HHS Public Access

Author manuscript

Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. Author manuscript; available in PMC 2015 November 01.

Published in final edited form as:

Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2015 November ; 22(6): 639–666. doi: 10.1080/13825585.2015.1020916.

APOE ε4 Genotype Predicts Memory for Everyday Activities

Heather R. Bailey[a], **Jesse Q. Sargent**[a], **Shaney Flores**[a], **Petra Nowotny**[b], **Alison Goate**[b], and **Jeffrey M. Zacks**[a]

[a]Department of Psychology, Washington University St. Louis, Campus Box 1125, St. Louis, MO 63130

[b]Department of Psychiatry, Washington University St. Louis, Campus Box 8134, St. Louis, MO 63110

Abstract

The *apolipoprotein E (ApoE) ε4* 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 ε4* carriers demonstrated worse everyday memory performance than did *ε4* non-carriers. In Study 2, *ApoE ε4* carriers had smaller 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 *ε4* 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 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 *(ε2, ε3*, and *ε4)*; the *ε4* 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 ε4* and AD and given the episodic memory deficits associated with AD, researchers have been interested in the relationship between *APOE ε4* status and performance on measures of episodic memory.

Correspondence concerning this article should be addressed to: Heather Bailey 414 Bluemont Hall Kansas State University Manhattan, KS 66506 hbailey@ksu.edu Phone: (785) 532-0807 Fax: (785) 532-5401.

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, 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. Previous research has evaluated the relationship between *APOE ε4* and prospective memory, but results generally show no effect of *APOE ε4* 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 ε4* and memory for everyday activities has not been examined, the current study evaluated whether *ε4* carrier status affects performance on tests of *everyday memory*[1]. 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., Wells & Penrod, 2011; Magliano, Dijkstra, & Zwaan, 1996; Lichtenstein & Brewer, 1980). The encoding and retrieval of this type of information involves the interaction of episodic, semantic, and working memory systems (Zacks et al., 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.

[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.

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 et al., 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 lifespan. 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 ε4* carrier status influences everyday memory, a number of studies of memory for verbal and pictorial materials have shown that *ε4* 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 et al., 2011). *APOE* genotype interacts with age such that the effect of the *ε4* 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, Evans, King, Dowell, Tabet, & Tofts, 2013). Schultz et al. (2008) found that *ε4* 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 et al., 2010), semantic memory (Boyle et al., 2010) and general cognitive ability (Deary et al., 2002).

Given that *APOE ε4* 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 ε4* 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* as genetic predictors of episodic and everyday memory. The methionine (*Met*) allele of the BDNF Val66Met 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 et al., 2008; but see Need et al., 2008), whereas there is conflicting evidence as to whether *T* carriers (Rodriguez-Rodriguez et al., 2009) or *non-T* carriers (Corneveaux et al., 2008) are at a greater risk for developing AD (for a review, see Schneider, Huentelman, Kremerskothen, Duning, Spoelgen, & Nikolich, 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 ε4* status affects everyday memory performance across the lifespan. Previous research suggests that the effects of *APOE ε4* 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 lifespan 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 seven minutes 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 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-minute 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 two-minute study period, participants were given five minutes 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 minutes 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) and the DNA was extracted from the saliva samples using the manufacturer's protocol. The single-nucleotide polymorphisms, which define the *APOE* ε2/ε3/ε4 isoforms, rs7412 and rs429358, and rs17070145 in *KIBRA*, were genotyped using the TaqMan® genotyping technology. The Val66Met (rs6265) polymorphism in *BDNF* was genotyped using a PCR-RFLP method using the following primers: F:5’-

ACTCTGGAGAGCGTGAAT-3'and R: 5'-ATACTGTCACACACGCTC-3'. The PCR products were digested with NlaIII (the VAL allele remains intact).

Procedure—Psychometric testing occurred in two 150-minute 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 (11 univariate outliers); we replaced 21 values that met this criterion using the expectation maximization (EM) 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 (|skewness| < 2.0, |kurtosis| < 2.0).

Results and Discussion

Although age was evaluated as a continuous variable for most of the statistical analyses, the frequency 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 *ε4* carriers and non-carriers 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: *ε4 carriers* (i.e., *2-4*[2], *3-4*, and *4-4*) and *non-carriers* (i.e., *2-2*, *2-3*, and *3-3*). There were 57 *ε4* carriers and 131 *ε4*-non-carriers. See Table 2 for the demographic information (i.e., age, gender, and education) for individuals in each group.

[2]*Given that the ε2 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.*

***Effect of the APOE ε4* 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 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; Backman 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), episodic memory scores were significantly lower in older adults, $\beta = -.367$, $p < .001$, and in *APOE ε4* carriers, $\beta = .166$, $p = .015$. The effect of *APOE ε4* carrier status was larger in older than younger adults; however, the Age × *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 *ε4* 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 ε4* 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 × *APOE* interaction was not significant, $\beta = -.273$, $p = .242$ (Figure 2). When the participants were split into a younger (20-49) and older (50-79) group, the effect of *ε4* 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 non-carriers. *APOE ε4* 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 non-carriers = 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 non-carriers = −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 *ε4* carriers performed significantly worse than did non-carriers on laboratory measures of episodic memory. Further, *ε4* 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 ε4* 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 ε4*-carrier status predicts memory for everyday activities in cognitively healthy older adults and those with mild dementia of the Alzheimer's type.

Frequently, *APOE ε4* 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 (Backman, Jones, Berger, Laukka, & Small, 2005) and mild cognitive impairment (Boyle, Buchman, Wilson, Kelly, and Bennett, 2010, but see Lange et al., 2002). Thus, we predicted that *APOE ε4* 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 ε4* 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, 2009). One of the hallmark neurophysiological

symptoms of AD is the accumulation of amyloid β protein (e.g., Masters, Simms, Weinman, Multhaup, McDonald, & Beyreuther, 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 ε4* 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 ε4* is related to amyloid β accumulation, but not tau (Morris et al., 2010). Although the exact role of *APOE ε4* in amyloid β metabolism is unknown, evidence suggests that the *ε4* allele is associated with a higher rate of deposition, lower rates of clearance, and less degradation of amyloid β (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 β.

Other potential mechanisms by which *APOE ε4* exerts its effects on neuronal integrity are through the distribution of cholesterol and neuronal repair (Mahley & Huang, 1999; Saunders, 2000). Although there is not one definitive mechanism by which *APOE ε4* influences brain structure, research has demonstrated that *APOE ε4* 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 ε4* 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 NINCDS-ADRDA standards (Jack Jr. et al., 2001; 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-minute 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 from 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.

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, 1988), Verbal Paired Associates from the Wechsler Memory Scale (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 × 1 mm × 1.25 mm resolution) were obtained for each subject. (Images for 7 participants were collected on a Siemens 1.5 Tesla Vision scanner, whereas images for 67 participants were collected on a Siemens 3 Tesla Trio scanner. Controlling for scanner type and the Scanner × 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[3].

Next, we computed a vascular risk composite variable to evaluate whether memory performance is influenced by the interaction between vascular risk and *APOE ε4*. A history of heart attack, atrial fibrillation, angioplasty, cardiac bypass procedures, congestive heart

[3]GDS scores were missing for 4 participants. Short Blessed Test and MMSE scores were missing for 3 participants.

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 ε4*-carrier status in predicting laboratory episodic memory performance or everyday memory, Fs < 1. Given these results, vascular risk was not included as a predictor in the remaining regression analyses.

The number of *ε4* carriers and non-carriers 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 *ε4*-carrier group and the *2-2*, *2-3*, and *3-3* genotypes into the non-carrier group, which resulted in 37 carriers and 60 non-carriers. The proportion of *ε4* carriers was higher in the CDR 1 group than in the other two groups, but not significantly so, X^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 (ts = 4.86 to 8.11, ps < .001, ds = 0.33 to 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 (rs = .79 to .92), as was performance on the everyday memory tasks (rs = .78 to .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.[4]

Effect of the *APOE ε4* allele on episodic and everyday memory—A 3 (CDR Group) × 2 (Carrier Status) 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, η^2 = .02,

[4]Why would the everyday event recognition measures be reliable in the Alzheimer's sample and not in the lifespan sample? One possibility is that written recall was used for the lifespan 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.

with the ε4 carriers (M = −0.32, SD = 0.94) performing worse than the non-carriers (M = 0.27, SD = 0.83). In all three groups, ε4 carriers performed worse than non-carriers, 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 × 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 ε4 carriers and non-carriers. Everyday memory performance as a function of CDR group and carrier status is shown in Figure 4. A 3 (CDR Group) × 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 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 non-carriers (M = 0.21, SD = 0.58). The CDR Group × 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 non-carriers 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 (ds = 0.03 to 0.99) and the individual everyday memory tasks (ds = 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 group, ε4 carrier status predicted 4% unique variance in everyday memory performance ($\beta = .19$, $p = .037$). That is, *APOE ε4* carrier status significantly predicted episodic memory and everyday memory above and beyond dementia status.

Medial temporal lobe volume mediates the relationship between *APOE ε4* and everyday memory—The ε4 allele is related to increased amyloid β 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 ε4* carrier status and everyday memory.

As predicted, an independent-samples *t*-test indicated that MTL volume was significantly lower in *ε4* carriers than in non-carriers, $t(70) = 2.932$, $p = .003$, $d = 0.71$. To examine whether *APOE* only predicts MTL volume because of potential third variables, we evaluated whether *APOE ε4* 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 ε4* carrier status predicted a significant amount of unique variance in MTL volume ($R^2 = 0.11$, $p = .005$).

Finally, given that *APOE ε4* 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 ε4* carrier status and everyday memory. In the first analysis, we regressed episodic memory onto *APOE ε4* carrier status, and in the second analysis we regressed episodic memory onto *APOE ε4* carrier status after entering MTL volume into the regression model. All regressions were conducted controlling for age.

APOE ε4 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 ε4* 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, & deToledo-Morrell, 2010). *APOE ε4* 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 ε4* 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 ε4* carrier status accounted for a non-significant amount of unique variance in everyday memory performance ($R^2 = .02$, $\beta = -0.14$, $p = .141$).

A similar pattern was observed for laboratory episodic memory: *APOE ε4* accounted for 13.6% of the variance in laboratory episodic memory performance ($\beta = -0.37$, $p = .001$). However after controlling for MTL volume, *APOE ε4* 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 ε4* carrier status and episodic memory performance (Table 8). *APOE ε4* 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).

***BNDF* 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 *ε4* 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 CDR scale.

General Discussion

In two separate samples, we found that older *ε4* carriers performed significantly worse than did non-carriers 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., Backman 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 non-carriers 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 minutes (approximately 8-10 minutes 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 minutes (Buschke, 1984; Small et al., 1999; Weschler & Stone, 1973).

Additionally, we found that the effect of *APOE* genotype was strongest in older adults. Older adult *ε4* non-carriers outperformed *ε4* carriers on the episodic and everyday memory measures, which is consistent with the resource modulation hypothesis (Lindenberger, Nagel, Chicherio, Li, Heekeren, & Backman, 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 *ε4* allele is due to the fact that it is actually advantageous to young adults. They reported that young *ε4* 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 *ε4* allele may be beneficial early in life but detrimental later in life. Many studies have demonstrated the beneficial effects of *APOE ε4* 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 *ε4* carriers than for non-carriers. However, when the participants were broken down into a younger and older group, the *APOE ε4* 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[5]. In future research it would be valuable to examine everyday memory performance in very young *ε4* carriers and non-carriers.

Finally, we found that the integrity of the MTL mediates the relationship between *APOE ε4* carrier status and everyday memory performance in older adults. MTL volume may be involved in this relationship because *APOE ε4* facilitates the accumulation of amyloid β or the alteration of tau in medial temporal structures – including the hippocampus (Mahley & Huang, 1999; Thal et al., 2006). The accumulation of amyloid β 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

[5]In regressions with age predicting everyday memory performance, the regression lines for *ε4* carriers and non-carriers 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 *ε4* 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 non-carriers. For episodic memory performance, the regression lines for *ε4* carriers and non-carriers 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 *ε4* carriers, whereas the estimated difference at 70 years of age was 0.548 standard deviations in favor of the non-carriers.

neurophysiological link between being an *APOE ε4* 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 ε4* 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by NIH grant R01 AG031150, PI Jeffrey M. Zacks; NIH grant F32 AG039162, PI Heather Bailey; NIA grants P50 AG05681, P01 AG03991, P01 AG26276, PI John C. Morris; and the generous support of Fred Simmons and Olga Mohan.

References

Adamson MM, Landy KM, Duong S, Fox-Bosetti S, Ashford JW, Murphy GM, Weiner M, Taylor JL. Apolipoprotein E ε4 influences on episodic recall and brain structures in aging pilots. Neurobiology of Aging. 2010; 31:1059–1063. [PubMed: 18760504]

Alexander DM, Williams LM, Gatt JM, Dobson-Stone C, Kuan SA, Todd EG, et al. The contribution of apolipoprotein E alleles on cognitive performance and dynamic neural activity over six decades. Biological Psychology. 2007; 75:229–238. [PubMed: 17433528]

Almeida OP, Schwab SG, Lautenschlager NT, Morar B, Greenop KR, Flicker L, Wildenauer D. KIBRA genetic polymorphism influences episodic memory in later life, but does not increase the risk of mild cognitive impairment. Journal of Cellular and Molecular Medicine. 2008; 12:1672–1676. [PubMed: 18194457]

Backman L, Jones S, Berger AK, Laukka EJ, Small BJ. Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. Neuropsychology. 2005; 19:520–531. [PubMed: 16060827]

Bailey HR, Zacks JM, Hambrick DZ, Zacks RT, Head D, Kurby CA, Sargent JQ. Medial temporal lobe volume predicts elders' everyday memory. Psychological Science. 2013; 24:1113–1122. [PubMed: 23630222]

Baxter LC, Caselli RJ, Johnson SC, Reiman E, Osborne D. Apolipoprotein E epsilon 4 affects new learning in cognitively normal individuals at risk for Alzheimer's disease. Neurobiology of Aging. 2003; 24:947–952. [PubMed: 12928055]

Berg L, McKeel DW Jr. Miller JP, Storandt M, Rubin EH, Morris JC, Baty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: Relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Archives of Neurology. 1998; 55:326–335. [PubMed: 9520006]

Bertreau-Pavy F, Park B, Raber J. Effects of sex and APOE epsilon4 on object recognition and spatial navigation in the elderly. Neuroscience. 2007; 147:6–17. [PubMed: 17509769]

Bondi MW, Salmon DP, Monsch AU, Galasko D, Butters N, Klauber MR, et al. Episodic memory changes are associated with the APOE-4 allele in nondemented older adults. Neurology. 1995; 45:2203–2206. [PubMed: 8848194]

Bourgeat P, Chetelat G, Villemagne VL, Fripp J, Raniga P, Pike K, Acosta O, Szoeke C, Ourselin S, Ames D, Ellis KA, Martins RN, Masters CL, Rowe CC, Salvado O. Beta-amyloid burden in the temporal neocortex is related to the hippocampal atrophy in elderly subjects without dementia. Neurology. 2010; 74:121–127. [PubMed: 20065247]

Boyle PA, Buchman AS, Wilson RS, Kelly JF, Bennett DA. The APOE ε4 allele is associated with incident mild cognitive impairment among community-dwelling older persons. Neuroepidemiology. 2010; 34:43–49. [PubMed: 19907191]

Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathologica. 1991; 82:239–259. [PubMed: 1759558]

Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, Snyder AZ. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. NeuroImage. 2004; 23:724–738. [PubMed: 15488422]

Bunce D, Bielak AAM, Anstey KJ, Cherbuin N, Batterham PJ, Easteal S. *APOE* genotype and cognitive change in young, middle-aged, and older adults living in the community. Journals of Gerontology: Series A. 2014; 69:379–386.

Buschke H. Selective reminding for analysis of memory and learning. Journal of Verbal Learning and Verbal Behavior. 1973; 12:543–550.

Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, et al. Longitudinal modeling of age-related memory decline and the *APOE ε4* effect. The New England Journal of Medicine. 2009; 361:255–263. [PubMed: 19605830]

Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmwchel DE, Gaskell PC Jr. Rimmier JB, Locke PA, Conneally PM, Schmader KE, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nature Genetics. 1994; 7:180–184. [PubMed: 7920638]

Corder EH, Saunders AM, Strittmatter WJ, Schmwchel DE, Gaskell PC Jr. Small GW, et al. Gene dose of aplipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. Aug 13.1993 261:921–923. [PubMed: 8346443]

Corneveaux JJ, Liang WS, Reiman EM, Webster JA, Myers AJ, Zismann VL, Joshipura KD, Pearson JV, Hu-Lince D, Craig DW, Coon KD, Dunckley T, Bandy D, Lee W, Chen K, Beach TG, Mastroeni D, Grover A, Ravid R, Sando SB, Aasly JO, Heun R, Jessen F, Kolsch H, Rogers J, Hutton ML, Melquist S, Petersen RC, Alexander GE, Caselli RJ, Papassotiropoulos A, Stephan DA, Huentelman MJ. Evidence for an association between KIBRA and late-onset Alzheimer's disease. Neurobiology of Aging. 2008; 31:901–909. [PubMed: 18789830]

Deary IJ, Whiteman MC, Pattie A, Starr JM, Hayward C, Wright AF, Carothers A, Whalley LJ. Cognitive change and the APOE ε4 allele. Nature. 2002; 418:932. [PubMed: 12198535]

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006; 31:968–980. [PubMed: 16530430]

Du AT, Schuff N, Kramer JH, Ganzer S, Zhu XP, Jagust WJ, Miller BL, Reed BR, Mungas D, Yaffe K, Chul HC, Weiner MW. Higher atrophy rate of entorhinal cortex than hippocampus in AD. Neurology. 2004; 62:422–427. [PubMed: 14872024]

Duchek JM, Balota DA, Cortese M. Prospective memory and apolipoprotein E in healthy aging and early Alzheimer's disease. Neuropsychology. 2006; 20:633–644. [PubMed: 17100508]

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val 66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112:257–269. [PubMed: 12553913]

ELSMEM: A Computerized Battery to Assess Executive, Linguistic, Spatial, and MEMory Abilities (http://www.psych.wustl.edu/coglab/index.html).

Evans S, Gray MA, Dowell NG, Tabet N, Tofts PS, King SL, Rusted JM. APOE e4 carriers show prospective memory enhancement under nicotine, and evidence for specialisation within medial BA10. Neuropsychopharmacology. 2013; 38:655–663. [PubMed: 23232444]

Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE. Distinct patterns of brain activity in young carriers of the APOE ε4 allele. PNAS. 2009; 106:7209–7214. [PubMed: 19357304]

Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC. The AD8, a brief informant interview to detect dementia. Neurology. 2005; 65:559–564. [PubMed: 16116116]

Gilewski MJ, Zelinski EM, Schaie KW. The Memory Functioning Questionnaire for assessment of memory complaints in adulthood and old age. Psychology and Aging. 1990; 5:482–490. [PubMed: 2278670]

Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology. 1988; 38:900–903. [PubMed: 3368071]

Hariri AR, Goldberg TE, Mattay VS, Kolachana JH, Egan MF, Weinberger DR. Brain-derived neurotrophic factor vall66met polymorphisms affect human memory-related hippocampal activity and predicts memory performance. The Journal of Neuroscience. 2003; 23:6690–6694. [PubMed: 12890761]

Holtzman DM. Role of ApoE/Abeta interactions in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy. Journal of Molecular Neuroscience. 2001; 17:147–155. [PubMed: 11816788]

Holtzman DM, Morris JC, Goate AM. Alzheimer's disease: The challenge of the second century. Science Translational Medicine. 2011; 6:1–17.

Jack CR Jr. Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH. Introduction to the recommendations from the National Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2011; 7:257–262.

Jack CR Jr. Twomey CK, Zinsmeister AR, Sharbrough FW, Petersen RC, Cascino GD. Anterior temporal lobes and hippocampal formations: Normative volumetric measurements. Radiology. 1989; 172:549–554. [PubMed: 2748838]

Jiang Q, Lee CYD, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Willson TM, Collins JL, Richardson JC, Smith JD, Comery TA, Riddell D, Holtzmann DM, Rontonoz P, Landreth GE. ApoE promotes the proteolytic degradation of Aβ. Neuron. 2008; 58:681–693. [PubMed: 18549781]

Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): sociodemographic correlates, reliability, validity and some norms. Psychological Medicine. 1989; 19:1015–1022. [PubMed: 2594878]

Kambeitz JP, Bhattacharyya S, Kambetiz-Ilankovic LM, Vallie I, Collier DA, McGuire P. Effect of BDNF val(66)met polymorphism on declarative memory and its neural substrate: A meta-analysis. Neuroscience and Biobehavioral Reviews. 2012; 36:2165–2177. [PubMed: 22813992]

Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short orientation-memory concentration test of cognitive impairment. American Journal of Psychiatry. 1983; 140:734–739. [PubMed: 6846631]

Kim J, Basak JM, Holtzmann DM. The role of apolipoprotein E in Alzheimer's disease. Neuron. 2009; 63:287–303. [PubMed: 19679070]

Kurby CA, Zacks JM. Age differences in the perception of hierarchical structure. Memory & Cognition. 2011; 39:75–91. [PubMed: 21264613]

Lange KL, Bondi MW, Salmon DP, Galasko D, Delis DC, Thomas RG, Thal LJ. Decline in verbal memory during preclinical Alzheimer's disease: Examination of the effect of APOE genotype. Journal of the International Neuropsychological Society. 2002; 8:943–955. [PubMed: 12405546]

Laukka EJ, Lovden M, Herlitz A, Karlsson S, Ferencz B, Pantzar A, Keller L, Graff C, Fratiglioni L, Backman L. Genetic effects of old-age cognitive functioning: A population-based study. Psychology and Aging. 2012; 28:262–274. [PubMed: 23276211]

Lichtenstein EH, Brewer WF. Memory for goal-directed events. Cognitive Psychology. 1980; 12:412–445.

Magliano JP, Dijkstra K, Zwaan RA. Generating predictive inferences while viewing a movie. Discourse Processes. 1996; 22:199–224.

Mahley RW, Huang Y. Apolipoprotein E: From artherosclerosis to Alzheimer's disease and beyond. Current Opinions on Lipodology. 1999; 10:207–217.

Mahley RW, Rall SC Jr. APOLIPOPROTEIN E: Far more than a lipid transport protein. Annual Review of Genomics and Human Genetics. 2000; 1:507–537.

Marchant NL, King SL, Tabet N, Rusted JM. Positive effects of cholinergic stimulation favor young APOE epsilon4 carriers. Neuropsychopharmacology. 2010; 35:1090–1096. [PubMed: 20072115]

Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. PNAS. 1985; 82:4245–4249. [PubMed: 3159021]

McDaniel MA, Shelton JT, Breneiser JE, Moynan S, Balota DA. Focal and non-focal prospective memory performance in very mild dementia: A signature decline. Neuropsychology. 2011; 25:387–396. [PubMed: 21443344]

McDonald CR. Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. Neurology. 2009; 73:457–465. [PubMed: 19667321]

McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]

Milnik A, Heck A, Vogler C, Heinze HJ, de Quervain DJF, Papassotiropoulos A. Association of KIBRA with episodic and working memory: A meta-analysis. American Journal of Medical Genetics Neuropsychiatric Genetics. 2012; 159B:958–969.

Mondadori CRA, de Quervain DJF, Buchmann A, Mustovic H, Wollmer MA, Schmidt CF, Boesiger P, Hock C, Nitsch RM, Papassotiropoulos A, Henke K. Better memory and neural efficiency in young apolipoprotein E ε4 carriers. Cerebral Cortex. 2007; 17:1934–1947. [PubMed: 17077159]

Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]

Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA. *APOE* predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Annals of Neurology. 2010; 67:122–131. [PubMed: 20186853]

Muse J, Emery M, Sambataro F, Lemaitre H, Tan HY, Chen Q, et al. WWC1 genotype modulates age-related decline in episodic memory function across the adult life span. Biological Psychiatry. 2014; 75:693–700. [PubMed: 24290728]

Need AC, Attix DK, McEvoy JM, Cirulli ET, Linney KN, Wagoner AP, Gumbs CE, Giegling I, Moller HJ, Francks C, Muglia P, Roses A, Gibson G, Weale ME, Rujescu D, Goldstein DB. Failure to replicate effect of Kibra on human memory in two large cohorts of European origin. American Journal of Medical Genetics B: Neuropsychiatric Genetics. 2008; 147B:667–668. [PubMed: 18205171]

Nilsson LG, Adolfsson R, Backman L, Cruts M, Nyberg L, Small BJ. The influence of APOE status on episodic and semantic memory: Data from a population-based study. Neuropsychology. 2006; 20:645–657. [PubMed: 17100509]

Packard CJ, Westendorp RG, Stott DJ, Caslake MJ, Murray HM, et al. Association between apolipoprotein E4 and cognitive decline in elderly adults. Journal of the American Geriatric Society. 2007; 55:1777–1785.

Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoerndli FJ, Craig DW, Pearson JV, Huynh KD, Brunner F, Corneveaux J, Osborne D, Wollmer MA, Aerni A, Coluccia D, Hanggi J, Mondadori CR, Buchmann A, Reiman EM, Caselli RJ, Henke K, de Quervain DJ. Common Kibra alleles are associated with human memory performance. Science. 2006; 314:475–478. [PubMed: 17053149]

Pashler H, Cepeda N, Wixted J, Rohrer D. When does feedback facilitate learning of words? Journal of Experimental Psychology: Learning, Memory, and Cognition. 2005; 31:3–8.

Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H, Kokmen E. Neuropathologic features of amnestic mild cognitive impairment. Archives of Neurology. 2006; 63:665–672. [PubMed: 16682536]

Pike KE, Villemagne VL, Good N, Chetelat G, Ames D, Szoeke C, Laws SM, Verdile G, Martins RN, Masters CL, Rowe CC. Cognition and beta-amyloid in preclinical Alzheimer's disease: Data from the AIBL study. Neuropsychologia. 2011; 49:2384–2390. [PubMed: 21529702]

Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet. 1993; 342:697–699. [PubMed: 8103819]

Price JL, Morris JC. Tangles and plaques in nondemented aging and “preclinical” Alzheimer's disease. Annals of Neurology. 1999; 45:358–368. [PubMed: 10072051]

Raz N, Rodrigue KM, Kennedy KM, Land S. Genetic and vascular modifiers of age-sensitive cognitive skills of COMT, BDNF, ApoE, and hypertension. Neuropsychology. 2009; 23:105–116. [PubMed: 19210038]

Reiman EM, Caselli RJ, Chen K, Alexander GE, Bandy D, Frost J. Declining brain activity in cognitively normal apolipoprotein E *ε4* heterozygotes: A foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease. PNAS. 2001; 98:3334–3339. [PubMed: 11248079]

Reinvang I, Winjevoll IL, Rootwelt H, Espeseth T. Working memory deficits in healthy APOE epsilon 4 carriers. Neuropsychologia. 2010; 48:566–573. [PubMed: 19879282]

Rodriguez-Rodriguez E, Infante J, Llorca J, Mateo I, Sanchez-Quintana C, Garcia-Gorostiaga I, Sanchez-Juan P, Berciano J, Combarros O. Age-dependent association of KIBRA genetic variation and Alzheimer's disease risk. Neurobiology of Aging. 2009; 30:322–324. [PubMed: 17707552]

Rosen VM, Caplan L, Sheesley L, Rodriguez R, Grafman J. An examination of daily activities and their scripts across the adult lifespan. Behavior Research Methods, Instruments, & Computers. 2003; 35:32–48.

Rusted JM, Evans SL, King SL, Dowell N, Tabet N, Tofts PS. APOE e4 polymorphism in young adults is associated with improved attention and indexed by distinct neural signatures. Neuroimage. 2013; 65:364–373. [PubMed: 23063453]

Sargent JQ, Zacks JM, Hambrick DZ, Zacks RT, Kurby CA, Bailey HR, Eisenberg ML, Beck TM. Event segmentation ability uniquely predicts memory across the lifespan. Cognition. 2013; 129:241–255. [PubMed: 23942350]

Schaper K, Kolsch H, Popp J, Wagner M, Jessen F. KIBRA gene variants are associated with episodic memory in healthy elderly. Neurobiology of Aging. 2008; 29:1123–1125. [PubMed: 17353070]

Schneider A, Huentelman MJ, Kremerskothen J, Duning K, Spoelgen R, Nikolich K. KIBRA: A new gateway to learning and memory? Frontiers in Aging Neuroscience. 2010; 2:1–9. [PubMed: 20552041]

Schultz M, Lyons M, Franz C, Grant M, Boake C, Jacobson K, Xian H, Schellenberg G, Eisen S, Kremen W. Apolipoprotein E genotype and memory in the sixth decade of life. Neurology. 2008; 70:1771–1777. [PubMed: 18235080]

Schwartz MF. The quantitative description of action disorganization after brain damage: A case. Cognitive Neuropsychology. 1991; 8:381–414.

Schwartz MF, Segal M, Veramonti T, Ferraro M, Buxbaum LJ. The Naturalistic Action Test: A standardized assessment for everyday action impairment. Neuropsychological Rehabilitation. 2002; 24:311–339.

Small BJ, Dixon RA, Hultsch DF, Hertzog C. Longitudinal changes in quantitative and qualitative indicators of word and story recall in young-old and old-old adults. Journals of Gerontology: Psychological Sciences. 1999; 54B:107–115.

Stoub TR, Rogalski EJ, Leurgans S, Bennett DA, deToledo-Morrell L. Rate of entorhinal and hippocampal atrophy in incipient and mild AD: Relation to memory function. Neurobiology of Aging. 2010; 31:1089–1098. [PubMed: 18809228]

Thal DT, Capetillo-Zarate E, Del Tredici K, Braak H. The development of amyloid β protein deposits in the aged brain. Science of Aging Knowledge Environment. 2006; 6:1–9.

Tuminello ER, Han SD. The apolipoprotein E antagonistic pleiotropy hypothesis: Review and recommendations. International Journal of Alzheimer's Disease. 2011; 2011:1–12.

Wechsler, D. Wechsler Adult Intelligence Scale—3rd Edition (WAIS-3®). Harcourt Assessment; San Antonio, TX: 1997.

Wechsler, D.; Stone, CP. Wechsler Memory Scale. Psychological Corporation; New York: 1973.

Wells, GL.; Penrod, SD. Eyewitness identification research: Strengths and weaknesses of alternative methods.. In: Rosenfeld, B.; Penrod, SD., editors. Research methods in forensic psychology. John Wiley and Sons; Hoboken, NJ: 2011.

Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. Neurobiology of Aging. 2011; 32:63–74. [PubMed: 19285755]

Zacks JM, Speer NK, Swallow KM, Braver TS, Reynolds JR. Event perception: A mind/brain perspective. Psychological Bulletin. 2007; 133:273–293. [PubMed: 17338600]

Zacks JM, Speer NK, Vettel JM, Jacoby LL. Event understanding and memory in healthy aging and dementia of the Alzheimer type. Psychology & Aging. 2006; 21:466–482. [PubMed: 16953710]

Zlokovic BV, Deane R, Sallstrom J, Chow N, Miano JM. Neurovascular pathways and Alzheimer amyloid beta-peptide. Brain Pathology. 2005; 15:78–83. [PubMed: 15779240]

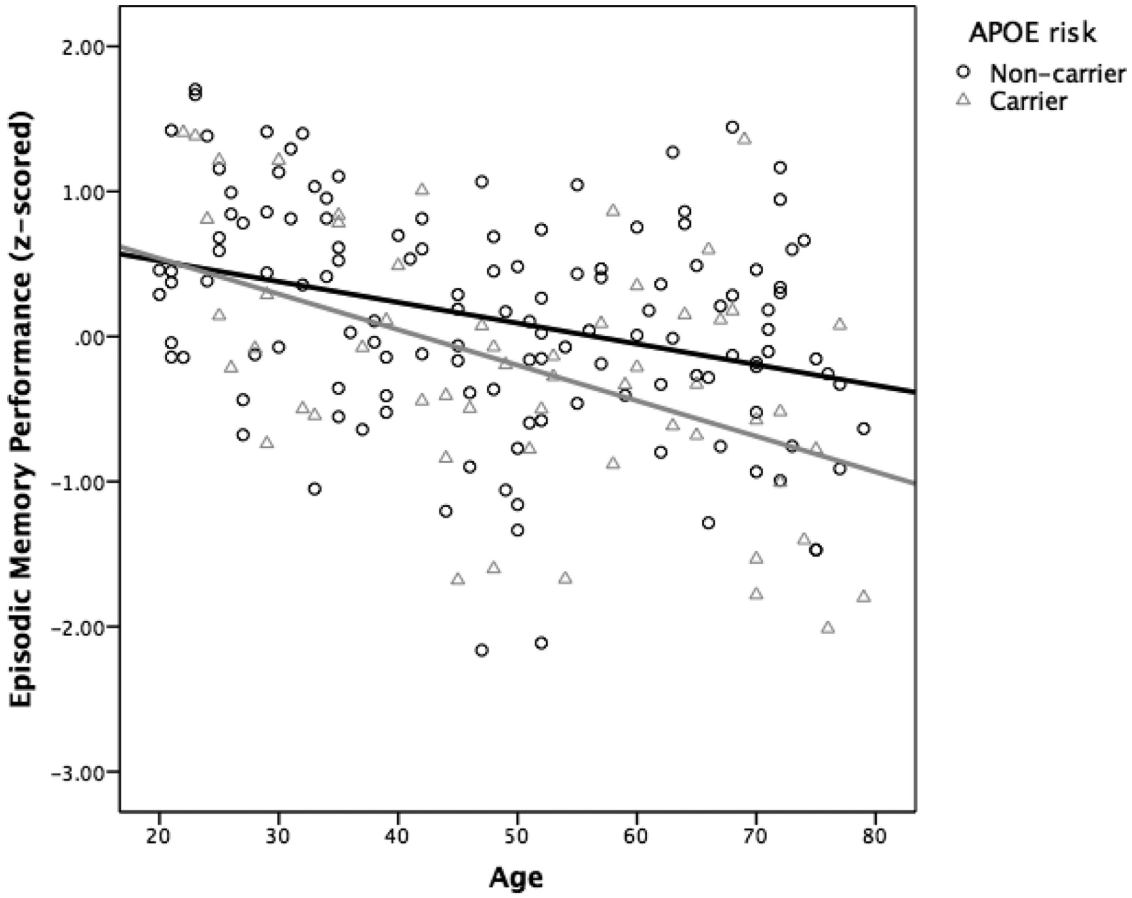

Figure 1.

Laboratory episodic memory performance for *APOE e4* carriers or non-carriers across the lifespan (Study 1).

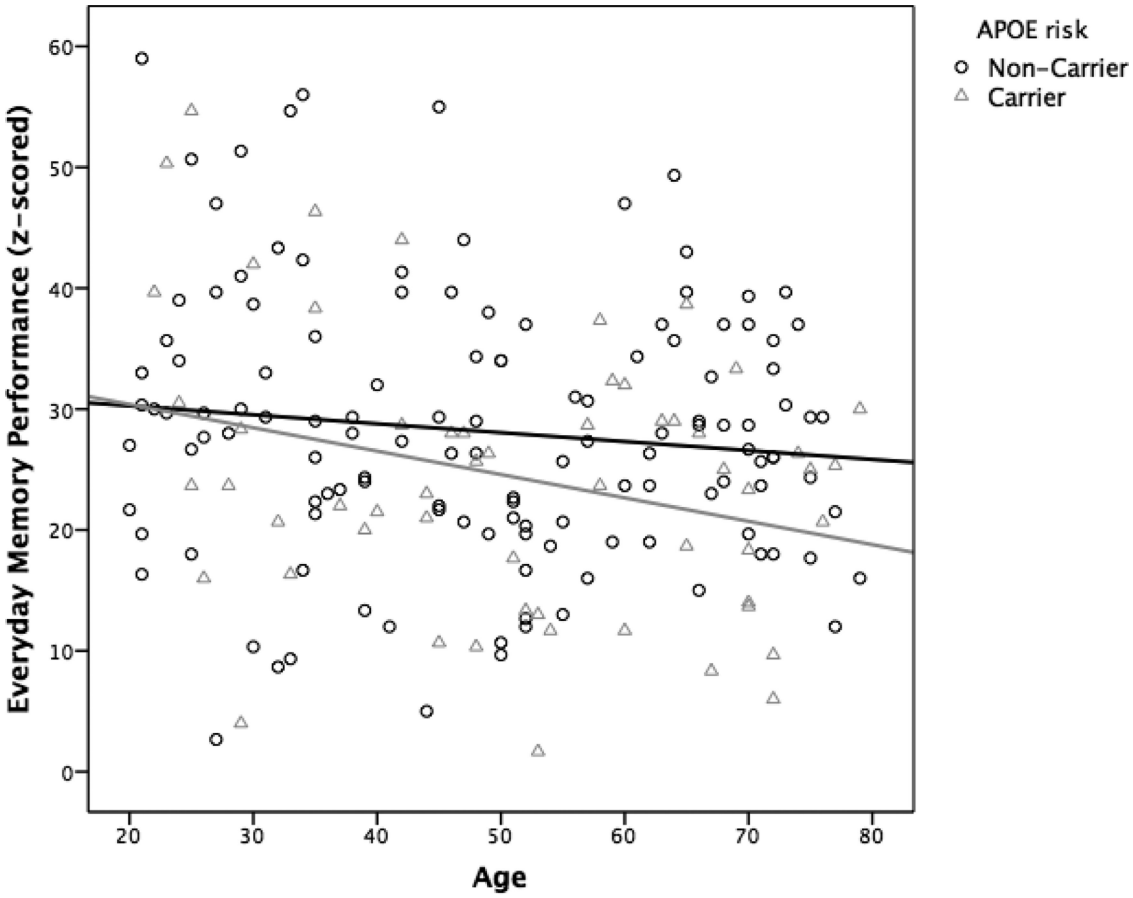

Figure 2.
Everyday memory performance for *APOE ε4* carriers or non-carriers across the lifespan (Study 1).

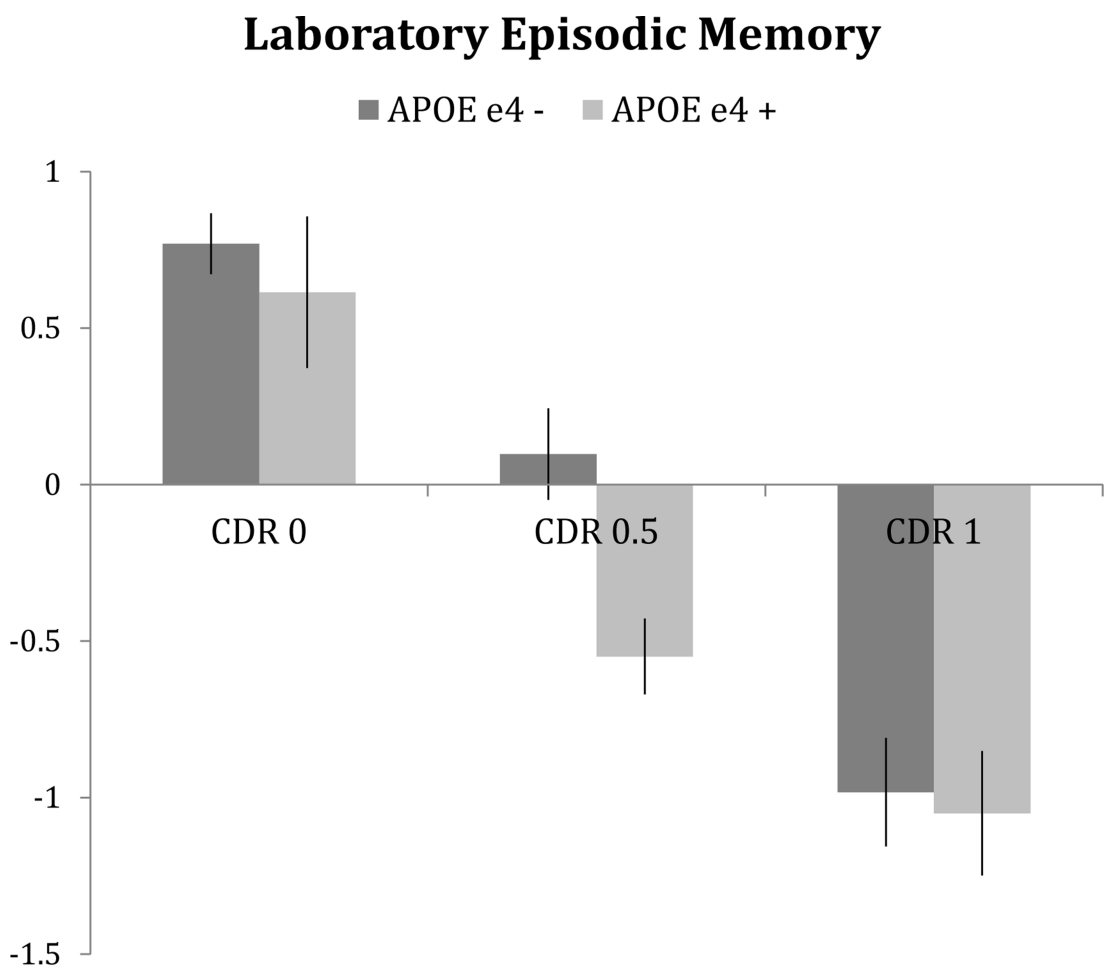

Figure 3.

Laboratory episodic memory performance for the different CDR groups who are either *APOE ε4* carriers or non-carriers (Study 2). Error bars represent ±1 standard error of the mean.

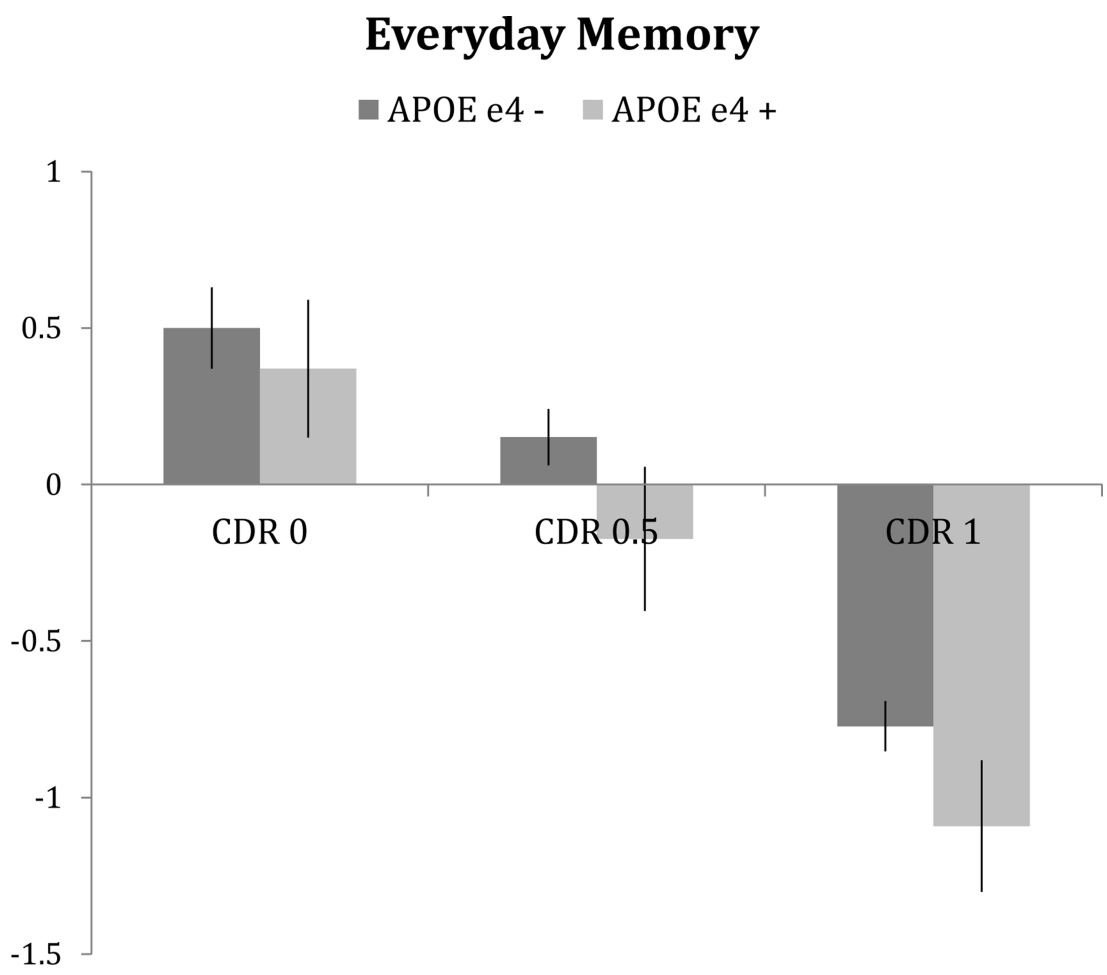

Figure 4.

Everyday memory performance for the different CDR groups who are either *APOE ε4* carriers or non-carriers (Study 2). Error bars represent ±1 standard error of the mean.

Table 1

Frequency of APOE ε4-carriers and non-carriers for Study 1 and Study 2.

Sample	*APOE ε4*-carriers	*APOE ε4* non-carriers
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.

Table 2

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

Sample	***APOE ε4*-carriers**		***APOE ε4* non-carriers**	
Variable	**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)

	***APOE ε4*-carriers**			***APOE ε4* non-carriers**		
CDR group	**0**	**0.5**	**1**	**0**	**0.5**	**1**
Study 2						
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

Note. 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			
	M	**Median**	**Range**	**M**	**Median**	**Range**	***d* (Young vs. Old)**
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

Note. 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

Study 1					
Variable	**1**	**2**	**3**	**4**	**5**
1 Selective Reminding	–				
2 Paired Associates	0.49	–			
3 Word List Recall	0.44	0.47	–		
4 Breakfast Recall	0.30	0.31	0.54	–	
5 Party Recall	0.27	0.38	0.51	0.56	–
6 Planting Recall	0.26	0.36	0.56	0.62	0.61

Study 2						
Variable	**1**	**2**	**3**	**4**	**5**	**6**
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

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

Table 5

Effect sizes for the differences between APOE ε4 carriers and non-carriers 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)

Note. 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.

Table 6

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

	CDR 0				CDR 0.5				CDR 1			
	M	**Median**	**Range**	***d* (0 vs. 0.5)**	**M**	**Median**	**Range**	***d* (0.5 vs. 1)**	**M**	**Median**	**Range**	***d* (0 vs. 1)**
Age	74.65	75.00	65-86	−0.57	77.97	78.50	66-86	0.06	77.61	78.50	63-90	−0.47
GDS	0.66	0.00	0-4	−0.65	1.52	1.00	0-7	−0.56	2.78	2.00	0-10	−1.02
Short Blessed Test	7.97	7.00	7-13	−0.80	10.26	9.00	4-21	−0.95	15.11	16.50	4-26	−1.59
MMSE	29.18	30.00	24-30	0.66	27.93	29.00	22-30	1.98	22.67	22.00	18-28	2.74
Breakfast Free Recall	22.18	21.00	1-61	0.88	12.84	13.50	0-31	1.26	4.00	3.00	0-23	1.94
Library Free Recall	13.03	12.50	1-34	0.64	6.63	6.00	0-24	1.29	1.79	2.00	0-10	1.86
Party Free Recall	26.65	22.50	1-74	0.77	13.16	10.00	0-57	1.00	2.68	1.00	0-12	1.65
Breakfast Recognition	0.71	0.70	.40-.90	0.50	0.65	0.65	.30-.90	1.09	0.50	0.50	.30-.80	1.60
Library Recognition	0.77	0.80	.20-.95	0.33	0.72	0.70	.35-1.0	1.12	0.55	0.53	.25-.80	1.58
Party Recognition	0.88	0.90	.20-1.0	0.66	0.78	0.80	.40-1.0	1.26	0.60	0.60	.40-.90	1.90
Breakfast Order Errors	0.66	0.33	.00-4.5	−0.74	1.41	1.00	.00-4.5	−1.44	3.24	3.00	.83-5.5	−2.20
Library Order Errors	1.48	1.50	.00-4.3	−0.99	2.58	2.50	.50-4.5	−1.05	3.70	3.83	1.0-5.0	−2.21
Party Order Errors	0.12	0.00	.00-.83	−0.37	0.23	0.17	.00-1.8	−1.36	1.54	1.33	.00-4.7	−1.51
Verbal Paired Associates	15.25	15	7-21	1.20	10.27	10	0-18	0.70	7.41	8	0-14	2.04
Selective Reminding Test	30.73	32	11-42	1.27	21.06	21	4-38	1.06	12.16	12	0-30	2.50
Logical Memory Immediate	14.03	15	0-21	0.99	9.29	8	0-18	1.21	3.81	2	0-14	2.27
Logical Memory Delayed	13.48	14	0-21	1.18	7.15	6	0-17	1.18	1.76	0	0-9	2.22
Entorhinal Volume	3926	3927	2821-5203	0.71	3469	3397	2084-4597	1.38	2544	2574	1615-3721	2.18
Hippocampal Volume	7526	7528	5836-9056	1.18	6491	6316	5001-8403	0.99	5671	5685	4730-6734	2.71
Parahippocampal Volume	3662	3645	2814-4693	0.34	3478	3473	2052-4542	0.87	2987	2965	1871-3846	1.38

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

Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. Author manuscript; available in PMC 2015 November 01.

Table 7

Cohen's d effect sizes for the differences between APOE ε4-carriers and non-carriers 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)

Note. 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.

Table 8

Hierarchical regression analyses predicting everyday memory and episodic memory

Predicting Everyday Memory	R^2	*p*	**Reduction in Variance**[a]
APOE status (alone)	.121	.002	
APOE status (after controlling for entorhinal volume)	.007	.401	94%
APOE status (after controlling for hippocampal volume)	.028	.115	77%
APOE status (after controlling for parahippocampal volume)	.049	.031	60%
Predicting Episodic Memory	R^2	*p*	**Reduction in Variance**
APOE status (alone)	.136	.001	
APOE status (after controlling for entorhinal volume)	.017	.210	88%
APOE status (after controlling for hippocampal volume)	.032	.064	76%
APOE status (after controlling for parahippocampal volume)	.071	.015	48%

Note.

[a]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) * 100 = 94%].