descriptive statistics for individual episodic memory tasks and everyday memory for Study 1.

	Young adults			Older adults			<i>d</i> (Young vs. Old)
	<i>M</i>	Median	Range	<i>M</i>	Median	Range	
Selective Reminding Test	48.5	49.0	29–62	44.4	45.0	24–60	0.59
Verbal Paired Associates	19.4	20.5	10–25	17.0	17.3	6.5–24	0.64
VLS Word List Recall	18.0	18.5	5–28.5	17.3	17.0	4.5–29	0.13
Breakfast Free Recall	21.9	21.0	3–52	19.5	19.0	2–45	0.27
Party Free Recall	38.9	39.0	2–72	31.6	33.0	2–61	0.48
Planting Free Recall	26.8	23.0	0–68	23.6	22.0	0–54	0.21
Breakfast Recognition	0.73	0.75	.20–1.0	0.68	0.70	.40–.95	0.38
Party Recognition	0.78	0.80	.50–1.0	0.77	0.75	.60–1.0	0.11
Planting Recognition	0.81	0.90	.50–1.0	0.78	0.80	.50–1.0	0.18
Breakfast Order Errors	0.55	0.50	.00–2.7	0.87	0.67	.00–3.0	–0.51
Party Order Errors	0.19	0.00	.00–4.0	0.20	0.00	.00–1.0	–0.02
Planting Order Errors	1.11	0.67	.00–4.2	1.59	1.33	.00–5.8	–0.45

Notes: VLS = Victoria Longitudinal Study free recall; the young adult group included participants aged 20–49, whereas the older adult group included participants aged 50–79.

Table 4. Correlations amongst laboratory episodic and everyday memory tasks.

Variable	1	2	3	4	5	
Study 1						
1 Selective Reminding	–					
2 Paired Associates	0.49	–				
3 Word List Recall	0.44	0.47	–			
5 Breakfast Recall	0.30	0.31	0.54	–		
6 Party Recall	0.26	0.36	0.56	0.62	0.61	
Variable	1	2	3	4	5	6
Study 2						
1 Selective Reminding	–					
2 Paired Associates	0.79	–				
3 Logical Memory Imm	0.79	0.80	–			
4 Logical Memory Delay	0.79	0.80	0.92	–		
5 Breakfast Recall	0.63	0.54	0.64	0.63	–	
6 Party Recall	0.50	0.51	0.53	0.53	0.78	–
7 Library Recall	0.57	0.51	0.55	0.53	0.83	0.82

Notes: Logical Memory Imm = Logical Memory immediate recall; Logical Memory Delay = Logical Memory delayed recall. All correlations are significant at the  $p < .001$  level.

episodic memory variables correlated positively with one another, as did the everyday memory variables (Table 4). The laboratory episodic memory composite was the average of the z-scores for the Selective Reminding test, Verbal Paired Associates, and Word List Recall. Cronbach's alpha was .70 across the three episodic memory tasks. The everyday memory composite was the average of the movie recall z-scores for all three movies. (The measures of recognition and order memory for the activity in the movies showed relatively poor item-level reliability. Cronbach's alpha across the three movies was .47 for recognition and .50 for order memory, whereas it was .79 for the movie recall test.)

We conducted a linear regression with age, *APOE* status, and their interaction predicting episodic memory performance. Together these variables predicted a significant amount of variance in episodic memory performance,  $R^2 = .183$ ,  $p < .001$ . Replicating previous findings (e.g., Adamson et al., 2010; Bäckman, Jones, Berger, Laukka, & Small, 2005; Bondi et al., 1995; Filippini et al., 2009; Nilsson et al., 2006; Pike et al., 2011; Schultz et al., 2008; Wisdom et al., 2011), episodic memory scores were significantly lower in older adults,  $\beta = -.367$ ,  $p < .001$ , and in *APOE*  $\epsilon 4$  carriers,  $\beta = .166$ ,  $p = .015$ . The effect of *APOE*  $\epsilon 4$  carrier status was larger in older than younger adults; however, the Age  $\times$  *APOE* interaction was not significant,  $\beta = -.320$ ,  $p = .142$  (see Figure 1). When the participants were split into a younger (20–49) and older (50–79) group, the effect of  $\epsilon 4$  status was significant for the older adults,  $t(91) = 2.37$ ,  $p = .02$ , Cohen's  $d = 0.74$ , but not for the younger adults,  $t(91) = 1.33$ ,  $p = .19$ ,  $d = 0.30$ .

We also conducted a linear regression with age, *APOE* status, and their interaction predicting everyday memory performance. Together these variables predicted a significant amount of variance in everyday memory performance,  $R^2 = .061$ ,  $p = .009$ . Everyday memory performance was significantly lower in older adults,  $\beta = -.167$ ,  $p = .021$ , and in *APOE*  $\epsilon 4$  carriers,  $\beta = .145$ ,  $p = .045$ . As with episodic memory, the effect of genotype on everyday memory was numerically larger for older than younger adults, but the Age  $\times$  *APOE* interaction was not significant,  $\beta = -.273$ ,  $p = .242$  (Figure 2). When the

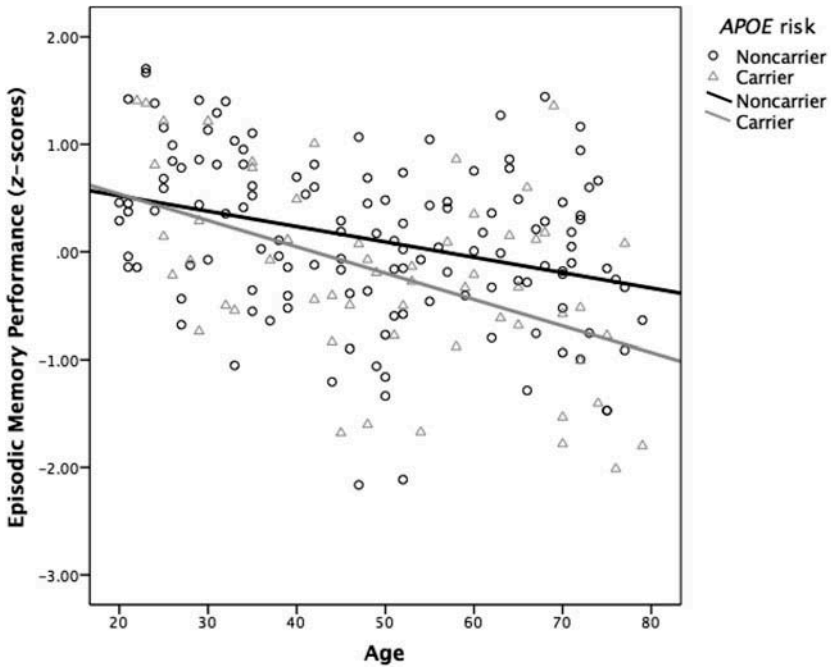


Figure 1. Laboratory episodic memory performance for *APOE ε4* carriers or noncarriers across the life span (Study 1).

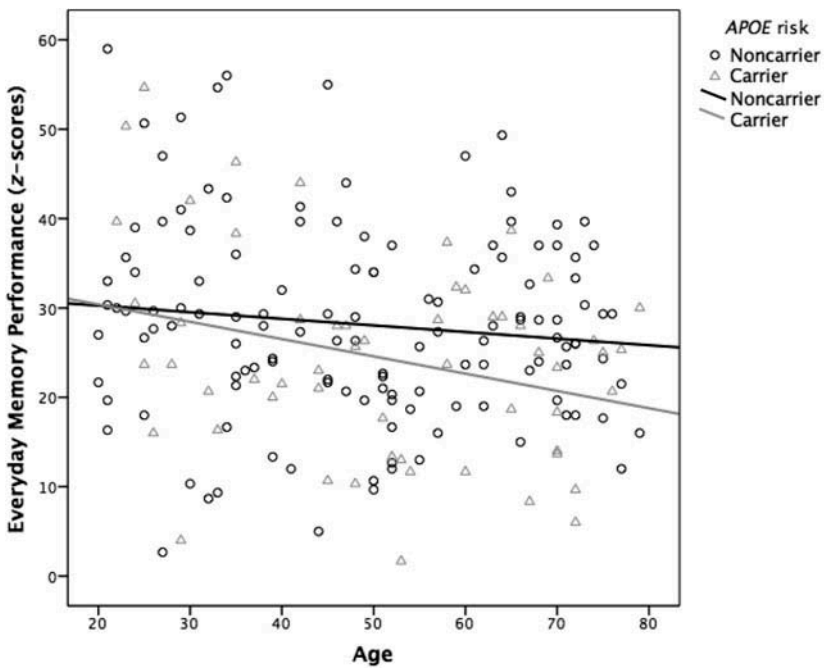


Figure 2. Everyday memory performance for *APOE ε4* carriers or noncarriers across the life span (Study 1).

Table 5. Effect sizes for the differences between *APOE*  $\epsilon 4$  carriers and noncarriers on the individual memory tasks for Study 1.

Age group	Selective Reminding	Paired Associates	VLS	Everyday Recall
All participants	0.34 (-0.69, 1.37)	0.41 (-0.15, 0.97)	0.27 (-0.50, 1.04)	0.36 (-1.22, 1.93)
Young adults	0.28 (-1.07, 1.63)	0.32 (0.14, 0.49)	0.16 (-1.05, 1.37)	0.19 (-2.30, 2.69)
Older adults	0.41 (-1.03, 1.85)	0.54 (0.35, 0.74)	0.40 (-0.57, 1.37)	0.57 (-1.26, 2.39)

Notes: VLS = Victoria Longitudinal Study free recall. The young adult group included participants aged 20–49, whereas the older adult group included participants aged 50–79. All values are Cohen's *d* effect sizes and the 95% confidence intervals for the effect sizes are in parentheses.

participants were split into a younger (20–49) and older (50–79) group, the effect of  $\epsilon 4$  status was significant for the older adults,  $t(91) = 2.38$ ,  $p = .02$ ,  $d = 0.57$ , but not for the younger adults,  $t(91) = 0.83$ ,  $p = .41$ ,  $d = 0.19$ .

Finally, we examined the effect sizes for performance on the individual memory tests because the laboratory episodic memory composite consisted of performance on three separate types of psychometric tests (i.e., selective reminding, cued recall, and free recall). Table 5 shows the effect sizes for the differences in performance between the carriers and noncarriers. *APOE*  $\epsilon 4$  carrier status had a similar effect on memory performance for the individual episodic memory tasks ( $d = 0.27$  to  $0.41$ ) and for the everyday memory task ( $d = 0.36$ ).

### BDNF and KIBRA

Only two comparisons relevant to *BDNF* and *KIBRA* genotypes approached significance, and one effect was opposite the predicted direction. That is, *BDNF Met* carriers (i.e., participants at risk, but see Laukka et al., 2012) performed significantly better than did *non-Met* carriers on word list recall, mean for *Met* carriers = 19.44; mean for noncarriers = 16.97;  $t(182) = 2.63$ ,  $p = .005$ ,  $d = 0.48$ . For *KIBRA*, carriers of the *T* allele performed marginally better than did those without the *T* allele on the laboratory episodic memory composite variable – however, this was only true of older adults aged 50–79, mean for *T* carriers =  $-0.04$ ; mean for noncarriers =  $-0.31$ ;  $t(90) = 1.58$ ,  $p = .06$ ,  $d = 0.34$ . Previous studies have shown mixed results regarding the effects of *KIBRA* on memory (Need et al., 2008), but in a large-scale meta-analysis Milnik et al. (2012) demonstrated *T* carriers outperform *C* carriers on measures of episodic memory. Further, our results are consistent with Muse et al. (2014), who found that effect of *T* carriers on episodic memory performance was stronger in older adults. No other comparisons approached significance.

### Summary

In sum, the results from Study 1 were consistent with previous work indicating that  $\epsilon 4$  carriers performed significantly worse than did noncarriers on laboratory measures of episodic memory. Further,  $\epsilon 4$  carriers demonstrated significantly worse memory for everyday activities. The effect of *APOE* genotype was numerically larger in older adults for both laboratory episodic memory and everyday memory, but the interactions between genotype and age were not significant.

## Study 2

In the first study, we found an effect of *APOE*  $\epsilon 4$  status on laboratory episodic memory and everyday memory performance for cognitively healthy older adults aged 50–79 years. Given that this genetic effect on everyday memory is a novel finding, we wanted to replicate it in a different sample of older adults. Specifically, we evaluated whether *APOE*  $\epsilon 4$ -carrier status predicts memory for everyday activities in cognitively healthy older adults and those with mild dementia of the Alzheimer's type.

Frequently, *APOE*  $\epsilon 4$  status distinguishes episodic memory performance in non-demented older adults (Bondi et al., 1995; Nilsson et al., 2006; Pike et al., 2011; Wisdom et al., 2011), but this relationship also has been extended to older adults diagnosed with preclinical AD (Bäckman et al., 2005) and mild cognitive impairment (Boyle et al., 2010; but see Lange et al., 2002). Thus, we predicted that *APOE*  $\epsilon 4$  carrier status would predict memory for everyday activities in cognitive healthy and mildly demented older adults.

Further, we wanted to evaluate the underlying neurophysiological mechanism that mediates this effect. We focused on the role of the medial temporal lobes (MTL) because the integrity of these structures has been linked to everyday memory (Bailey et al., 2013). In this study, cognitively healthy and mildly demented older adults with larger MTL volumes performed better on measures of everyday memory than did those with smaller MTL volumes. Moreover, Reiman et al. (2001) found that cognitively healthy *APOE*  $\epsilon 4$  carriers showed reduced metabolic rate for glucose in several brain regions including the parahippocampal gyrus.

Another reason to focus on the MTL is that older adults in the early stages of AD show decreased MTL volume (McDonald et al., 2009). One of the hallmark neurophysiological symptoms of AD is the accumulation of amyloid  $\beta$  protein (e.g., Masters et al., 1985), particularly in the hippocampus (Thal, Capetillo-Zarate, Del Tredici, & Braak, 2006). Another neurophysiological hallmark of AD is the alteration of tau, which leads to the formation of neurofibrillary tangles (Braak & Braak, 1991; Price & Morris, 1999). Importantly, the accumulation of neurofibrillary tangles is associated with cognitive decline (Petersen et al., 2006).

Is *APOE*  $\epsilon 4$  related to these AD biomarkers? *APOE* may be associated with the decomposition of microtubules (i.e., tau; Mahley & Huang, 1999); however, some evidence suggests that *APOE*  $\epsilon 4$  is related to amyloid  $\beta$  accumulation, but not tau (Morris et al., 2010). Although the exact role of *APOE*  $\epsilon 4$  in amyloid  $\beta$  metabolism is unknown, evidence suggests that the  $\epsilon 4$  allele is associated with a higher rate of deposition, lower rates of clearance, and less degradation of amyloid  $\beta$  (Holtzman, 2001; Holtzman, Morris, & Goate, 2011; Jiang et al., 2008; Kim, Basak, & Holtzman, 2009; Zlokovic, Deane, Sallstrom, Chow, & Miano, 2005). This abnormal deposition and clearance process plays a role in the neuronal degeneration, particularly in the medial temporal regions (Bourgeat et al., 2010). That is, MTL atrophy found in cognitively healthy and demented older adults is caused, in part, by the accumulation of amyloid  $\beta$ .

Other potential mechanisms by which *APOE*  $\epsilon 4$  exerts its effects on neuronal integrity are through the distribution of cholesterol and neuronal repair (Mahley & Huang, 1999). Although there is not one definitive mechanism by which *APOE*  $\epsilon 4$  influences brain structure, research has demonstrated that *APOE*  $\epsilon 4$  is associated with MTL volume and that MTL volume is related to everyday memory performance. Thus, we evaluated whether MTL volume mediates the relationship between *APOE*  $\epsilon 4$  carrier status and everyday memory performance.

In the second study, we assessed everyday memory performance in both cognitively healthy and mildly demented older adults. As in Study 1, these participants watched one practice movie and three experimental movies of everyday activities and completed memory tasks related to the activity in the movies. They also provided a saliva sample for genetic analyses. Finally, MTL volumetric data were obtained from structural MRI scans for each participant.

## **Method**

### ***Participants***

All participants were recruited through the Knight Alzheimer's Disease Research Center (ADRC) at Washington University in St. Louis. The presence of dementia was assessed according to National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) standards (Jack et al., 2011; McKhann et al., 1984). The Clinical Dementia Rating (CDR) scale (Morris, 1993) was then used as a global dementia staging instrument. The CDR is based on a 90-min clinical interview of both the participant and a collateral source (often a spouse, child, or close friend) conducted by a neurologist or a psychiatrist (Morris et al., 2001). This interview assesses changes in participants' cognitive and functional abilities in the areas of memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. CDR scores can be 0 (no dementia), 0.5 (questionable/very mild dementia), 1 (mild dementia), or 2 (moderate dementia); however in the current study, we only recruited those with a CDR status of 0, 0.5, and 1. Information from the clinical interview and the collateral source is used to arrive at an etiological diagnosis. Diagnosis and staging of AD is conducted independent of neuropsychological data and is based on intra-individual decline. Many of the CDR 0.5 individuals in our sample may have been classified as MCI elsewhere; however, the clinical diagnosis of the CDR 0.5 stage using these procedures has been confirmed by the postmortem diagnosis of AD in 93% of cases (Berg et al., 1998).

We collected demographic information as well as measures of depression and global cognitive functioning. Data for the Geriatric Depression Scale (GDS), Mini-Mental State Exam (MMSE), and Short Blessed Test are presented for each CDR group in Table 6. We also obtained vascular health information for 80 participants, which included a history of heart attack, atrial fibrillation, angioplasty, cardiac bypass procedures, congestive heart failure, hypertension, and the presence of a pacemaker.

Participants were excluded if they had other neurological disorders (e.g., Parkinson's disease, Huntington's disease), neurological damage (e.g., due to seizures or head trauma), other types of dementia (e.g., vascular, Lewy bodies), or mood disorders. We recruited 40 (25 female) CDR 0 individuals, 38 (15 female) CDR 0.5 individuals, and 19 (7 female) CDR 1 individuals. The age range for all participants was 63–90 years and the overall mean age was 76.5 ( $SE = 0.6$ ) years.

### ***Materials***

The behavioral data were collected within an average of 152 days ( $SE = 6.2$ , median = 149, range = 59 – 304 days) of a participant's clinical interview and an average of 574 days ( $SE = 80.4$ , median = 403, range = 0 – 3318) of their structural MRI scans.

Table 6. Descriptive statistics for individual everyday memory and episodic memory tasks for Study 2.

	CDR 0				CDR 0.5				CDR 1			
	$d$		$d$		$d$		$d$		$d$		$d$	
	$M$	Range	Median	Range	$M$	Range	Median	Range	$M$	Range	Median	Range
Age	74.65	65–86	75.00	65–86	77.97	78.50	78.50	66–86	77.61	78.50	78.50	63–90
GDS	0.66	0–4	0.00	0–4	1.52	1.00	1.00	0–7	2.78	2.00	2.00	0–10
Short Blessed Test	7.97	7–13	7.00	7–13	10.26	9.00	9.00	4–21	15.11	16.50	16.50	4–26
MMSE	29.18	24–30	30.00	24–30	27.93	29.00	29.00	22–30	22.67	22.00	22.00	18–28
Breakfast Free Recall	22.18	1–61	21.00	1–61	12.84	13.50	13.50	0–31	4.00	3.00	3.00	0–23
Library Free Recall	13.03	1–34	12.50	1–34	6.63	6.00	6.00	0–24	1.79	2.00	2.00	0–10
Party Free Recall	26.65	1–74	22.50	1–74	13.16	10.00	10.00	0–57	2.68	1.00	1.00	0–12
Breakfast Recognition	0.71	.40–.90	0.70	.40–.90	0.65	0.65	0.65	.30–.90	0.50	0.50	0.50	.30–.80
Library Recognition	0.77	.80–.95	0.80	.20–.95	0.72	0.70	0.70	.35–1.0	1.12	0.55	0.53	.25–.80
Party Recognition	0.88	.90–1.0	0.90	.20–1.0	0.78	0.80	0.80	.40–1.0	1.26	0.60	0.60	.40–.90
Breakfast Order Errors	0.66	.00–4.5	0.33	.00–4.5	1.41	1.00	1.00	.00–4.5	–1.44	3.24	3.00	.83–5.5
Library Order Errors	1.48	.00–4.3	1.50	.00–4.3	2.58	2.50	2.50	.50–4.5	–1.05	3.70	3.83	1.0–5.0
Party Order Errors	0.12	.00–.83	0.00	.00–.83	0.23	0.17	0.17	.00–1.8	–1.36	1.54	1.33	.00–4.7
Verbal Paired Associates	15.25	7–21	15	7–21	10.27	10	10	0–18	7.41	8	8	0–14
Selective Reminding Test	30.73	11–42	32	11–42	21.06	21	21	4–38	12.16	12	12	0–30
Logical Memory	14.03	0–21	15	0–21	9.29	8	8	0–18	3.81	2	2	0–14
Immediate												
Logical Memory Delayed	13.48	0–21	14	0–21	7.15	6	6	0–17	1.18	1.76	0	0–9
Entorhinal Volume	3926	2821–5203	3927	2821–5203	3469	3397	3397	2084–4597	2544	2574	2574	1615–3721
Hippocampal Volume	7526	5836–9056	7528	5836–9056	6491	6316	6316	5001–8403	5671	5685	5685	4730–6734
Parahippocampal Volume	3662	2814–4693	3645	2814–4693	3478	3473	3473	2052–4542	2987	2965	2965	1871–3846

Notes:  $M$  = mean;  $d$  = Cohen's  $d$  measure of effect size. GDS = Geriatric Depression Scale, which range from 0 to 30. Scores on the Short Blessed Test can range from 0 to 28. MMSE = Mini-Mental State Examination, which can range from 0 to 30. Volume measurements are cubic millimeters.

### *Everyday memory tasks*

Everyday memory was tested the same way as in Study 1. However, given that a large portion of this sample consisted of mildly demented participants, participants completed the recall measure by speaking rather than writing or typing.

### *Laboratory episodic memory tasks*

A cognitive ability battery (ELSMEM, 2009) designed to assess a broad spectrum of abilities was administered to all participants, usually a week or two after their clinical assessment. For the current study, we obtained participants' scores on the episodic memory tasks, which included the sum of the three free recall trials from the Selective Reminding Test (Grober, Buschke, Crystal, Bang, & Dresner, 1988), Verbal Paired Associates from the WMS (Wechsler & Stone, 1973), and immediate and delayed recall of the WMS Logical Memory (Wechsler & Stone, 1973).

### *MRI acquisition and analyses*

Participation at the ADRC includes structural MRI scans every other year. Some participants had undergone multiple scans, and we accessed the scan that occurred closest to their behavioral session. Some participants ( $n = 28$ ) had never completed a scan, so the MRI sample included volume estimates for 28 CDR 0, 31 CDR 0.5, and 15 CDR 1 participants. T1-weighted MP-RAGE scans (TR = 9.7 ms, TE = 4 ms, TI = 20 ms, 1 mm  $\times$  1 mm  $\times$  1.25 mm resolution) were obtained for each subject. (Images for 7 participants were collected on a Siemens 1.5 Tesla Vision scanner (Siemens, Erlangen, Germany), whereas images for 67 participants were collected on a Siemens 3 Tesla Trio scanner (Siemens). Controlling for scanner type and the scanner  $\times$  volume interaction did not change the amount of variance the volume measures accounted for in the cognitive variables. Thus, scanner type was not included in any further analyses.)

Gray matter volume estimates were obtained using the FreeSurfer 5.1 image analysis suite. The MTL region of interest (ROI) was based on the Desikan–Killiany atlas (Desikan et al., 2006). MTL was defined as the entorhinal cortex, hippocampus, and parahippocampal gyrus regions (which includes the perirhinal and parahippocampal cortex). Cronbach's alpha for the volumetric measures for the three MTL regions was .79. Volumes were summed across hemispheres and then normalized to control for intracranial volume using linear regression (e.g., Buckner et al., 2004; Jack et al., 1989).

### *Genotyping*

The same genotyping methodology used in Study 1 was used in this study.

### **Procedure**

Data analyzed in this study were collected as a part of a larger study of dementia (Bailey et al., 2013). Participants were seated in front of a laptop computer and watched the practice movie. After they finished the practice, the experimenter answered any questions and restated the instructions. Then, they watched the same breakfast and party movies from Study 1, and also a movie about a female actor checking out a book at a library (249 s), in that order. Following each movie, the participants completed the recall task, the



forced-choice recognition task, and finally the order memory task. After the third movie, they completed a short form of the Naturalistic Action Test (Schwartz, Segal, Veramonti, Ferraro, & Buxbaum, 2002) followed by a script knowledge test based on the procedure described by Rosen, Caplan, Sheesley, Rodriguez, and Grafman (2003). Next, participants watched each movie again – including the example movie; however, no memory tests followed this viewing. (The Naturalistic Action Test, script knowledge test, and the second movie viewing were collected for separate projects and will not be discussed further.) The institutional review board at Washington University St. Louis approved this study.

## Results and discussion

The mean age, GDS, Short Blessed Test, and MMSE scores are presented in Table 6 for each CDR group. The CDR 0 group was significantly younger than the CDR 0.5 group,  $t(79) = 2.49, p = .01, d = 0.55$ , and the CDR 1 group,  $t(58) = 1.75, p = .04, d = 0.47$ . GDS scores significantly differed by CDR group,  $F(2, 93) = 9.55, p < .001, \eta^2 = .24$ , with the CDR 0 and CDR 0.5 participants reporting lower levels of depression compared to the CDR 1 individuals. Scores on the Short Blessed Test also differed significantly by CDR group,  $F(2, 94) = 23.01, p < .001$ , with CDR 0 participants performing better than CDR 0.5 participants, and CDR 0.5 participants performing better than CDR 1 participants. Finally, MMSE scores also differed significantly by CDR group,  $F(2, 94) = 59.18, p < .001$ , with the CDR 0 and CDR 0.5 participants performing higher than the CDR 1 individuals.<sup>3</sup>

Next, we computed a vascular risk composite variable to evaluate whether memory performance is influenced by the interaction between vascular risk and *APOE*  $\epsilon 4$ . A history of heart attack, atrial fibrillation, angioplasty, cardiac bypass procedures, congestive heart failure, hypertension, and the presence of a pacemaker (both recent and remote) were coded as “1” ( $n = 52$ ), and the absence was coded as “0” ( $n = 28$ ). Vascular risk did not interact with *APOE*  $\epsilon 4$ -carrier status in predicting laboratory episodic memory performance or everyday memory,  $F_s < 1$ . Given these results, vascular risk was not included as a predictor in the remaining regression analyses.

The number of  $\epsilon 4$  carriers and noncarriers is shown in Table 1 for the participants from each CDR group. (For the frequency of each genotype within each CDR group, see Table S1 in the Supplementary Materials.) Again, for the analyses we combined the 2–4, 3–4, and 4–4 genotypes into the  $\epsilon 4$ -carrier group and the 2–2, 2–3, and 3–3 genotypes into the noncarrier group, which resulted in 37 carriers and 60 noncarriers. The proportion of  $\epsilon 4$  carriers was higher in the CDR 1 group than in the other two groups, but not significantly so,  $\chi^2(2, n = 97) = 4.29, p = .117$ . See Table 2 for the demographic information (i.e., age and gender) for individuals in each group.

Descriptive statistics for each of the everyday memory and episodic memory measures are presented by CDR status in Table 6. On all measures, independent-samples *t*-tests indicated that CDR 0 participants significantly outperformed both CDR 0.5 and CDR 1 participants, and CDR 0.5 participants significantly outperformed CDR 1 participants ( $t_s = 4.86–8.11, p_s < .001, d_s = 0.33–2.50$ ).

Correlations amongst performance on all of the memory tasks are presented in Table 4. Performance across the laboratory episodic memory tasks was strongly and positively correlated ( $r_s = .79–.92$ ), as was performance on the everyday memory tasks ( $r_s = .78–.83$ ). Further, in this sample all three everyday memory tasks showed good item-level reliability. Cronbach’s alpha across the three movies was .86 for recall, .81 for

recognition, and .78 for order memory. Based on these correlations, we created composite variables by averaging the  $z$ -scores. The episodic memory composite was the average of the  $z$ -scored values for the Selective Reminding, Verbal Paired Associates, Logical Memory Immediate, and Logical Memory Delayed tasks. Cronbach's alpha was .92 across the four episodic memory tasks. The everyday memory composite was the average of the recall, recognition, and order memory  $z$ -scores for each of the three movies.<sup>4</sup>

### *Effect of the APOE $\epsilon 4$ allele on episodic and everyday memory*

A 3 (CDR Group)  $\times$  2 (Carrier Status) analysis of covariance (ANCOVA) was conducted to evaluate performance on the episodic memory composite variable with age as a covariate. Figure 3 depicts the episodic memory performance by CDR group and carrier status. The main effect of CDR Group was significant,  $F(2, 97) = 41.91, p < .001, \eta^2 = .46$ . Tukey's  $b$  post hoc analysis indicated that the CDR 0 group ( $M = 0.72, SD = 0.62$ ) outperformed both of the other groups and the CDR 0.5 group ( $M = -0.14, SD = 0.70$ ) outperformed the CDR 1 group ( $M = -1.02, SD = 0.58$ ). The main effect of Carrier Status was also significant,  $F(1, 97) = 4.11, p = .046, \eta^2 = .02$ , with the  $\epsilon 4$  carriers ( $M = -0.32, SD = 0.94$ ) performing worse than the noncarriers ( $M = 0.27, SD = 0.83$ ). In all three groups,  $\epsilon 4$  carriers performed worse than noncarriers, but this difference reached significance only for the CDR 0.5 group,  $t(28) = 3.39, p = .001, d = 1.08$  (95% CI:  $0.85 < d < 1.24$ ). The CDR Group  $\times$  Carrier Status interaction was not significant,  $F(2, 97) = 1.88, p = .16, \eta^2 = .02$ . The effect of age was not significant,  $F < 1.0$ .

Next, we examined everyday memory performance for  $\epsilon 4$  carriers and noncarriers. Everyday memory performance as a function of CDR group and carrier status is shown in Figure 4. A 3 (CDR Group)  $\times$  2 (Carrier Status) ANCOVA was conducted on the everyday memory composite with age as a covariate. The main effect of CDR Group was significant,  $F(2, 71) = 19.29, p < .001, \eta^2 = .27$ . Again, Tukey's  $b$  post hoc analysis

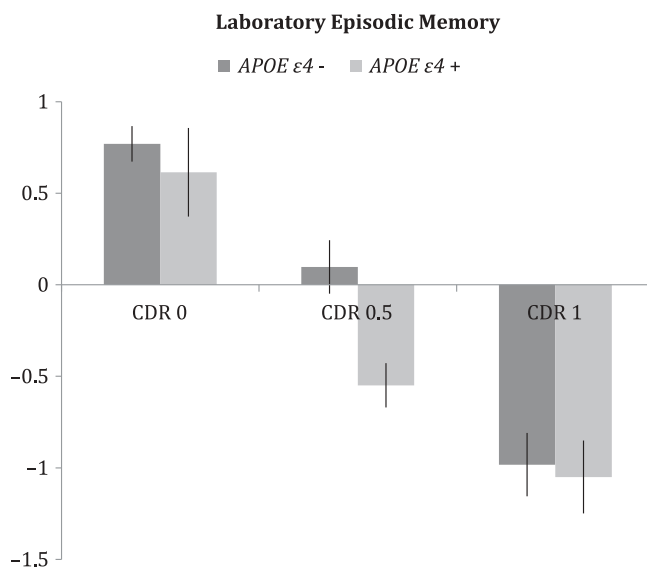


Figure 3. Laboratory episodic memory performance for the different CDR groups who are either APOE  $\epsilon 4$  carriers or noncarriers (Study 2). Error bars represent  $\pm 1$  standard error of the mean.

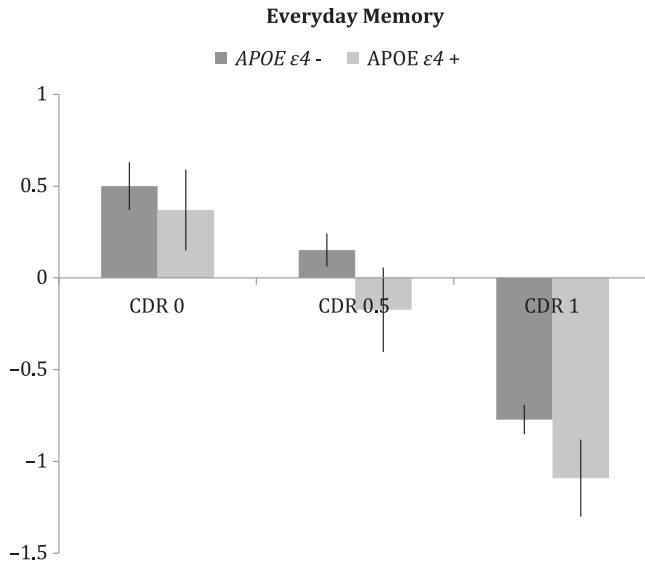


Figure 4. Everyday memory performance for the different CDR groups who are either *APOE* ε4 carriers or noncarriers (Study 2). Error bars represent  $\pm 1$  standard error of the mean.

indicated the CDR 0 group ( $M = 0.45$ ,  $SD = 0.61$ ) performed the best followed by the CDR 0.5 group ( $M = 0.03$ ,  $SD = 0.51$ ) and finally the CDR 1 group ( $M = -0.98$ ,  $SD = 0.56$ ). The main effect of Carrier Status was also significant,  $F(1, 71) = 4.36$ ,  $p = .041$ ,  $\eta^2 = .03$ , with ε4 carriers ( $M = -0.30$ ,  $SD = 0.88$ ) performing worse than noncarriers ( $M = 0.21$ ,  $SD = 0.58$ ). The CDR Group  $\times$  Carrier Status interaction was not significant,  $F < 1.0$ . The effect of age was significant,  $F(1, 71) = 6.33$ ,  $p = .014$ ,  $\eta^2 = .05$ .

*APOE* ε4 carrier status differentiated episodic and everyday memory performance. The effect sizes for the differences in performance between carriers and noncarriers on the individual memory tasks are displayed in Table 7. Replicating the results from Study 1, the effect sizes were similar across the individual laboratory episodic memory tasks ( $d_s = 0.03$ – $0.99$ ) and the individual everyday memory tasks ( $d_s = 0.09$  to  $0.81$ ).

### **Effect of dementia severity**

Importantly, this was a selective sample that overrepresented very mildly and mildly demented participants who have a higher probability of being ε4 carriers and having lower memory performance. To examine whether the observed differences in episodic memory and everyday memory performance were due to dementia status, we assessed whether *APOE* ε4 carrier status predicts memory performance after controlling for CDR group using two sets of hierarchical regression analyses. Episodic memory was the dependent variable in the first set of regression analyses and everyday memory was the dependent variable in the second set. For both, CDR group was entered as a predictor into Step 1 of the regression model and *APOE* ε4 carrier status was entered as a predictor into Step 2.

CDR group accounted for 51% of the variance in episodic memory performance. However after controlling for CDR group, *APOE* ε4 carrier status accounted for 3% unique variance in episodic memory ( $\beta = .18$ ,  $p = .014$ ). For everyday memory, CDR group accounted for 43% of the variability in performance. After controlling for CDR

Table 7. Cohen's *d* effect sizes for the differences between *APOE ε4* carriers and noncarriers on the individual memory tasks for Study 2.

CDR Group	Selective Reminding	Paired Associates	Log Mem Immed	Log Mem Delay	Everyday Recall	Everyday Recog	Everyday Order Memory
CDR 0	0.44 (-1.50, 2.39)	0.13 (-1.06, 1.31)	0.19 (-1.27, 1.64)	0.07 (-1.52, 1.65)	0.41 (-3.31, 4.13)	0.81 (0.78, 0.84)	-0.09 (-0.27, 0.09)
CDR 0.5	0.91 (-1.41, 3.22)	0.82 (-0.38, 2.02)	0.87 (-0.48, 2.22)	0.99 (-0.58, 2.58)	0.50 (-1.97, 2.98)	0.17 (0.14, 0.20)	-0.64 (-0.85, -0.43)
CDR 1	0.03 (-3.16, 3.23)	0.10 (-1.53, 1.74)	0.19 (-1.37, 1.77)	0.24 (-1.10, 1.57)	0.28 (-1.28, 1.83)	0.62 (0.57, 0.67)	-0.12 (-0.51, 0.28)

Notes: Log Mem Immed = Logical Memory immediate recall; Log Mem Delay = Logical Memory delayed recall; Everyday Recog = recognition performance for the movies. All values are Cohen's *d* effect sizes and the 95% confidence intervals for the effect sizes are in parentheses.

group,  $\epsilon 4$  carrier status predicted 4% unique variance in everyday memory performance ( $\beta = .19, p = .037$ ). That is, *APOE*  $\epsilon 4$  carrier status significantly predicted episodic memory and everyday memory above and beyond dementia status.

### ***Medial temporal lobe volume mediates the relationship between *APOE* $\epsilon 4$ and everyday memory***

The  $\epsilon 4$  allele is related to increased amyloid  $\beta$  accumulation and to increased numbers of neurofibrillary tangles in MTL (Bourgeat et al., 2010; Braak & Braak, 1991). Further, previous work examining the neurological correlates of everyday memory identified a relationship between MTL volume and everyday memory performance (Bailey et al., 2013). Thus, we were interested in whether MTL volume mediates the relationship between *APOE*  $\epsilon 4$  carrier status and everyday memory.

As predicted, an independent-samples *t*-test indicated that MTL volume was significantly lower in  $\epsilon 4$  carriers than in noncarriers,  $t(70) = 2.932, p = .003, d = 0.71$ . To examine whether *APOE* only predicts MTL volume because of potential third variables, we evaluated whether *APOE*  $\epsilon 4$  predicted MTL volume even after controlling for age and CDR group. In a hierarchical regression analysis predicting MTL volume, age and CDR were entered in Step 1 and carrier status was entered in Step 2. Age and dementia status accounted for a significant portion of variance in MTL volume ( $R^2 = .06, p = .005$ ); however, *APOE*  $\epsilon 4$  carrier status predicted a significant amount of unique variance in MTL volume ( $R^2 = 0.11, p = .005$ ).

Finally, given that *APOE*  $\epsilon 4$  carrier status is associated with MTL volume and that MTL volume is associated with everyday memory ( $R^2 = 0.34, p < .001$ ; Bailey et al., 2013), we conducted another set of hierarchical regression analyses to examine whether MTL volume mediates the observed relationship between *APOE*  $\epsilon 4$  carrier status and everyday memory. In the first analysis, we regressed episodic memory onto *APOE*  $\epsilon 4$  carrier status, and in the second analysis, we regressed episodic memory onto *APOE*  $\epsilon 4$  carrier status after entering MTL volume into the regression model. All regressions were conducted controlling for age.

*APOE*  $\epsilon 4$  carrier status accounted for 12.1% of the variance in everyday memory ( $\beta = -0.35, p = .002$ ). This value dropped to 2.7% ( $\beta = -0.18, p = .092$ ) after statistically controlling for MTL volume ( $\beta = 0.59, p < .001$ ), which was an 78% reduction ( $F(1, 68) = 4.67, p = .034$ ). The same hierarchical regressions were conducted separately for each MTL region – entorhinal cortex, hippocampus, and parahippocampal gyrus. Volume in the three regions each accounted for a large percentage of the variance shared between *APOE*  $\epsilon 4$  carrier status and everyday memory performance (see Table 8). Interestingly, the predictive power for each of the MTL regions corresponded to the rate of atrophy commonly observed in the progression of AD (e.g., Du et al., 2004; Stoub, Rogalski, Leurgans, Bennett, & Detolledo-Morrell, 2010). *APOE*  $\epsilon 4$  carrier status accounted for 12.1% of the variance in everyday memory, but it only accounted for 0.7% after controlling for entorhinal volume (94% reduction), 2.8% after controlling for hippocampal volume (77% reduction), and 4.9% after controlling for parahippocampal volume (60% reduction). These results suggest that *APOE*  $\epsilon 4$  influences MTL volume, and MTL volume affects everyday memory performance. The same results were observed when controlling for dementia status as well. That is, after controlling for CDR group ( $\beta = -0.48, p < .001$ ) and MTL volume ( $\beta = 0.27, p = .024$ ), *APOE*  $\epsilon 4$  carrier status accounted for a nonsignificant amount of unique variance in everyday memory performance ( $R^2 = .02, \beta = -0.14, p = .141$ ).

Table 8. Hierarchical regression analyses predicting everyday memory and episodic memory.

	$R^2$	$p$	Reduction in variance <sup>a</sup>
<b>Predicting Everyday Memory</b>			
<i>APOE</i> status (alone)	.121	.002	
<i>APOE</i> status (after controlling for entorhinal volume)	.007	.401	94%
<i>APOE</i> status (after controlling for hippocampal volume)	.028	.115	77%
<i>APOE</i> status (after controlling for parahippocampal volume)	.049	.031	60%
	$R^2$	$p$	Reduction in variance
<b>Predicting Episodic Memory</b>			
<i>APOE</i> status (alone)	.136	.001	
<i>APOE</i> status (after controlling for entorhinal volume)	.017	.210	88%
<i>APOE</i> status (after controlling for hippocampal volume)	.032	.064	76%
<i>APOE</i> status (after controlling for parahippocampal volume)	.071	.015	48%

Note: <sup>a</sup>Reduction in variance was calculated as the percentage of variance in memory accounted for by *APOE* status before and after accounting for brain volume [e.g.,  $(.121 - .007)/(.121) \times 100 = 94\%$ ].

A similar pattern was observed for laboratory episodic memory: *APOE*  $\epsilon 4$  accounted for 13.6% of the variance in laboratory episodic memory performance ( $\beta = -0.37$ ,  $p = .001$ ). However after controlling for MTL volume, *APOE*  $\epsilon 4$  only accounted for 2.5% of the variance in laboratory episodic memory ( $\beta = -.17$ ,  $p = .105$ ), which is an 82% reduction. Again, each individual MTL region accounted for a large percentage of the variance shared between *APOE*  $\epsilon 4$  carrier status and episodic memory performance (Table 8). *APOE*  $\epsilon 4$  carrier status accounted for 13.6% of the variance in episodic memory, but it only accounted for 1.7% after controlling for entorhinal volume (88% reduction), 3.2% after controlling for hippocampal volume (76% reduction), and 7.1% after controlling for parahippocampal volume (48% reduction).

### **BDNF and KIBRA**

No effects of *BDNF* or *KIBRA* genotypes approached significance.

### **Summary**

In sum, *APOE* predicted memory for everyday activities, which replicated the findings from Study 1 in a different sample of older adults. We also replicated the standard finding that *APOE* genotype predicts episodic memory performance in a sample of non-demented and mildly demented older adults. Further, differences in MTL volume mediated the relationship between *APOE* and everyday memory. This result suggests that carrying the  $\epsilon 4$  allele results in increased MTL atrophy, and MTL atrophy results in decreased everyday memory ability. Importantly, these results held even after controlling for dementia

status, which indicates that MTL volume captures genetically determined changes in neuronal integrity and AD-related neuropathology not captured by the CDR scale.

### General discussion

In two separate samples, we found that older  $\epsilon 4$  carriers performed significantly worse than did noncarriers on measures of everyday memory. Importantly, *APOE* genotype predicted everyday memory in cognitively healthy older adults (Study 1). It also predicted everyday memory beyond age and dementia status in a sample of cognitively healthy and mildly demented older adults (Study 2). Thus, these everyday memory measures capture genetically determined cognitive decline that occurs prior to a clinical diagnosis of dementia and throughout the early clinical dementia phase. This finding could have important practical implications for clinicians.

The effect of *APOE* on laboratory episodic memory in older adults has been repeatedly demonstrated (e.g., Bäckman et al., 2005; Bondi et al., 1995; Filippini et al., 2009; Nilsson et al., 2006; Pike et al., 2011; Schultz et al., 2008; Wisdom et al., 2011) and was replicated here. However, the everyday memory measures used here have two distinctive features that are theoretically and clinically important. First, the stimuli are ecologically valid. Compared to tests of memorized words or word pairs, recall memory for the actions of people engaged in everyday activities corresponds more closely to the tasks that older adults and the caregivers of AD patients most often complain about (Gilewski et al., 1990; Jorm & Jacomb, 1989). Second, in the current study the measurement of everyday memory was efficient. We found that the effect sizes for the difference in performance between older carriers and older noncarriers were similar for the individual laboratory episodic memory tasks and the individual everyday memory tasks. Importantly, the administration of everyday memory measures – including the viewing and recall of 3 movies – takes a total of approximately 25–30 min (approximately 8–10 min per movie). On the other hand, the administration of a battery of at least three episodic memory tasks often used during clinical interviews (e.g., selective reminding, verbal paired associates, and list learning for diagnosing AD) takes approximately 55–75 min (Buschke, 1973; Small et al., 1999; Weschler & Stone, 1973).

Additionally, we found that the effect of *APOE* genotype was strongest in older adults. Older adult  $\epsilon 4$  noncarriers outperformed  $\epsilon 4$  carriers on the episodic and everyday memory measures, which is consistent with the resource modulation hypothesis (Lindenberger et al., 2008). This hypothesis states that various genes will have a stronger influence on cognition as the neurochemical, anatomical, and functional brain resources (e.g., dopamine and white matter) associated with normal aging decrease.

Regarding the effects in young adults, Mondadori et al. (2007) argued that survival of the  $\epsilon 4$  allele is due to the fact that it is actually advantageous to young adults. They reported that young  $\epsilon 4$  carriers showed better memory performance and decreased neural activity, which they state is a “more economic use of learning-related neural resources” (p. 1940). Tuminello and Han (2011) reviewed evidence similar to these findings and proposed that the *APOE* gene may be an example of antagonistic pleiotropy. Antagonistic pleiotropy is a concept in evolutionary theories of aging in which the same allele has opposite effects at different ages. In the case of *APOE*, the  $\epsilon 4$  allele may be beneficial early in life but detrimental later in life. Many studies have demonstrated the beneficial effects of *APOE*  $\epsilon 4$  in young adults (Alexander et al., 2007; Evans et al., 2013; Marchant, King, Tabet, & Rusted, 2010; Rusted et al., 2013; but see Bunce et al., 2014).

The present data do not provide much evidence for this hypothesis: Throughout the age range sampled in Study 1, everyday memory performance and episodic memory performance was strictly worse for  $\epsilon 4$  carriers than for noncarriers. However, when the participants were broken down into a younger and older group, the *APOE*  $\epsilon 4$  effects were significant only on older adults, and extrapolating from the data the regression lines do cross for the very youngest ages in both cases. This provides a weak piece of evidence for an antagonistic pleiotropy effect.<sup>5</sup> In future research it would be valuable to examine everyday memory performance in very young  $\epsilon 4$  carriers and noncarriers.

Finally, we found that the integrity of the MTL mediates the relationship between *APOE*  $\epsilon 4$  carrier status and everyday memory performance in older adults. MTL volume may be involved in this relationship because *APOE*  $\epsilon 4$  facilitates the accumulation of amyloid  $\beta$  or the alteration of tau in medial temporal structures – including the hippocampus (Mahley & Huang, 1999; Thal et al., 2006). The accumulation of amyloid  $\beta$  and neurofibrillary tangles eventually leads to neuronal degeneration (i.e., atrophy in the MTL), and previous work has demonstrated that decreased MTL volume is associated with poorer everyday memory (Bailey et al., 2013). Thus, results from Study 2 suggest that MTL volume may be a neurophysiological link between being an *APOE*  $\epsilon 4$  carrier and having poorer memory for everyday activities in older adults.

We should note that in comparison to other large-scale genetics studies, the sample size within our genotypes was relatively small, particularly within each CDR group in Study 2. Nonetheless, we found that the *APOE*  $\epsilon 4$  allele, which has previously been linked with lower performance on some laboratory measures of memory, also predicted memory for everyday activities. The *APOE* genotype is associated with the ability to remember details of a recent conversation with a loved one or the activities performed on a previous day, for example. Importantly, these are some of the most common complaints amongst cognitively healthy older adults and those in the early stages of AD (Gilewski et al., 1990; Jorm & Jacomb, 1989). Thus, the measures of everyday memory used in the current studies may be a useful diagnostic tool to capture genetically determined cognitive declines in older adults.

### Disclosure statement

No potential conflict of interest was reported by the authors.

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### Supplemental data

Supplemental data for this article can be accessed at <http://dx.doi.org/10.1080/13825585.2015.1020916>.

### Notes

1. Historically, everyday memory has been a controversial term. For some, it refers to a collection of field studies of naturally occurring memoranda, which has been criticized for lack of experimental control (e.g., Banaji & Crowder, 1989). More broadly, the field has used the



- term to refer to memory tasks and materials that approximate important features of memory for everyday events. This is how we will use the term.
- Given that the  $\epsilon 2$  allele has been associated with better cognitive performance (e.g., Corder et al., 1994), we also conducted all of the analyses excluding participants with 2–4 genotypes (2 in Study 1; 2 in Study 2). For some comparisons, the effects became slightly stronger and, for other comparisons, the effects became slightly weaker; however, excluding the 2–4 participants did not change the significance of any of our results or conclusions.
  - GDS scores were missing for 4 participants. Short Blessed Test and MMSE scores were missing for 3 participants.
  - Why would the everyday event recognition measures be reliable in the Alzheimer's sample and not in the life span sample? One possibility is that written recall was used for the life span sample, whereas oral recall was used for the Alzheimer's sample. Written recall may provide more feedback regarding memory for the activity, and feedback has been shown to strengthen a memory trace (Pashler, Cepeda, Wixted, & Rohrer, 2005). Thus, the recall test format may influence what the recognition and order memory tests assess, which can influence their internal consistency.
  - In regressions with age predicting everyday memory performance, the regression lines for  $\epsilon 4$  carriers and noncarriers crossed at age 21.1 years. The estimated difference in everyday memory performance at 10 years of age was 1.33 fine-grained units of activity recalled (or 0.109 standard deviations) in favor of the  $\epsilon 4$  carriers, whereas the estimated difference at 70 years of age was 5.81 fine-grained units (or 0.551 standard deviations) in favor of the noncarriers. For episodic memory performance, the regression lines for  $\epsilon 4$  carriers and noncarriers crossed at age 20.0 years. The estimated difference in episodic memory performance at 10 years of age was 0.110 standard deviations in favor of the  $\epsilon 4$  carriers, whereas the estimated difference at 70 years of age was 0.548 standard deviations in favor of the noncarriers.

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