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Apolipoprotein E and Prospective Memory in Normally Aging Adults

Ira Driscoll and Mark A. McDaniel
University of New Mexico

Melissa J. Guynn
New Mexico State University

The ϵ4 allele of apolipoprotein E (APOE) is an established risk factor for Alzheimer's disease, despite uncertainty as to its effect on cognitive function in normal aging. Some evidence suggests poor episodic memory and executive functioning in ϵ4 allele carriers. Prospective memory has been overlooked in investigations of the relationship between APOE and cognition. The authors used a laboratory paradigm to examine the relationship between prospective memory and APOE status in healthy elderly adults, and they varied the association (high vs. low) between a target word and a response word. The authors found a significant deficit in prospective memory for ϵ4 allele carriers but no effect of association in either group. The results suggest the deficit was due to failure of the prospective component of the task.

Seven percent of elderly adults over age 65 develop an affliction that is perhaps the most tragic of all age-related conditions—Alzheimer's disease (AD)—and in the next 30 years, the prevalence of AD is expected to triple (Rosen, Bergeson, Putman, Harwell, & Sunderland, 2002). AD, a debilitating neurological disorder characterized by a progressive loss of cognitive function, has damaging effects on the quality of life of older adults. Memory loss, especially for recent events, is one of the earliest and most characteristic signs of AD. There are anecdotal accounts that people in the early stages of AD also have great difficulty with prospective memory. *Prospective memory* refers to the ability to remember to perform an intended action at a particular point in the future, and prospective memory tasks are pervasive in daily activities. Individuals in early stages of AD fail to remember tasks they need to do and fail to remember to do these tasks at the appropriate times (Camp, Foss, Stevens, & O'Hanlon, 1996). Despite the potential of prospective memory failures to result in serious consequences (e.g., forgetting to take medication), little research has addressed such memory failures in pathological aging.

Recently, efforts have been directed toward understanding the disease process of AD with the goals of prevention and/or treatment. The presence of the ϵ4 allele of the apolipoprotein E (APOE) gene has been associated with increased risk and decreased age of onset for AD (cf. Corder et al., 1993) and constitutes a well-established risk factor related to the disease (cf. Kehoe et al., 1999). APOE presents a genetic polymorphism with three common alleles: ϵ2, ϵ3, and ϵ4. APOE ϵ3 is found in 77%–78% of the general population, whereas APOE ϵ2 (7%–8%) and APOE ϵ4 (14%–16%) are less common. The ϵ4 allele of the APOE gene has been implicated in all of the major biochemical disturbances associated with AD, such as beta amyloid deposits, neurofibrillary tangle formation, neuronal cell death, oxidative stress, synaptic plasticity, and cholinergic signaling dysfunction (Cedazo-Minguez & Cowburn, 2001). It has been estimated that overall, prevalence of dementia by age 90 is only about 50% for the ϵ4 allele noncarriers (Henderson et al., 1995), and about 60% of AD patients are ϵ4 allele carriers (Mayeux et al., 1998; but see Evans et al., 1997, for a population-based study). Nonetheless, genotyping for APOE has not proven useful as a predictive tool because AD can develop in the absence of the ϵ4 allele, and conversely, a number of the ϵ4 allele carriers avoid the disease. That is, it is possible to reach extremely old age with normal cognition, despite having the APOE ϵ4 allele and its associated risk for AD (cf. Rebeck et al., 1994).

The picture is even more complicated when it comes to normal aging without dementia. Efforts have focused on examining whether the APOE ϵ4 allele confers a risk for cognitive impairment in normal aging. Understanding the relationship between APOE and age-related cognitive impairment in normal aging is important and may also have implications for the diagnosis, treatment, and prevention of AD in the future. There has been some evidence suggesting poor cognitive performance of ϵ4 allele carriers compared with noncarriers (cf. Caselli et al., 1999; O'Hara et al., 1998; Wilson et al., 2002; Yaffe, Cauley, Sands, & Browner, 1997). Yet, the same studies have suggested that the presence of the ϵ4 allele has a selective influence on cognitive performance because no differences have been seen on more global measures of cognitive function (cf. Caselli et al., 1999). Furthermore, a study by Bookheimer et al. (2000) demonstrated that elderly ϵ4 allele carriers showed alterations on measures of brain function in the absence of morphological or cognitive changes.

Small, Rosnick, Fratiglioni, and Backman (2003) recently conducted a meta-analysis that included 36 studies with over 2,000 ϵ4 carriers and over 6,000 noncarriers. Modest ϵ4 allele-related deficits were observed for recall and recognition measures of episodic memory ($d = .08$; J. Cohen, 1977) and executive functioning ($d = .08$). Small et al. (2003) concluded that the presence of the ϵ4 allele is related to subtle deficits in memory and executive function in nonclinical populations. This conclusion is consistent with many

Ira Driscoll and Mark A. McDaniel, Department of Psychology, University of New Mexico; Melissa J. Guynn, Department of Psychology, New Mexico State University.

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Correspondence concerning this article should be addressed to Mark A. McDaniel, who is now at the Department of Psychology, Washington University in St. Louis, One Brookings Drive, St. Louis, MO 63130-4899. E-mail: mmcdanie@artsci.wustl.edu

studies that failed to observe statistically significant differences in cognitive performance as a function of APOE status (Bondi, Salmon, Galasko, Thomas, & Thal, 1999; R. M. Cohen, Small, Lalonde, Friz, & Sunderland, 2001; Corder et al., 1996; Kim et al., 2002; Plassman et al., 1997; Small, Basun, & Backman, 1998; Small et al., 2000; G. E. Smith et al., 1998; Winnock et al., 2002). In summary, research has demonstrated that many individuals reach old age without obvious cognitive impairment despite the presence of one or two APOE ϵ4 alleles (Hyman et al., 1996).

However, a major limitation in the literature examining the relationship between APOE genotype and cognitive functioning is the reliance on a relatively narrow set of tasks for assessing cognitive function. Only a few standard episodic memory tasks are typically used, and to our knowledge, prospective memory measures have not been included in any study investigating the relation between the ϵ4 allele and cognitive function (Small et al., 2003). Intact prospective memory is critical in the daily life of an older adult. For example, remembering to take medications at certain times of the day and remembering health-related appointments are life-maintaining prospective memory tasks frequently required of older adults (see McDaniel & Einstein, in press). Given the absence of prospective memory measures in studies on APOE genotype and cognition, we decided to investigate the relationship between APOE status and prospective memory in healthy, community-dwelling elderly individuals.

Exclusion of prospective memory from existing studies on APOE genotype and cognition may in part reflect researchers' unfamiliarity with recently introduced laboratory paradigms for investigating prospective memory. Einstein and McDaniel (1990), among others (e.g., Maylor, 1993), have developed a sensitive and fruitful laboratory paradigm for examining prospective memory in older adults (see, for instance, Cherry & LeCompte, 1999; Einstein, Holland, McDaniel, & Guynn, 1992; Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995; Einstein, Smith, McDaniel, & Shaw, 1997; McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999). Within this literature, researchers have distinguished between event- and time-based prospective memory (Einstein & McDaniel, 1990, 1996). *Event-based prospective memory* involves remembering to perform an action when a specific event occurs, such as remembering to give a message to a friend when you see her. *Time-based prospective memory* involves remembering to perform an action at a certain time, such as remembering to take medication at 2:00 p.m., or after a certain amount of time has passed, such as remembering to take cookies out of the oven in 10 min. Time-based prospective memory has tended to produce more robust age-related deficits and lower performance in general compared with event-based prospective memory (Einstein et al., 1995; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997; see also Henry, MacLeod, Phillips, & Crawford, 2004, for a meta-analytic review). In this study, we focused on event-based prospective memory.

It has been suggested previously that prospective memory decline could be an early diagnostic sign of AD (Kixmiller, Fitzsimmons, Heerey, & Randall-Walker, 2003), and prospective memory failure is also a devastating aspect of AD (Camp et al., 1996). Thus, given the link between the APOE ϵ4 allele and AD and evidence suggesting some changes in cognition associated with the APOE ϵ4 allele, one might expect to see a deficit in prospective memory in elderly ϵ4 allele carriers without dementia. More specifically, our current focus was on a type of event-based task that typically is associated with minimal age-related decline (see McDaniel & Einstein, 2000, for a detailed theoretical analysis and Henry et al., 2004, for supporting evidence). We reasoned that with this task, significant impairment associated with APOE ϵ4 allele presence might not be masked by impaired performance because of normal aging per se and thus might be revealed more clearly.

In this type of prospective memory task, the event that cues prospective remembering is focal to the ongoing activity being performed by the participant. In the typical laboratory paradigm, participants are busily engaged in an ongoing activity, such as rating semantic aspects of word stimuli (Einstein et al., 1997). The prospective memory task requires participants to try to remember on their own to perform a simple intended action if a particular target event (a word) appears during the ongoing activity (a rating task). In our paradigm (Einstein & McDaniel, 1990), the prospective memory event cue is one of the items being focally processed as a part of the ongoing activity, rather than some other aspect of the display (e.g., a background pattern, as in Park et al., 1997). Another general feature of the paradigm is that the prospective memory instruction is typically presented at the outset of the experiment and is followed by tasks (distractor tasks) other than the ongoing activity to displace the prospective memory task from working memory. Thus, the Einstein–McDaniel paradigm (Einstein & McDaniel, 1990) is intended to capture critical features of event-based prospective memory in everyday life. Execution of the intended activity often must be delayed over a period filled with distraction, the intended activity typically cannot be maintained in working memory because of other ongoing demands (Einstein, McDaniel, Manzi, Cochran, & Baker, 2000), and execution of the intended activity typically must be remembered while the participant is absorbed in the other ongoing demands.

One question that arises in prospective memory research is whether prospective memory differs from other forms of episodic memory. Although this question is currently of some debate (e.g., Crowder, 1996; Roediger, 1996), studies with event-based paradigms similar to that used in our study have not shown significant correlations between explicit retrospective measures (recall and recognition) and prospective memory (Einstein & McDaniel, 1990; McDaniel & Einstein, 1992). Further, age-related effects on prospective memory do not parallel those obtained with recognition and recall measures (e.g., Einstein & McDaniel, 1990; Henry et al., 2004). Thus, the evidence suggests that prospective memory does not manifest identical properties as explicit retrospective episodic memory (recall and recognition). We adopted the orientation that prospective memory is supported by the interaction of multiple component processes (cf. McDaniel & Einstein, 1992) with a retrospective component that shares many of the functional characteristics of explicit retrospective episodic memory (for a review, see West, Jakubek, & Wymbs, 2002) and a prospective component that involves processes not as common in typical retrospective tasks (Guynn, McDaniel, & Einstein, 2001; McDaniel et al., 1999; R. E. Smith, 2003). For example, the prospective component of the task of remembering to give a friend a message requires that one remember the intention to do something upon encountering the friend, and the retrospective component requires that one remember the contents of the message.

The foregoing analysis suggests that when prospective memory differences are obtained across groups, it can be uncertain whether

the differences depend on the prospective component, the retrospective component, or both (Einstein et al., 1992). To help isolate any effects of the APOE genotype on the prospective versus the retrospective component of prospective remembering, in the present study we manipulated the association between the target word and the response word. The prospective memory task required participants to write a particular response word if a designated target word appeared during the ongoing activity. We varied the relationship between the target word and the response word. In one condition, the target word was highly associated with the response word (e.g., *spaghetti–sauce*), and in the other condition, the target word was not associated with the response word (e.g., *thread–pencil*). We reasoned that the retrospective component in the high-associate condition could be easily remembered because of prior knowledge. Thus, if APOE-related differences are as robust in the high-associate condition as in the low-associate condition, then the prospective component would be implicated in any prospective memory decline.

Method

Participants

Thirty-two elderly adults (15 men and 17 women) between the ages of 60 and 87 years (M = 78 years, SD = 4.81) were recruited from an ongoing study of nutrition, genetics, and health by the New Mexico Aging Process Study (NMAPS; Garry, Hunt, Koehler, VanderJagt, & Vellas, 1992). All participants were healthy, community-dwelling individuals without dementia, depression, or a history of neurological or psychiatric disorders, and all had normal or corrected-to-normal vision. Each participant in the NMAPS pool was screened for a number of clinical conditions (coronary heart disease; significant peripheral vascular disease; insulin-dependent diabetes; hepatic disease; history of internal cancer requiring surgery, x-ray, or chemotherapy in the past 10 years; hepatitis; untreated hypertension; and conditions requiring medication other than thyroid or estrogen replacement medication or minor antihypertensives) prior to their entry into the study. In addition, participants were evaluated on a battery of cognitive and physical measures, health habits and attitudes, morbidity, number of falls, diet, physical activity, nutritional status, and body composition. Furthermore, we obtained scores for the modified Mini-Mental State Examination (3MS; Teng & Chui, 1987), the Fuld Object Memory Test (FULD; Fuld, 1977), the Color Trail Test—A and B (CTT–A and CTT–B; D'Elia, Satz, Uchiyama, & White, 1997), and the Clock Drawing Test—1 and 2 (CDT–1 and CDT–2; Wolf-Klein, Silverstone, Levy, & Brod, 1989) from the NMAPS data pool. The Activities of Daily Living (ADL; Lawton & Brody, 1969) scores (1 = *independent;* 2 = *needs some help;* and 3 = *completely unable*) for both 2001 and 2002 were obtained as well. Each participant had a structural MRI scan at the time of testing, which was reviewed by a radiologist. All radiology reports were normal for the age of the participant. The age and background data for the sample are presented in Table 1.

The procedure of Hixson and Vernier (1991) was used for restriction enzyme isoform genotyping for the APOE alleles (ϵ2, ϵ3, and ϵ4). Participants were divided into two groups: ϵ4− and ϵ4+. Those selected for the ϵ4− group represented ϵ3 homozygotes (n = 16; 8 men and 8 women). The participants in the ϵ4+ group were all ϵ3/ϵ4 heterozygotes (n = 16; 7 men and 9 women). One male participant from the ϵ4+ group was unable to complete the prospective memory task and was excluded from all subsequent analyses.

Table 1
Background Information

	ϵ4−		ϵ4+		
Test	*M*	*SD*	*M*	*SD*	*p*
Age	77.6	5.5	78.7	4.1	.53
3MS	98.2	1.6	96.3	3.6	.06
FULD	9.5	0.8	8.9	1.1	.11
CTT–A	24.1	2.3	23.9	2.6	.89
CTT–B	18.7	5.0	17.2	4.8	.41
CDT–1	3.5	0.9	3.6	0.8	.75
CDT–2	3.8	0.4	3.5	1.1	.23
ADL 01	1.03	0.08	1.0	0	.24
ADL 02	1.05	0.09	1.02	0.04	.33

Note. 3MS = Modified Mini-Mental State Examination; FULD = Fuld Object Memory Test; CTT–A = Color Trail Test—A (number completed in 60 s); CTT–B = Color Trail Test—B (number completed in 60 s); CDT–1 = Clock Drawing Test—1 (presence and sequence of numbers); CDT–2 = Clock Drawing Test—2 (presence and placement of hands on the clock); ADL 01 = Activities of Daily Living for year 2001; ADL 02 = Activities of Daily Living for year 2002 (1 = *independent*; 2 = *needs some help*; 3 = *completely unable*).

Procedure

Participants were first given a general explanation of the tasks they would perform, followed by instructions for the primary portion of the experiment (word rating cover task). They were instructed to rate words presented in the center of a computer screen on a scale from 1 to 5 (1 = *low,* 3 = *neutral,* and 5 = *high*) on one of the following four dimensions: Concreteness, Pleasantness, Meaningfulness, and Vividness. Only one word was presented at a time for 7 s, and the kind of rating task to perform was displayed with the word and the rating scale. Simultaneously with the visual presentation, an experimenter read aloud the word to be rated and the dimension on which the word was to be rated. Participants were asked to write the first letter of the dimension (e.g., *P* for Pleasantness) and their rating of the word. Participants were also given one example and eight practice trials.

After the instructions and practice on the word rating task, participants were told that we were also interested in their ability to remember to perform an action in the future. Participants were told that if they ever encountered a particular target word as a word to be rated, they were to write a particular response word in addition to the rating for the target word. If participants could not remember the response word, they were to write an *X* instead. Participants were asked to repeat the instructions to ensure that they understood them.

The strength of the target–response association was varied so that the words were either high or low in association. There were four possible high-associate pairs (*spaghetti–sauce, steeple–church, eraser–pencil,* and *thread–needle*) and four possible low-associate pairs (*thread–pencil, eraser–needle, spaghetti–church,* and *steeple–sauce*). Each participant saw only one high-associate pair and one low-associate pair, and the two pairs contained different target and response words. For each participant, the target word for the high-associate condition (e.g., *spaghetti*) was presented three times in the experiment, as was the target word for the low-associate condition (e. g., *thread*). The presentation of the high-associate target word was intermixed throughout one block of trials of the word rating cover activity, and the presentation of the low-associate target word was intermixed throughout another block of trials. The pairs were used equally often across participants.

After being given the prospective memory instructions, participants were asked to write the date, the time, and some demographic information (age, sex, and ethnicity) and then to repeat the prospective memory instructions. Participants then performed a retrospective (recognition) memory task in which 12 unrelated words were presented on a computer screen at the rate of 1 every 5 s and read aloud by each participant. Participants had been informed that their memory for these words would be tested, and so, after

the word presentation, participants were given a paper-and-pencil recognition test in which the 12 studied words were randomly intermixed with 12 nonstudied words. Participants wrote a *Y* if the word was previously studied and an *N* if the word was not studied. These tasks served to introduce a delay between the prospective memory instructions and the opportunity to perform the prospective memory task (see Einstein & McDaniel, 1990), and they also provided an index of retrospective episodic memory.

After the recognition task, participants began the word rating cover task. No additional instructions concerning the prospective memory task were provided. After participants completed the word rating task, we assessed their retrospective memory for the prospective memory response word by asking them to write the response word when given the target word. This procedure (word rating cover task instructions and practice, prospective memory instructions, demographic questionnaire, recognition task, one block of 51 cover trials, and retrospective memory questionnaire) was used once with a high-associate target–response pair and once with a low-associate target–response pair, and the order of presentation was counterbalanced across participants.

Results

For analysis purposes, participants were divided into two groups: $\epsilon4+$ and $\epsilon4-$. Separate one-way analyses of variance (ANOVAs) on the background data (see Table 1) revealed no significant group differences in age ($p > .5$); 3MS scores, $F(1, 29) = 3.88$, $p = .06$; FULD, $F(1, 29) = 2.49$, $p = .11$; CTT–A, $F(1, 29) = 0.02$, $p = .89$; CTT–B, $F(1, 29) = 0.71$, $p = .41$; CDT–1, $F(1, 29) = 0.10$, $p = .749$; CDT–2, $F(1, 29) = 1.48$, $p = .23$; ADL for 2001, $F(1, 24) = 1.43$, $p = .24$; and ADL for 2002, $F(1, 27) = 0.98$, $p = .33$. Below, we report analyses associated with the prospective memory task, followed by those associated with the retrospective (recognition) memory task.

Prospective Memory

The measure of prospective memory was the number of times that participants wrote the response word (e.g., *sauce*) when the target word (e.g., *spaghetti*) appeared . There were no *X* responses, even though participants could respond with an *X* if they forgot the exact response word when presented with a target word. Separate between-subjects ANOVAs were computed for the low- and high-associate conditions, with allele group as the independent variable. Effect size was also computed with an unbiased estimate of the proportion-of-variance-accounted-for-by-allele group (omega squared, ω^2; Maxwell & Delaney, 2003). For the low-associate condition, the $\epsilon4-$ group ($M = 2.13$, $SD = 1.31$) performed significantly better than the $\epsilon4+$ group ($M = 0.56$, $SD = 1.09$), $F(1, 30) = 13.41$, $p = .001$, $\omega^2 = .28$. The same pattern, only amplified, was obtained in the high-associate condition, in which the $\epsilon4-$ group ($M = 2.56$, $SD = 1.03$) again performed significantly better than the $\epsilon4+$ group ($M = 0.75$, $SD = 1.24$), $F(1, 30) = 20.25$, $p < .001$, $\omega^2 = .38$.

Within each allele group there was no significant difference in prospective memory between the high- and low-associate conditions (ps $> .05$). Furthermore, the participants who performed well in the high-associate condition also performed well in the low-associate condition, regardless of allele group membership, as confirmed by a nonsignificant paired-sample t test, $t(1, 30) = 1.604$, $p = .12$. The correlation between high- and low-associate conditions was also significant ($r = .722$, $p < .001$).

Because the responses seemed to occur primarily in an all-or-none manner, the participants were also divided into those who completed the prospective memory task successfully (defined as at least one correct prospective memory response) and those who did not (defined as no correct prospective memory response). One $\epsilon4+$ and 2 $\epsilon4-$ participants responded to two out of three prospective memory target words in the low-associate condition; also, 1 $\epsilon4+$ and 1 $\epsilon4-$ participant responded to two out of three prospective memory target words in the high-associate condition. All other participants responded either to zero or to all three prospective memory target words. In the low-associate condition, 75% (12 of 16) of the $\epsilon4-$ participants and 27% (4 of 15) of the $\epsilon4+$ participants responded with the response word when the target word occurred, $\chi^2(1, N = 31) = 7.242$, $p = .007$; Fisher's exact = .012. In the high-associate condition, 88% (14 of 16) of the $\epsilon4-$ participants and 30% (5 of 15) of the $\epsilon4+$ participants responded with the response word when the target word occurred, $\chi^2(1, N = 31) = 9.574$, $p = .002$; Fisher's exact = .003.

After they completed the word rating cover task, participants were tested for their retrospective memory for the response words when given the target words (e.g., *What word were you supposed to write down if you saw the word* spaghetti?). There was a significant difference, $\chi^2(1, N = 31) = 9.574$, $p = .025$; Fisher's exact = .037, between the number of participants in the $\epsilon4-$ group (15 of 16) and the number in the $\epsilon4+$ group (9 of 15) who recalled the low-associate response word. There was no group difference in recall of the high-associate response word; 100% of the $\epsilon4-$ and $\epsilon4+$ participants answered correctly.

Retrospective Memory

Performance on recognition tasks was collapsed across the high- and low-associate conditions into one overall score (one recognition task was performed in the high-associate condition, and one was performed in the low-associate condition). A recognition score was computed for each participant to obtain a measure that reflected both the hits and false alarms (FA): (hits − FA)/1 − FA. Table 2 provides the mean hits, FAs, and recognition scores for each APOE group. A one-way ANOVA with APOE group as the independent variable revealed a significant difference in recognition scores, $F(1, 30) = 5.01$, $p = .03$, $\omega^2 = .11$, with the $\epsilon4-$ participants performing better than the $\epsilon4+$ participants. Separate ANOVAs on the hits and FAs also revealed a significant group difference in the number of hits, $F(1, 30) = 4.53$, $p = .04$, $\omega^2 = .10$, but not in the number of FAs, $F(1, 30) = 1.21$, $p = .28$.

Given that the $\epsilon4+$ group performed significantly lower than the $\epsilon4-$ group on the recognition test and the prospective memory task, we wanted to determine whether there was a relationship between recognition memory and prospective memory. We did not

Table 2
Mean Retrospective Memory Scores

Group	Hits	FAs	Recognition score
$\epsilon4-$	21.8*	1.3	19.6*
$\epsilon4+$	20.2*	1.7	16.7*

Note. FAs = false alarms; recognition score = (Hits − FA)/1 − FA.
* $p < .05$.

find a significant relationship between recognition performance and prospective memory in either the high-associate condition ($r = .07$, $p = .79$) or the low-associate condition ($r = .11$, $p = .69$) for the $\epsilon4-$ group. Similarly, for the $\epsilon4+$ group, we found no significant relationship between recognition and prospective memory scores in either the high-associate condition ($r = .12$, $p = .68$) or the low-associate condition ($r = .49$, $p = .07$).

Discussion

This study was the first to evaluate the prospective memory of elderly APOE $\epsilon4$ carriers ($\epsilon4+$) versus noncarriers ($\epsilon4-$), with the aim of assessing whether the polymorphism of the APOE genotype affects prospective memory in normally aging older adults. A number of important findings emerged. Most critical was our finding of a significant deficit in prospective memory performance for the $\epsilon4+$ group relative to the $\epsilon4-$ group in both the high- and low-associate conditions. Further, the results suggest that the observed $\epsilon4$ allele-related deficit involved the prospective component of the prospective memory task. As outlined in the introduction, a prospective memory task can be considered to involve both a prospective and a retrospective memory component (Einstein et al., 1992), and failure to perform the prospective memory task could be caused by forgetting either or both components. Accordingly, the high-associate condition was implemented to facilitate memory for the retrospective component (i.e., recall of the response word), and indeed, the high-associate condition did produce perfect retrospective memory for the response word. Specifically, when participants were instructed to recall the appropriate response word when given the target word, all participants in both the $\epsilon4+$ and $\epsilon4-$ groups recalled the word. Thus, the significant deficit for the $\epsilon4+$ participants on the prospective memory task in the high-associate condition reflected a failure to remember to perform the intended action at the appropriate moment—that is, a failure in the prospective component.

The particular components involved in the $\epsilon4$ allele-related deficit in the low-associate condition are somewhat less certain. Forty percent of the $\epsilon4+$ participants did not recall the appropriate response word during the retrospective memory test, which could have contributed to the low prospective memory scores in this group. Prospective memory scores were even lower, however, with 67% of the $\epsilon4+$ group failing to remember to perform the prospective memory task at the appropriate moment. Thus, at least 27% of the $\epsilon4+$ participants forgot the prospective component of the task. The above considerations notwithstanding, the most parsimonious interpretation is that even in the low-associate condition, the poor prospective memory of nearly all $\epsilon4+$ participants reflected a failure to remember to perform the intended action at the appropriate moment—again, a failure of the prospective component. If these participants (i.e., the 40% just noted) forgot only the retrospective component, then when these same participants performed in the high-associate condition, their prospective memory should have improved. Instead, prospective memory for the $\epsilon4+$ participants was just as poor in the high-associate condition (in which retrospective memory for the intended action was perfect) as in the low-associate condition. Further, the correlation in performance between the high- and low-associate conditions was high, suggesting similarities in performance across the two conditions.

It is noteworthy that our results for the retrospective memory tests converge with previous reports on the relationship between APOE status and episodic retrospective memory. We observed a significant decrement in recognition for carriers versus noncarriers, and the effect size was medium in magnitude (.11 compared with the values .01, .09, and .25 that were set by J. Cohen, 1977, to represent small, medium, and large effect sizes, respectively, when using proportion of variance to assess effect size). These results are consistent with Small et al.'s (2003) meta-analysis indicating small effect sizes of APOE status on retrospective episodic memory, with slightly larger effects observed for recognition than for recall. Also, the evidence suggests that prospective memory does not manifest identical properties as explicit retrospective episodic memory (e.g., recognition), as we discussed in the introduction. This position is supported by the lack of significant relationships between the recognition and prospective memory scores in both the $\epsilon4-$ and $\epsilon4+$ groups.

In contrast, the effect size of APOE status on prospective memory was robust enough to be considered a large effect for both the low- and high-associate conditions. This finding suggests the need to modify the prevailing view that negative effects of the APOE $\epsilon4$ allele on cognition in older adults without dementia are in general subtle if detected and robust only when assessed longitudinally (Small et al., 2000). Our results are especially interesting given previous suggestions that the potency of the $\epsilon4$ allele may be related to the participant's age, with APOE possibly exerting maximal effects before age 70 (Blacker et al., 1997). By contrast, the mean age for both groups in the present study was approximately 77 years.

Our participants were clinically asymptomatic and did not meet criteria for AD (McKhann et al., 1984). We note, however, that we applied the criteria of the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association to the MRI scans we had available to rule out cerebral atrophy (rather than performing CT scans). Furthermore, the two groups were very well matched on a number of cognitive and health-related parameters. In light of these similarities across the two APOE groups, we believe that the sizeable difference in prospective memory could have considerable practical significance. In particular, prospective memory deficits could be a real-world concern that APOE $\epsilon4$ allele carriers, even those not considered cognitively impaired, need to accommodate. Intervening to ensure adequate prospective memory for $\epsilon4+$ individuals would be especially important with regard to health-related prospective memory tasks (McDaniel & Einstein, in press). Our results also suggest that laboratory prospective memory tasks of the type in our study might be useful in assessing prospective memory in clinical populations.

The fact that the current study revealed APOE-related deficits on retrospective memory that paralleled the results of prior studies, and that it also revealed a considerably large APOE-related deficit on prospective memory, suggests that prospective memory may be an important exception to what is usually thought of as a subtle effect of APOE status on cognition (Bondi et al., 1999; R. M. Cohen et al., 2001; Corder et al., 1996; Kim et al., 2002; Plassman et al., 1997; Small et al., 1998, 2000; G. E. Smith et al., 1998; Winnock et al., 2002). Thus, prospective memory merits attention in research on the cognitive functions affected by the presence of the APOE $\epsilon4$ allele in normal aging. Behavioral studies of pro-

spective memory should complement research on the disease process of AD to provide the most comprehensive effort to understand, diagnose, treat, and prevent this debilitating neurological disorder.

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