Neuropsychology
2006, Vol. 20, No. 6, 633–644

0894-4105/06/$12.00 DOI: 10.1037/0894-4105.20.6.633

Prospective Memory and Apolipoprotein E in Healthy Aging and Early Stage Alzheimer's Disease

Janet M. Duchek and David A. Balota
Washington University

Michael Cortese
College of Charleston

The present study examined whether prospective memory performance discriminates healthy aging from very mild dementia of the Alzheimer type (DAT) and individuals at risk for DAT because of the presence of the apolipoprotein E (ApoE) ε4 allele. Four groups (young subjects, young-old control subjects, old-old control subjects, and subjects with very mild DAT) engaged in an event-based prospective memory task wherein they responded to a specific word embedded in a general knowledge test. Results indicated that prospective memory performance was clearly impaired in the very mild DAT group relative to the healthy older control groups. Moreover, prospective memory performance appears to capture unique variance in discriminating these 2 groups above and beyond standard retrospective memory tests. However, prospective memory was not affected by ApoE status in the young-old control group and, contrary to predictions, the ε4+ old-old control subjects showed better performance than did the ε4– subjects. In contrast to the healthy individuals, in the very mild DAT group, ε4+ subjects showed deficits in performance relative to the ε4– subjects. Discussion focuses on prospective memory as a cognitive indicator of early stage DAT.

Keywords: prospective memory, apolipoprotein E, Alzheimer's disease

In recent years, there has been great interest in the ability to diagnose dementia of the Alzheimer type (DAT) at the earliest possible stage of the disease process. This early diagnosis is critical to families and clinicians in planning the management of the disease with respect to possible drug treatment and behavioral interventions. The clinical diagnosis of early stage DAT is difficult to make and depends on the detection of subtle changes in cognitive function over time and a reliable informant who can document such changes (Carr, Gray, Baty, & Morris, 2000). Thus, considerable research effort has gone into identifying aspects of cognition and/or cognitive tasks that discriminate healthy aging from the earliest stages of DAT and also predict the progression of the disease (Morris, 2003).

Because the clinical detection of early onset DAT is somewhat elusive, it has been suggested that some healthy "control" samples reported in the literature may include individuals who are in the very earliest stages of Alzheimer's disease (AD) but are presently undetected because of the subtle nature of their cognitive changes. This conjecture has been supported in longitudinal studies of cognitive function and neuropathological findings in presumed healthy older adults (e.g., Morris et al., 1996; Price & Morris, 1999; Rubin et al., 1998). For example, Morris et al. (1996) reported 7 of 21 longitudinally studied healthy older adults had high plaque densities in neocortex at autopsy consistent with AD. Retrospective analysis of these subjects' records indicated there was subtle clinical and psychometric impairment prior to death. Furthermore, in a recent study of 97 healthy control subjects, 39%–47% of these individuals received a neuropathological diagnosis of AD at autopsy (Morris et al., 2004). Likewise, Sliwinski and colleagues (Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003; Sliwinski, Lipton, Buschke, & Stewart, 1996) have argued that memory loss in the preclinical stage is apparent 5–7 years prior to the clinical diagnosis of dementia, and therefore, estimates of cognitive change in healthy aging samples may be negatively biased in cross-sectional comparisons. Thus, preclinical or very mild AD may be present in some older individuals who appear to be clinically "normal," underscoring the need to reliably identify specific cognitive changes that may serve as an early marker for DAT.

Episodic memory loss has long been considered a hallmark symptom of AD. For example, standardized neuropsychological tests of memory performance have been found to be predictive of the onset of dementia (Rubin et al., 1998; Storandt, Grant, Miller, & Morris, 2002) and to discriminate between healthy control subjects and those with mild DAT (Storandt & Hill, 1989). Most memory tasks that are typically used for this purpose are tests that examine retrospective memory for recently presented events. Another aspect of memory that is impaired in DAT is prospective memory (Huppert, Johnson, & Nickson, 2000; Maylor, Smith, Della Sala, & Logie, 2002). Prospective memory refers to the ability to maintain an intention across time and then perform that

Janet M. Duchek and David A. Balota, Department of Psychology, Washington University; Michael Cortese, Department of Psychology, College of Charleston.

Michael Cortese is now at the Department of Psychology, University of Nebraska—Omaha.

This work was supported by National Institute on Aging (NIA) Grants PO1AGO3991 and P50AGO5681. Thanks are extended to Martha Storandt for providing the psychometric test support, John Morris and the clinicians at the Washington University Alzheimer's Disease Research Center for their careful recruitment and description of the healthy older adult and DAT subject groups, and Alison Goate for providing the genotyping on the healthy older adult and DAT subject groups. We also thank Susan Sergent-Marshall for her help at various stages of this project.

Correspondence concerning this article should be sent to Janet M. Duchek, Department of Psychology, Washington University, St. Louis, MO 63130. E-mail: jduchek@artsci.wustl.edu

action at some specified time in the future and is considered to be relatively independent of retrospective memory (Salthouse, Berish, & Siedlecki, 2004). Such a memory system has obvious practical implications especially in older adults, such as taking medications at the appropriate times during the day.

An important distinction has been made in the literature between event-based and time-based prospective memory (Einstein & McDaniel, 1990, 1996). Event-based prospective memory involves remembering to perform an intended action when a specific event occurs (e.g., remembering to mail a letter when you pass the post office). Time-based prospective memory involves remembering to perform an intended action at a specified time (e.g., remembering to take something out of the oven in 45 min). Research indicates there are larger age-related deficits in performance on time-based prospective memory tasks relative to event-based tasks (Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995; Henry, MacLeod, Phillips, & Crawford, 2004; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997) because of the increased strategic demands in time-based tasks.

Prospective memory has also been linked to frontal lobe functioning in older adults (e.g., Burgess & Shallice, 1997; Glisky, 1996; R. L. West, 1996). In one such study, McDaniel, Glisky, Rubin, Guynn, and Routhieaux (1999) examined four groups of older individuals who were partitioned on the basis of their performance on a set of neuropsychological tests reflecting frontal and medial-temporal function (i.e., high frontal/high medial temporal, high frontal/low medial temporal, low frontal/high medial temporal, low frontal/low medial temporal). Subjects engaged in an event-based prospective memory task with high or low salient cues. The results indicated that prospective memory performance was related to frontal functioning. That is, high frontal subjects showed better prospective memory than did low frontal subjects. However, there was no significant difference in prospective memory performance for high versus low medial-temporal subjects (although there was a trend toward better prospective memory performance for high medial-temporal subjects). The authors concluded that the specific components of prospective memory, such as maintaining the intention across time and monitoring the task situation for the relevant cue, might be mediated by frontal mechanisms. They also concluded that because there is evidence of a breakdown in frontal lobe integrity in healthy aging (see Raz et al., 1997; R. L. West, 1996), prospective memory is likely to be affected with increasing age. In fact, recent neuroimaging evidence of these subcomponent processes appears to converge on the link between neural mechanisms mediated by the frontal lobes (Burgess, Quayle, & Frith, 2001) and declining prospective memory performance in older adults (R. West, 2005).

Given that there is considerable neuropathology seen in the frontal lobes, even in the early stages of DAT (e.g., Morris et al., 1996), it would not be surprising if there was further decline in prospective memory in early stage DAT relative to healthy aging. As noted, prospective memory deficits have indeed been reported in DAT. Using an event-based prospective memory task in a large population-based study ($N = 388$), Huppert et al. (2000) found a high prevalence of prospective memory impairment in individuals with probable DAT (as defined by an AGECAT organicity score of O3 or above), indicating that only 8% of the DAT sample was able to successfully perform the task. Huppert and Beardsall (1993) have argued that prospective memory decline may be a good indicator of early stage DAT (however, see Maylor, 1995, for discussion of alternative interpretations of their data). In a more recent study, Maylor et al. (2002) found that performance in both event-based and time-based prospective memory tasks was impaired in DAT patients, relative to healthy older control subjects. However, Maylor et al. also noted that the DAT patients were more impaired than control subjects on retrospective memory tasks (e.g., digit span and free recall) than they were on the prospective memory tasks; thus, prospective memory may not necessarily serve as a more sensitive marker for DAT than would retrospective memory tasks. Of course, as Maylor et al. pointed out, the DAT patients in their study were not in the very mildest stages of the disease. On average, the subjects had been attending a memory clinic for 31.5 months, with Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) scores ranging from 16 to 30 (Experiment 1, $M = 22.1$, and Experiment 2, $M = 20.9$). Thus, given a sample of individuals who are in the earliest clinically detectable stages of the disease process, one might still find that prospective memory performance does indeed serve as an early unique marker for the onset of DAT above and beyond standard retrospective measures.

In this light, there have been some intriguing studies that have attempted to identify early cognitive markers for AD by comparing nondemented individuals who are simply at risk for AD with nondemented individuals who are not at risk for AD, due to the apolipoprotein E (ApoE) genotype. Specifically, the presence of the ε4 allele of this gene is a well-established risk factor for AD (e.g., Blacker et al., 1997; Corder et al., 1993; Henderson et al., 1995). However, studies comparing individuals with the ε4 allele (ε4+) to those without the ε4 allele (ε4−) have produced mixed results. Several studies have failed to observe differences in standard neuropsychological tests as a function of ApoE genotype (e.g., Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Kim et al., 2002; Small, Basun, & Backman, 1998; Small et al., 2000). In contrast, other studies have reported differences in selective aspects of cognitive performance as a function of ApoE status (e.g., Caselli et al., 2004; O'Hara et al., 1998; Wilson et al., 2002). Specifically, both middle-aged and older nondemented individuals with the ε4 allele have shown poorer memory performance or greater memory decline across time compared with individuals without the ε4 allele. Yet these groups often show no performance differences across other cognitive domains (e.g., attention, language, visual–spatial ability), as measured by standard neuropsychological tests (Caselli et al., 1999, 2004; O'Hara et al., 1998; Wilson et al., 2002; Yaffe, Cauley, Sands, & Browner, 1997). A recent meta-analysis by Small, Rosnick, Fratiglioni, and Backman (2004) indicated that the presence of the ε4 allele in nondemented individuals is related to subtle deficits in memory and, of interest, executive function.

It is important to note that all of the aforementioned studies have included the use of standard neuropsychological tests to assess cognition. Recent evidence utilizing more detailed experimental procedures to examine specific components of information processing has produced interesting results related to potential early cognitive markers for AD. For example, Greenwood, Sunderland, Friz, and Parasuraman (2000) compared ε2, ε3, ε4 groups of middle-aged individuals who were all in the normal range on a set of standard neuropsychological measures. They found that the ε4 individuals produced a spatial attention deficit that was consistent

with those found in individuals with early stage AD. Specifically, the ε4 individuals had more difficulty disengaging attention from a cued location and also were less likely to appropriately scale attention based on a visual cue in a visual search task. In a similar vein, Rosen, Bergeson, Putman, Harwell, and Sunderland (2002) have explored the relationship between ApoE status and the central executive component of working memory. Utilizing an operation span task (Engle, Kane, & Tuholski, 1999) that requires subjects to divide their attention between performing math operations and remembering words, Rosen et al. (2002) found that even though the ε4+ and ε4− individuals did not differ on a set of standardized neuropsychological tests, the ε4+ group showed decreased operation spans compared with the ε4− group. More recently, Rosen et al. (2004) have reported category fluency deficits in nondemented individuals with the ε4 allele compared with individuals without the ε4 allele. Again, the ε4+ group exhibited normal performance on standardized neuropsychological tests. Finally, Greenwood, Lambert, Sunderland, and Parasuraman (2005) reported deficits in maintaining the location of a target in working memory over time and using information to modulate memory for spatial location in ε4+ individuals. It is interesting to note that there has been accumulating evidence of the importance of breakdowns in attentional systems in early stage DAT (see Balota & Faust, 2001; Perry & Hodges, 1999, for reviews). Taken together, this research indicates that subtle aspects of attentional processing and/or working memory may be deficient in nondemented individuals with the ε4 allele and may serve as an early marker for DAT, in the absence of deficits in more global measures of cognition.

Given the potential changes in working memory in ε4+ individuals and the relation between prospective memory and working memory, one might predict that ApoE 4 presence would modulate prospective memory performance. In fact, Driscoll, McDaniel, and Guynn (2005) have recently explored prospective memory deficits in nondemented older adults with the ε4 allele. Driscoll et al. utilized an event-based prospective memory task, wherein subjects engaged in a word-rating task and were instructed to write down a specific response word (e.g., *sauce*) whenever they encountered a specific target word (e.g., *spaghetti*) during the word-rating task. In an attempt to differentiate the prospective versus retrospective component of the task (Guynn, McDaniel, & Einstein, 2001), the association between the target and response word was varied (i.e., high vs. low). Driscoll et al. reasoned that the high associate condition (*spaghetti–sauce*) should facilitate the retrospective component of the task (i.e., recall for the response word) and thus any prospective memory deficit found in this high associate condition could be attributed to the prospective memory component of the task rather than the retrospective component. Indeed, they found a deficit in prospective memory performance in the ε4+ group compared with the ε4− group, in both the high and low associate conditions, supporting the notion that prospective memory performance distinguishes nondemented older adults who are at risk for DAT because of the presence of the ε4 allele from those who are ε4−.

At this point, it is important to raise the possibility that some of the samples of nondemented older adults in the aforementioned studies, such as Driscoll et al. (2005), may have included individuals in the very earliest stages of the disease process that are difficult to detect using standard neuropsychological tests or clinical procedures. The present study relies on the Washington University Clinical Dementia Rating scale (CDR; Berg, 1988; Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993) to identify individuals at the earliest detectable stages of DAT. Because of the considerable variability in performance on cognitive measures in the population, the CDR relies heavily on changes in cognition across time, as reflected in both reports by the collateral source and the individual, to diagnose the earliest stages of DAT and has been shown to be highly predictive of progression to more severe degrees of dementia.

The utility of the CDR in early diagnosis has been recently illustrated by Storandt, Grant, Miller, and Morris (in press). In this study, the authors compared the rate of progression of individuals who initially met criteria for mild cognitive impairment (MCI; which presumes no dementia) and individuals with a CDR of 0.5 (very mild DAT) who initially did not meet criteria for MCI. It is surprising to note that the rate of decline was greater for the MCI group compared with the CDR 0.5 DAT group, with both a psychometric composite and time to reach a more advanced stage of DAT (i.e., CDR 1) as outcome measures. This study indicates that it is possible to detect very mild DAT with the CDR at an even earlier stage than what is considered to be MCI without dementia, and as Morris (2006) has recently argued, MCI most likely represents pathological AD.[1] Thus without the use of clinical procedures that represent state of the art in DAT diagnosis, it is difficult to discern if the "control" samples in the literature truly represent healthy aging (also, see Sliwinski et al., 1996, 2003). In fact, when one compares the ε4+ versus ε4− individuals from the Driscoll et al. (2005) study (their Table 1), it is apparent that the ε4+ group had lower Modified Mini-Mental State Examination (3MS; Teng & Chui, 1987) scores than did the ε4− group ($p = .03$, one-tailed test), perhaps suggesting that this group may have included some individuals in the preclinical or earliest stages of DAT.

The purpose of the present study was twofold. First, we examined whether prospective memory performance discriminates healthy aging from very mild DAT and thus can serve as an early cognitive marker for the onset of the disease. In the present study, four groups of subjects afforded an examination of prospective memory changes associated in both healthy aging (young, young-old healthy 65–80 years, old-old healthy over 80 years) and in subjects in the earliest detectable stage of DAT (very mild DAT, CDR 0.5). Second, following on the recent results of Driscoll et al. (2005), we further examined the relationship between ApoE 4 status and prospective memory in two groups of healthy older adults (young-old and old-old) and individuals with very mild DAT (CDR 0.5) to assess whether prospective memory performance can discriminate individuals at risk versus those not at risk for DAT in a clinically well-characterized sample.

[1] Morris (2006) recently argued that amnestic MCI does not represent a transitional stage between healthy aging and AD but rather the designation of MCI actually represents very early stage AD. As Morris pointed out, the clinical phenotype (e.g., memory loss, impairment in instrumental activities of daily living, neuropsychiatric symptoms), the overrepresentation of the ε4 allele, and the neuropathology of MCI mirror that of mild AD. Thus, it is possible that one may use the CDR to identify AD at an earlier stage than with MCI.

Method

Subjects

A total of 76 individuals participated in this study. Sixty older subjects were recruited from the Washington University Alzheimer's Disease Research Center (ADRC). All of the ADRC subjects were originally screened for depression, hypertension, reversible dementias, and other disorders that could potentially produce cognitive impairment. The inclusionary and exclusionary criteria for DAT are consistent with the National Institute of Neurological and Communications Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984). The severity of dementia was assessed according to the CDR, in which CDR 0, 0.5, 1, 2, and 3 represent no dementia, very mild dementia, mild dementia, moderate dementia, and severe dementia, respectively. The CDR is based on a 90-min interview with both the subject and a collateral source. This interview assesses the subject and also relies on information available from the collateral source concerning the subject. This interview assesses the subjects' cognitive abilities in the areas of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Both the reliability of the CDR and the validation of the diagnosis (based upon autopsy) by the research team have been excellent (93% diagnostic accuracy) and well documented (e.g., Berg et al., 1998). Of the 60 older subjects, 20 were healthy older control subjects under 80 years of age (young-old: age, $M = 72.5$ years, $SD = 3.44$, range = 65–78 years; education, $M = 14.5$ years, $SD = 2.74$), 13 were healthy older control subjects over 80 years of age (old-old: age, $M = 86.8$ years, $SD = 4.77$, range = 80–93 years; education, $M = 15.0$ years, $SD = 3.98$), and 27 were classified as having very mild DAT (age, $M = 78.0$ years, $SD = 7.45$, range = 63–92 years; education, $M = 14.2$ years, $SD = 3.20$). In addition to the 60 older subjects recruited from the ADRC, we also recruited 16 young individuals from the undergraduate psychology department subject pool (age, $M = 20.2$ years, $SD = 1.69$, range = 18–24 years).

Genotyping for the ApoE alleles (ε2, ε3, ε4) was available for the subjects from the ADRC (with the exception of 1 subject from the very mild DAT group). Subjects were grouped according to the presence (ε4+) versus absence (ε4−) of an ε4 allele. Table 1 displays the number of ε4+ and ε4− subjects as a function of group. There were no differences in age or education for ε4+ versus ε4− subjects in any of the groups (all ps $>$ .23). All ε4+ subjects in the young-old group were heterozygotes (2/4, $n = 1$; 3/4, $n = 6$). Likewise, the 3 ε4+ subjects in the old-old group were heterozygotes (2/4, $n = 1$; 3/4, $n = 2$). In the very mild DAT group, there were 14 subjects who were ε4+ heterozygotes (2/4, $n = 1$; 3/4, $n = 13$), and 4 who were homozygotes (i.e., 4/4).

Psychometrics

Table 2 displays the results of a standard set of psychometric measures as a function of DAT and ApoE 4 status. Memory was assessed with Logical Memory, Forward and Backward Digit Span, Associate Memory, Associate Recognition, and Mental Control measures from the Wechsler Memory Scale (WMS; Wechsler & Stone, 1973). The Word Fluency Test S-P (Thurstone & Thurstone, 1949) was administered, in which subjects had to name as many words as possible in a 60-s period. General intelligence was assessed with Information, Block Design, and Digit Symbol subtests of the Wechsler Adult Intelligence Scale (Wechsler, 1955). Visual perceptual–motor performance was assessed with the Benton Copy Test (Benton, 1963), and Parts A and B of the Trail Making Test (Armitage, 1946). Finally, the Boston Naming Test (Goodglass & Kaplan, 1983b), the American version of the Adult Reading Test (AMNART; Grober & Sliwinski, 1991) and the Animal Naming Test (Goodglass & Kaplan, 1983a) were administered as tests of semantic/lexical retrieval. As shown in Table 2, the DAT individuals produced lower performance on these measures than did the healthy control subjects. Also, ApoE 4 status did not discriminate performance on any of the psychometric tests for any of the subject groups, with the exception of Animal Naming Test scores in the young-old control group, $t(18) = 2.74$, $p = .013$, for which the difference in mean performance is in the unpredicted direction (i.e., the ε4+ subjects show greater fluency than did the ε4− subjects). Thus, in this sample, there is no evidence from the psychometric tests that ε4+ individuals were globally impaired on psychometric test performance compared with ε4− individuals.

Apparatus

A PC was used to control the display of the stimuli and to collect subjects' responses. Display of all stimuli was synchronized with the vertical retrace of the monitor to control for presentation duration. The stimuli were displayed on a 14-in. video graphics array monitor.

Materials and Procedure

The prospective memory task was a general knowledge test similar to that used in Einstein et al. (1995, Experiment 3). The test consisted of 70 questions that tapped general knowledge (e.g., "The fastest animal in the world is the . . .?"). For each question, there were two alternative answers presented on the screen. Subjects were instructed to read each question carefully and to choose the correct alternative by pressing the designated key on the keyboard. Subjects were encouraged to guess if they did not know the correct answer, and feedback was provided after answering each question.

Prior to starting the general knowledge test, subjects were told that they should look for questions about presidents of the United States while performing the general knowledge test. Whenever they saw a question concerning a president, they were instructed to press the space bar before answering the question (e.g., "The fourth president of the United States was . . .?"). Subjects were told it was important to keep these instructions in

Table 1
Age and Education as a Function of Group and Apolipoprotein E Status

	Young-old				Old-old				Very mild DAT			
	ε4+ ($n = 7$)		ε4− ($n = 13$)		ε4+ ($n = 3$)		ε4− ($n = 10$)		ε4+ ($n = 18$)		ε4− ($n = 8$)	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age in years	72.1	2.8	72.6	3.8	85.9	5.1	87.0	4.9	76.5	6.9	80.3	8.3
Education in years	15.3	3.8	14.1	2.1	14.7	4.6	15.1	4.0	14.3	3.1	14.3	3.8

Note. Values are means (and standard deviations). ε4+ = participants having the apolipoprotein E 4 allele; ε4− = participants lacking the apolipoprotein E 4 allele; young-old = participants between 65 and 80 years old; old-old = participants more than 80 years old; very mild DAT = participants in the earliest detectable stage of dementia of the Alzheimer's type (Clinical Dementia Rating = 0.5).

Table 2
Psychometric Means and Standard Deviations as a Function of Group and Apolipoprotein E Status

	Young-old				Old-old				Very mild DAT			
	ε4+		ε4−		ε4+		ε4−		ε4+		ε4−	
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
WMS Logical Memory	11.50	4.91	10.46	3.59	12.50	1.32	10.65	4.18	4.42	2.18	6.31	3.61
Forward Digit Span	7.00	1.15	6.62	1.19	6.67	1.15	7.20	1.23	6.44	1.10	5.75	1.04
Backward Digit Span	5.71	1.13	4.69	1.11	6.00	1.73	5.80	1.48	4.39	0.98	4.25	1.04
Associate Memory	17.14	3.25	17.58	3.22	17.50	2.29	15.40	4.51	8.58	2.51	10.13	3.44
Associate Recognition	7.00	0.00	7.00	0.00	7.00	0.00	6.90	0.32	5.83	1.29	6.44	1.17
Mental Control	8.14	1.46	8.15	1.14	8.67	0.58	6.80	1.81	6.61	1.75	5.63	2.77
Word Fluency Test S-P	36.57	9.81	31.92	10.81	37.33	16.78	32.20	17.02	22.78	6.95	24.38	6.21
WAIS Information	23.86	5.30	21.31	4.53	24.00	2.00	20.10	6.97	16.67	5.73	18.38	5.29
Block Design	36.57	7.07	30.54	7.94	32.00	0.00	29.70	11.04	26.39	11.51	26.00	13.48
Digit Symbol	49.71	14.20	55.00	7.75	53.47	15.20	46.20	11.00	39.67	14.56	29.38	9.21
Benton Copy Test no. correct	9.86	0.38	9.92	.28	10.00	0.00	9.70	0.48	9.55	0.62	9.75	0.46
Trail Making Test–Part A	27.14	8.03	34.46	11.3	35.33	15.7	38.90	10.50	51.50	29.30	64.63	49.10
Trail Making Test–Part B	82.14	47.40	87.15	32.20	58.50	7.79	108.60	40.10	126.11	41.20	149.63	47.20
Boston Naming Test	59.00	2.24	56.38	4.35	56.00	4.00	54.20	6.07	48.33	8.79	48.75	7.46
AMNART	37.29	7.16	33.92	8.55	35.33	5.86	35.00	10.07	29.88	7.30	28.13	8.31
Animal Naming Test	28.57	6.65	22.62	3.18*	20.67	5.86	18.00	7.21	13.89	5.03	15.88	5.36

Note. Young-old = participants between 60 and 80 years old; old-old = participants older than 80 years; DAT = dementia of the Alzheimer's type (Clinical Dementia Rating = 0.5); ε4 = allele indicating apolipoprotein E status; WMS = Wechsler Mental Scale; WAIS = Wechsler Adult Intelligence Scale; AMNART = American version of the Adult Reading Test.
* $p = .013$.

mind because they would not receive them again. At this time, subjects were asked to repeat back these instructions to the experimenter to ensure that they fully understood the task. This constituted the prospective memory task. Next subjects engaged in a filler task for approximately 15 min before starting the general knowledge test. Eight critical questions that referred to presidents of the United States were embedded throughout the 70 general knowledge questions. Critical questions appeared relatively equally throughout the list (on average every 8.625 questions). Questions and alternatives were presented on the screen until subjects made a response. Subjects were given unlimited time to press the space bar in response to a president question and/or choose an alternative to the question.

Results

We present the prospective memory data as a function of subject group first to examine whether aspects of prospective memory performance discriminate healthy aging from very early stage DAT. Next, we present these same data as a function of subject group and ApoE status to determine whether the presence versus absence of the ε4 allele affects prospective memory. Finally, we present analyses on the psychometric data, comparing ε4+ versus ε4− subjects within each group to examine whether prospective memory is particularly sensitive to ApoE status, relative to more general measures of cognition.

Prospective Memory Performance—Accuracy

The measure of prospective memory was the number of times (out of 8) that subjects remembered to press the space bar when a critical (i.e., president) question was presented. The mean proportion correct as a function of group is displayed in Figure 1. As can be seen in Figure 1, the proportion correct varied as a function of group with the young and young-old groups showing the highest prospective memory performance, followed by the old-old control subjects. The very mild DAT group clearly showed a decrement in prospective memory performance. These observations were supported by a one-way analysis of variance (ANOVA) with group as the between-subjects factor. As expected, there was a significant main effect of group, $F(3, 72) = 25.69$, $MSE = 0.094$, $p < .001$. Post hoc analyses indicated there was no significant difference in proportion correct between the young versus young-old groups, $t(34) = 0.85$, $p = .40$. However, there was a significant difference between the young-old versus old-old, $t(31) = 2.31$, $p = .027$, and between the young-old and the very mild DAT, $t(45) = 7.64$, $p < .001$, groups. Finally, the comparison between the old-old versus very mild DAT group was also reliable, $t(38) = 3.32$, $p = .002$.

Because the critical questions were embedded throughout the general knowledge test, it is useful to examine prospective memory performance across test questions. It is possible that the subjects with very mild DAT may have had relatively accurate memory for the instructions at the beginning of the test but then have lost the intention across time as they became distracted by the general knowledge trivia-type questions. The mean proportion correct per critical question as a function of group is displayed in Figure 2. It is clear from Figure 2 that this was not the case. In the very mild DAT group, accuracy was quite low across all eight critical questions, indicating that they did not maintain the prospective memory component across the 15-min filler task. A Group × Question mixed-factor ANOVA yielded a significant main effect of group, $F(2, 72) = 25.96$, $MSE = 0.74$, $p < .001$, and a main effect of question, $F(7, 504) = 10.63$, $MSE = 0.067$, $p < .001$, indicating lower accuracy on Critical Question 7 across all the groups. This last finding is most likely due to the wording of this question (i.e., "Where is John F. Kennedy buried?") that did not include the actual word *president*. More important, the analysis

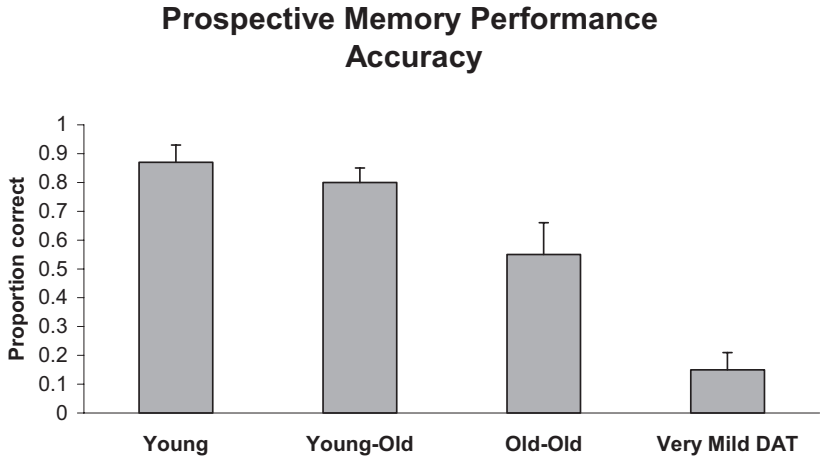

Figure 1. Mean proportion correct on prospective memory task as a function of group.

did not yield a significant Group × Question interaction, $F(21, 504) = 1.50$, $MSE = 0.067$, $p = .07$.

General Knowledge Test—Accuracy

The mean proportion correct for the general knowledge test as a function of group is displayed in Table 3. It appears that the old-old and very mild DAT groups' accuracy was slightly lower than that of the young and young-old groups. A one-way ANOVA indicated there was a significant effect of group, $F(3, 72) = 3.40$, $MSE = 0.015$, $p = .022$. Post hoc analyses indicated that there was a significant difference in accuracy between the young-old and the very mild DAT subjects, $t(45) = 3.30$, $p = .002$, and a marginally significant difference between the young-old and the old-old subjects, $t(31) = 1.74$, $p = .092$. Also, as shown in Table 3, the old-old group and the very mild DAT group were virtually identical on the general knowledge test ($t < 1.00$). The lack of a difference between the old-old and the very mild DAT group, coupled with the finding that the very mild DAT group was still lower than the old-old control group in the prospective memory task, indicates that the latter difference is not simply due to differences in difficulty on the general knowledge task.

ApoE and Prospective Memory Performance—Accuracy

The mean proportion correct as a function of group and ApoE status is displayed in Figure 3. As can be seen in Figure 3, the proportion correct varied as a function of ApoE status within the groups. There appears to have been no difference in prospective memory performance as a function of ApoE status in the young-old control subjects. There does, however, appear to have been a surprising difference in the old-old control subjects, wherein the ε4+ subjects showed better prospective memory performance than did the ε4– subjects. In contrast to the healthy control subjects, in

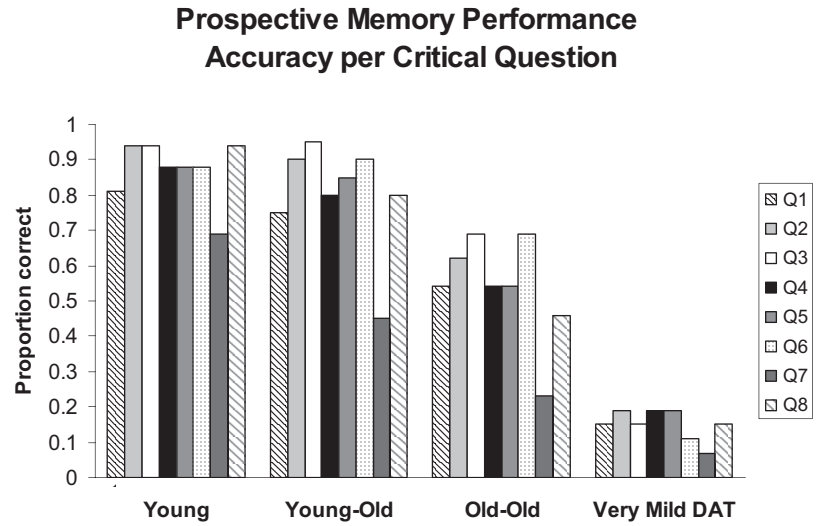

Figure 2. Mean proportion correct on prospective memory task as a function of critical question and group. Q1–Q8 = Critical Questions 1–8.

Table 3
Proportion Correct on the General Knowledge Test as a Function of Group and Apolipoprotein E Status

	ε4+		ε4−		Overall	
Group	*M*	*SD*	*M*	*SD*	*M*	*SD*
Young					.74	.09
Young-old	.78	.09	.73	.08	.74	.09
Old-old	.76	.06	.62	.24	.65	.22
Very mild DAT	.65	.08	.67	.14	.66	.09

Note. ε4+ = participants having the apolipoprotein E 4 allele; ε4− = participants lacking the apolipoprotein E 4 allele; young-old = participants between 65 and 80 years old; old-old = participants more than 80 years old; very mild DAT = participants in the earliest detectable stage of dementia of the Alzheimer's type (Clinical Dementia Rating = 0.5).

the very mild DAT group, the ε4+ subjects showed poorer performance compared with the ε4− subjects. The results of a 3 (group) × 2 (ApoE status) ANOVA supported these observations. There was a significant main effect of group, $F(2, 53) = 22.78$, $MSE = 0.083$, $p < .001$, and no main effect for ApoE status, $F(1, 53) = 0.91$, $MSE = 0.083$, $p = .35$. The Group × ApoE Status interaction was reliable, $F(2, 53) = 7.85$, $MSE = 0.083$, $p = .001$. Post hoc analyses indicated there was no difference in proportion correct as a function of ApoE status in the young-old control group, $t(18) = 0.59$, $p = .565$. In the old-old control group, the ε4+ subjects showed significantly better performance than did the ε4– subjects, $t(11) = 2.32$, $p < .05$, whereas in the very mild DAT group, the ε4+ subjects showed significantly worse performance than did the ε4– subjects, $t(24) = -2.66$, $p = .014$. Of course, one must be cautious because of the small sample sizes when comparing the ε4+ versus ε4– subjects within the groups, especially in the old-old control group, in which there were only 3 ε4+ subjects. We pursue this issue further in the Discussion section.

ApoE and General Knowledge Test—Accuracy

The mean proportion correct for the general knowledge test as a function of group and ApoE status is displayed in Table 3. A 3 (group) × 2 (ApoE status) ANOVA indicated the main effect of group, $F(2, 53) = 2.66$, $MSE = 0.017$, $p = .079$, approached significance. Neither the main effect of ApoE status ($p = .134$) nor the Group × ApoE Status interaction was significant ($p = .25$). Thus, ApoE status did not have an effect on overall accuracy in the general knowledge test.

Discussion

The purpose of the present study was to determine whether prospective memory performance (a) discriminates healthy aging from early stage DAT and (b) varies as a function of ApoE status in both healthy aging and early stage DAT. The results are straightforward on both accounts. We first discuss prospective memory performance as an early predictor of DAT followed by a discussion of the relationship between prospective memory and ApoE status as a risk factor for DAT.

Prospective Memory Performance as an Early Predictor of DAT

Several interesting findings emerged when comparing prospective memory performance across both age and level of dementia.

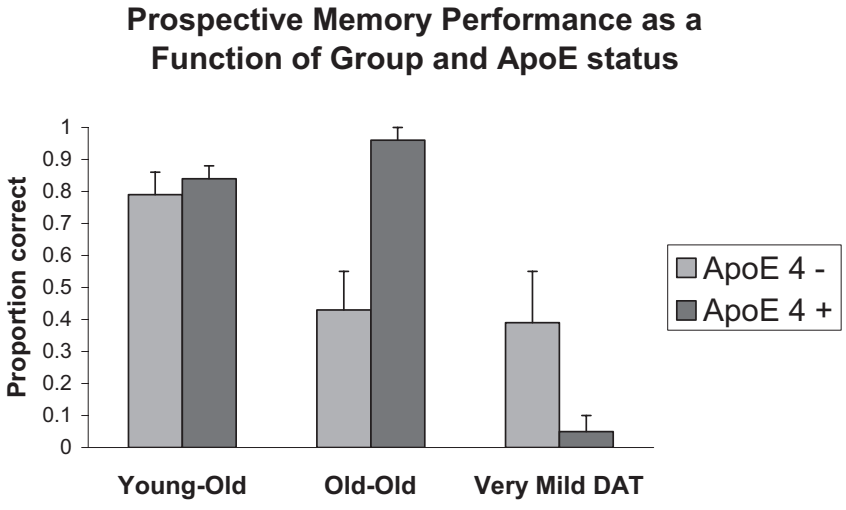

Figure 3. Mean proportion correct on prospective memory task as a function of group and apolipoprotein E (ApoE) status.

First, there was no difference in prospective memory for young subjects when compared with young-old healthy control subjects (under 80 years). At first glance this lack of an age effect may seem counterintuitive; however, this result has been reported in previous studies utilizing event-based prospective memory tasks like the one used in the present study (e.g., Einstein & McDaniel, 1990; Einstein et al., 1995). McDaniel and Einstein (2000) have argued that older adults are often able to take advantage of the cue that is provided in event-based tasks to retrieve the intended action (e.g., the word *president* in the present task), unlike time-based tasks for which there is no external cue to serve as a reminder to initiate the intended action. As previously mentioned, age-related prospective memory decrements are generally greater in time-based tasks relative to event-based tasks (Einstein et al., 1995; Park et al., 1997).

Perhaps more intriguing was the decrement in prospective memory performance as a function of advanced healthy aging. The old-old control subjects (over 80 years) had more difficulty remembering to perform the intended action than did the young-old control subjects. This is somewhat surprising given that the young-old control subjects showed similar performance to young subjects. This decrement as a function of healthy aging can potentially be interpreted as consistent with arguments regarding the loss of frontal integrity with increasing age (Dempster, 1992; Moscovitch & Winocur, 1992; Raz et al., 1997; R. L. West, 1996). In support of this notion, Shimamura and Jurica (1994) found that a group of older control subjects (71–80 years) performed more poorly than did young-old control subjects (61–70 years) on a self-ordered pointing task that presumably taps working memory and the ability to hold information online and monitor previous responses. It is not surprising that the self-ordered pointing task has been used as a test of frontal lobe function (Petrides & Milner, 1982) in the past. Thus, there appears to be some support for an age-graded decline in the older adult range in the ability to maintain intentions or information across time. In fact, the Animal Naming Test was the only psychometric test in the present study that reliably discriminated performance between the young-old versus old-old control subjects (Table 1). Of course, performance on this test also involves the ability to monitor previous responses online and appears to decline with increasing age. It is also interesting to note that prospective memory performance was highly correlated with Trail Making Test–Part B, which may also tap frontal functions, in the old-old control subjects ($r = -.72$, $p = .009$) but in not the young-old control subjects ($r = .004$, $p = .98$).

Finally, prospective memory performance clearly distinguished both healthy control groups from the very mild DAT group. As can be seen in Figure 1, prospective memory is substantially deficient in the very earliest stages of detectable DAT. Only 5 of 27 very mild DAT individuals ever remembered to press the spacebar on the critical questions (compared with 9 of 13 old-old, 19 of 20 young-old, and 15 of 16 young subjects). Moreover, this decrement in performance was apparent throughout the general knowledge test. It seems unlikely that this deficit in the very mild DAT group was due to being distracted by the general knowledge test because their overall performance was not different from the old-old control subjects (.66 vs. .65, respectively). Nonetheless, 81.5% of the very mild DAT individuals were unable to maintain the intention across the 15-min distractor task. Of course, this raises the question whether these individuals could even retrieve the prospective task instructions at the end of the task. We did query 17 of 22 of these individuals at the end of the general knowledge test. Subjects were first asked if they remembered the extra instructions they were given at the beginning of the general knowledge test. If subjects responded "no," they were further prompted by asking them if they remembered something about pressing a special key when they received a certain type of question. If subjects responded "yes" in either case, they were asked to repeat the original instructions. The results of this query indicated that 35.3% of the very mild DAT subjects remembered the instructions at the first question, and 35.3% remembered the instructions after the second prompt. Thus, 70.6% of the queried subjects did show retrospective memory for the intended action but had a clear deficit in the prospective component of the task. However, 29.4% of the DAT subjects that did not perform the intended action also did not appear to remember the instructions even after repeated prompting. Although the sample size is very small ($n = 5$) in this last group, there was no difference in age, education, or psychometric performance for DAT subjects who did versus those who did not remember the prospective memory instructions (all ps $> .11$).

Although the present results clearly indicate that prospective memory performance is sensitive to the effects of early dementia, most of the psychometric tests discriminated between healthy aging and very mild DAT (see Table 1). It is interesting to note that the psychometric tests that provided the best discrimination between healthy aging and early stage DAT assess retrospective memory (e.g., Logical Memory and Associate Memory subscales of the WMS) and/or more attentional control processes (e.g., the WMS Mental Control subscale, Word Fluency Test S-P, Animal Naming Test, or Trail Making Test–Part B). Thus, the question arises as to whether prospective memory performance adds any additional discriminative power above and beyond the psychometric tests. In an effort to address this question, we performed a stepwise logistic regression to determine whether prospective memory performance significantly contributed to the discrimination between CDR 0 versus CDR 0.5 subjects after a composite psychometric score was entered into the regression equation (i.e., a general psychometric factor score was computed after standardizing the individual psychometric tests using a nondemented group from a previous report as a reference group; see Rubin et al., 1998, for details). Indeed, prospective memory performance does significantly add to the discrimination of healthy aging and early stage DAT ($p = .014$) after the global factor score was partialed out. Two additional stepwise logistic regression analyses were performed to determine whether prospective memory performance significantly contributed to the discrimination between CDR 0 versus CDR 0.5 subjects after both memory retrieval-based (WMS Logical Memory, WMS Associate Memory, Wechsler Adult Intelligence Scale Information, and Boston Naming Test) and attentional (Forward and Backward Digit Span, Word Fluency Test S-P, and WMS Mental Control) psychometric composite scores were entered into the regression equation. Both of the attentional and memory retrieval composites and corresponding measures were based on the factor analysis work of Kanne, Balota, Storandt, McKeel, and Morris (1998). Again, prospective memory performance added to the discrimination of healthy aging and early stage DAT (memory retrieval, $p = .06$; attentional, $p < .001$). These latter findings lend support to the early argument made by Huppert

and Beardsall (1993) that prospective memory may serve as a marker for early stage DAT. Although Maylor et al. (2002) reported greater retrospective memory impairment in DAT, it is again important to note that their subjects were not necessarily in the early stages of DAT (MMSE scores 17–30). The current study clearly indicates that prospective memory performance does add to the discrimination of healthy aging and early stage DAT beyond retrospective memory performance and attentional performance on standard psychometric tests. Given the importance of prospective memory to everyday living and issues of safety (e.g., taking medications) that are highly relevant to maintaining independence in the early stages of AD, it is important to better understand the prevalence and nature of the prospective memory loss in early stage DAT.

ApoE and Prospective Memory in Healthy Aging and DAT

A secondary purpose of the study was to examine the relationship between ApoE status as a risk factor for DAT and prospective memory performance. As previously mentioned, Driscoll et al. (2005) recently reported that ε4+ individuals showed poorer event-based prospective memory than did ε4− individuals in a sample of healthy older adults. Driscoll et al. argued that prospective memory is quite sensitive to ApoE status and thus may serve as an early marker for subsequent cognitive decline in healthy older adults. In the present study, we did not find any evidence that event-based prospective memory performance was affected by ApoE 4 status in the carefully screened young-old healthy control group, and in fact, there was a tendency for the opposite pattern in the healthy control group over 80 years of age. As previously mentioned, one possible reason for the difference is that the sample of healthy older adults in the Driscoll et al. study may have included individuals who were in the very earliest stages of DAT. This would be quite consistent with the present observation of a large decrement in prospective memory performance in the very mild DAT group. Although subjects in their study were screened for dementia on the basis of various cognitive measures (e.g., 3MS, Clock Drawing Test; Wolf-Klein, Silverstone, Levy, & Brod, 1989) and structural magnetic resonance imaging, it is still possible that some of the ε4+ individuals were in the presymptomatic stage of AD, as indicated by the lower 3MS scores in the ε4+ group noted above. Based on the results of previous studies (Morris et al., 1996; Rubin et al., 1998; Sliwinski et al., 1996, 2003), even individuals who are carefully assessed longitudinally and considered to be healthy control subjects may in fact be showing subtle cognitive impairment and have brain pathology indicative of early stage DAT.

This underscores the need for sensitive and reliable behavioral measures to make the diagnosis of DAT in the earliest possible stage of the disease process. The determination of dementia and assignment of the CDR in the present study is based solely on clinical information that is obtained in a semistructured interview with the subject and collateral source, without reference to performance on standard psychometric measures (see Morris et al., 2001, for a more complete description). The information that is derived from the collateral source is particularly useful in determining if the subject has experienced a gradual onset and progressive decline in memory and other cognitive abilities relative to the individual's previous state of functioning. In fact, Carr et al. (2000) found that informant-reported memory problems were a better predictor of the diagnosis of DAT than self-reported memory problems. Thus, unless studies with older adult samples are using well-established clinical procedures for determining cognitive status, it is difficult to know if these "control" samples truly reflect healthy aging or are contaminated with individuals in the very earliest stages of AD based on psychometric measures alone.

An intriguing result was found in the old-old control subjects related to ApoE 4 status and prospective memory. Contrary to predictions, the ε4+ subjects showed better performance than did the ε4– subjects in the old-old control group. Interestingly, there is some evidence in the literature that supports this intriguing reverse relationship between age, ApoE 4 status, and cognitive performance. For example, it has been suggested that the presence of the ε4 allele as a risk factor of AD actually declines with increasing age (i.e., after age 70) and is more related to the earlier onset of DAT (Blacker et al., 1997; Breitner et al., 1999; Farrer et al., 1997; however, see Payami et al., 1997; Riley et al., 2000). This could potentially explain why there were so few ε4+ individuals ($n = 3$) in the old-old control group. Consistent with the present results, Smith et al. (1998) reported that ε4+ subjects under 80 years of age showed poorer delayed recall performance than did ε4– subjects; however, the opposite pattern held for subjects over 80 years of age. Furthermore, in a recent meta-analysis regarding ApoE status and cognition, Small et al. (2004) reported that the magnitude of the cognitive deficits associated with ε4 presence was inversely related to age. We found a similar result when we correlated prospective memory accuracy with age collapsed across both healthy control groups as a function of ApoE status. For the ε4+ subjects ($n = 11$), there was a strong positive correlation between age and prospective memory performance ($r = .75$, $p = .013$); however, there was a negative correlation between age and prospective memory performance for the ε4− subjects ($n = 25$; $r = -.42$, $p = .044$). Taken together these results might indicate that the ε4 allele loses its potency as a risk factor for AD in advanced age (e.g., over 80 years of age) as a consequence of selective survival. One might consider this reflection of an age-related genetic test: Those individuals who remain healthy nondemented control subjects over the age of 80 have passed the genetic test, whereas those individuals who are either demented or succumbed to death as a result of age-related variables such as cardiovascular disease have failed the test.[2] Of course, the present data must be interpreted with caution given the small sample of adults over 80 who are ε4+ and must await further replication with larger samples of subjects.

Although the present results did not provide support for ε4+-related deficits in prospective memory performance in healthy older adults, prospective memory performance was clearly affected by ε4 status in the very mild DAT group. That is, there was a prospective memory deficit in ε4+ individuals ($n = 18$) with very mild DAT compared with ε4– individuals ($n = 8$). As previously mentioned, only 5 individuals with very mild DAT ever remembered to press the spacebar during the general knowledge test and, of interest, 4 out of 5 of these individuals were ε4–,

[2] We thank James Becker for the survival interpretation of the data from the healthy control subjects over 80 years of age.

further suggesting that prospective memory is sensitive to ε4 status, at least in the earliest detectable stages of DAT. Again, it is especially interesting to note that there was no difference in psychometric performance for ε4+ versus ε4− individuals in the very mild DAT group, despite a relatively large difference in prospective memory performance. This result is consistent with other studies in which ε4+-related deficits are apparent only when experimental procedures are used that tap more subtle aspects of attention and/or memory, rather than those that tap more global measures of cognition (e.g., Greenwood et al., 2005; Rosen et al., 2002, 2004). Moreover, these results mimic the pattern found in Driscoll et al. (2005) and may further support the possibility that that study included subjects who may have been classified at the CDR 0.5 level, if they would have undergone the CDR procedure.

In sum, the present study provides evidence that prospective memory performance is sensitive to both increasing age and the onset of very mild DAT. Thus, in addition to measures of retrospective memory that have been traditionally used for the early diagnosis of DAT, prospective memory should also be assessed as an early cognitive indicator of DAT and could alert caregivers to behavioral interventions (e.g., cues in the environment) to promote safety and independence in the earliest stages of the disease. The present study also provided evidence for the relationship between ApoE status and prospective memory, but only in the very earliest detectable forms of DAT.

References

Armitage, S. G. (1946). An analysis of certain psychological tests used in evaluation of brain injury. *Psychological Monographs, 60,* 1–48.

Balota, D. A., & Faust, M. E. (2001). Attention in dementia of the Alzheimer's type. In F. Boller & S. F. Cappa (Eds.), *Handbook of neuropsychology* (2nd ed., pp. 51–80.) New York: Elsevier Science.

Benton, A. L. (1963). *The revised Visual Retention Test: Clinical and experimental applications.* San Antonio, TX: Psychological Corporation.

Berg, L. (1988). Clinical Dementia Rating (CDR). *Psychopharmacology Bulletin, 24,* 637–639.

Berg, L., McKeel, D. W., Miller, P. J., Storandt, M., Rubin, E. H., Morris, J. C., et al. (1998). Clinicopathologic studies in cognitively healthy aging and Alzheimer disease: Relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Archives of Neurology, 55,* 326–335.

Blacker, D., Haines, J. L., Rodes, L., Terwedow, H., Go, R. C., Harell, L. E., et al. (1997). APOE-4 and age at onset of Alzheimer's disease: The NIMH Genetics Initiative. *Neurology, 48,* 139–147.

Bondi, M. W., Salmon, D. P., Galasko, D., Thomas, R. G., & Thal, L. J. (1999). Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. *Psychology and Aging, 14,* 295–303.

Breitner, J. C. S., Wyse, B. W., Anthony, J. C., Welsh-Bohmer, K. A., Steffens, D. C., Norton, M. C., et al. (1999). APOE-ε4 count predicts age when prevalence of AD increases, then declines: The Cache County Study. *Neurology, 53,* 321–331.

Burgess, P. W., Quayle, A., & Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia, 39,* 545–555.

Burgess, P. W., & Shallice, T. (1997). The relationship between prospective and retrospective memory: Neuropsychological evidence. In M. A. Conway (Ed.), *Cognitive models of memory* (pp. 247–272). Cambridge, MA: MIT Press.

Carr, D. B., Gray, S., Baty, J., & Morris, J. C. (2000). The value of informant vs. individual's complaints of memory impairment in early dementia. *Neurology, 55,* 1724–1726.

Caselli, R. J., Graff-Radford, N. R., Reiman, E. M., Weaver, A., Osborne, D., Lucas, J., et al. (1999). Preclinical memory decline in cognitively normal apolipoprotein E-e4 homozygotes. *Neurology, 53,* 201–207.

Caselli, R. J., Reiman, E. M., Osborne, D., Hentz, J. G., Baxter, L. C., Hernandez, J. L., et al. (2004). Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. *Neurology, 62,* 1990–1995.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., et al. (1993, 13 August). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science, 261,* 921–923.

Dempster, F. N. (1992). The rise and fall of the inhibitory mechanism: Toward a unified theory of cognitive development and aging. *Developmental Review, 12,* 45–75.

Driscoll, I., McDaniel, M. A., & Guynn, M. J. (2005). Apolipoprotein E and prospective memory in normally aging adults. *Neuropsychology, 19,* 28–34.

Einstein, G. O., & McDaniel, M. A. (1990). Normal aging and prospective memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 16,* 717–726.

Einstein, G. O., & McDaniel, M. A. (1996). Retrieval processes in prospective memory: Theoretical approaches and some new empirical findings. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 115–141). Mahwah, NJ: Erlbaum.

Einstein, G. O., McDaniel, M. A., Richardson, S. L., Guynn, M. J., & Cunfer, A. R. (1995). Aging and prospective memory: Examining the influences of self-initiated retrieval processes. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21,* 996–1007.

Engle, R. W., Kane, M. J., & Tuholski, S. W. (1999). Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 102–134). New York: Cambridge University Press.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B. T., Kukull, W. A., Mayeux, R., et al. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. *JAMA, 278,* 1349–1356.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State: A practical method for grading the state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189–198.

Glisky, E. L. (1996). Prospective memory and the frontal lobes. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 249–266). Mahwah, NJ: Erlbaum.

Goodglass, H. & Kaplan, E. (1983a). *Boston Diagnostic Aphasia Examination Booklet: III. Oral expression, J. Animal naming (fluency in controlled association).* Philadelphia: Lea & Febiger.

Goodglass, H., & Kaplan, E. (1983b). *Boston Naming Test.* Philadelphia: Lea & Febiger.

Greenwood, P. M., Lambert, C., Sunderland, T., & Parasuraman, R. (2005). Effects of apolipoprotein E genotype on spatial attention, working memory, and their interaction in healthy, middle-aged adults: Results from the National Institute of Mental Health's BIOCARD study. *Neuropsychology, 19,* 199–211.

Greenwood, P. M., Sunderland, T., Friz, J. L., & Parasuraman, R. (2000). Genetics and visual attention: Selective deficits in healthy adult carriers of the epsilon 4 allele of the apolipoprotein E gene. *Proceedings of the National Academy of Sciences of the United States of America, 97,* 11661–11666.

Grober, E. & Sliwinski, M. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology, 13,* 933–949.

Guynn, M. J., McDaniel, M. A., & Einstein, G. O. (2001). Remembering to perform actions: A different type of memory? In H. D. Zimmer, R. L. Cohen, M. J. Guynn, J. Engelkamp, R. Kormi-Nouri, & M. A. Foley (Eds.), *Memory for action: A distinct form of episodic memory?* (pp. 25–48). Oxford, England: Oxford University Press.

Henderson, A. S., Easteal, S., Jorm, A. F., Mackinnon, A. J., Korten, A. E., Christensen, H., et al. (1995). Apolipoprotein-E allele epsilon-4, dementia, and cognitive decline in a population sample. *Lancet, 346,* 1387–1390.

Henry, J. D., MacLeod, M. S., Phillips, L. H., & Crawford, J. R. (2004). A meta-analytic review of prospective memory and aging. *Psychology and Aging, 19,* 27–39.

Hughes, C. P., Berg, L., Danzinger, W., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *British Journal of Psychiatry, 140,* 566–572.

Huppert, F. A., & Beardsall, L. (1993). Prospective memory impairment as an early indicator of dementia. *Journal of Clinical and Experimental Neuropsychology, 15,* 805–821.

Huppert, F. A., Johnson, T., & Nickson, J. (2000). High prevalence of prospective memory impairment in the elderly and in early-stage dementia: Findings from a population-based study. *Applied Cognitive Psychology, 14,* S63–S81.

Kanne, S. M., Balota, D. A., Storandt, M., McKeel, D. W., & Morris, J. C. (1998). Relating anatomy to function in Alzheimer's disease. *Neurology, 50,* 979–985.

Kim, K. W., Youn, J. C., Jhoo, J. H., Lee, D. Y., Lee, K. U., Lee, J. H., et al. (2002). Apolipoprotein E epsilon 4 allele is not associated with the cognitive impairment in community-dwelling normal elderly individuals. *International Journal of Geriatric Psychiatry, 17,* 635–640.

Maylor, E. A. (1995). Prospective memory in normal ageing and dementia. *Neurocase, 1,* 285–289.

Maylor, E. A., Smith, G., Della Sala, S., & Logie, R. H. (2002). Prospective and retrospective memory in normal aging and dementia: An experimental study. *Memory & Cognition, 30,* 871–884.

McDaniel, M. A., & Einstein, G. O. (2000). Strategic and automatic processes in prospective memory retrieval: A multiprocess framework. *Applied Cognitive Psychology, 14,* S127–S144.

McDaniel, M. A., Glisky, E. L., Rubin, S. R., Guynn, M. J., & Routhieaux, B. C. (1999). Prospective memory: A neuropsychological study. *Neuropsychology, 13,* 103–110.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34,* 934–939.

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology, 43,* 2412–2414.

Morris, J. C. (2003). Dementia update 2003. *Alzheimer's Disease and Associated Disorders, 17,* 245–258.

Morris, J. C. (2006). Mild cognitive impairment is early-stage Alzheimer disease. *Archives of Neurology, 63,* 15–16.

Morris, J. C., Price, J. L., McKeel, D. W., Higdon, R., Buckles, V. D., & NNA Study Group. (2004). The neurobiology of nondemented aging. *Neurobiology of Aging, 25*(Suppl. 2), 137.

Morris, J. C., Storandt, M., McKeel, D. W., Jr., Rubin, E. H., Price, J. L., Grant, E. A., & Berg, L. (1996). Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. *Neurology, 46,* 707–719.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L. Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease, *Archives of Neurology*, 58, 397–405.

Moscovitch, M., & Winocur, G. (1992). The neuropsychology of memory and aging. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (pp. 315–372). Hillsdale, NJ: Erlbaum.

O'Hara, R., Yesavage, J. A., Kraemer, H. C., Mauricio, M., Friedman, L. F., & Murphy, G. M., Jr. (1998). The APOE epsilon 4 allele is associated with decline on delayed recall performance in community-dwelling older adults. *Journal of the American Geriatric Society, 46,* 1493–1498.

Park, D. C., Hertzog, C., Kidder, D. P., Morrell, R. W., & Mayhorn, C. B. (1997). Effect of aging on event-based and time-based prospective memory. *Psychology and Aging, 12,* 314–327.

Payami, H., Grimslid, H., Oken, B., Camicioli, R., Sexton, G., Dame, A., et al. (1997). A prospective study of cognitive health in the elderly (Oregon Brain Aging Study): Effects of family history and apolipoprotein E genotype. *American Journal of Human Genetics, 60,* 948–956.

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease: A critical review. *Brain,* 122, 383–404.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal-and temporal-lobe lesions in man. *Neuropsychologia, 20,* 249–262.

Price, J. L., & Morris, J. C. (1999). Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Annals of Neurology, 45,* 358–368.

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., et al. (1997). Selective aging of the human cerebral cortex observed in vivo: Differential vulnerability of the prefrontal gray matter. *Cerebral Cortex, 7,* 268–282.

Riley, K. P., Snowdon, D. A., Saunders, A. M., Roses, A. D., Mortimer, J. A., & Nanyakkara, N. (2000). Cognitive function and apolipoprotein E in very old adults: Findings from the Nun Study. *Journals of Gerontology, Series B: Psychological Sciences and Social Sciences, 55,* S69–S75.

Rosen, V. M., Bergeson, J. L., Putman, K., Harwell, A., & Sunderland, T. (2002). Working memory and apolipoprotein E: What's the connection? *Neuropsychologia, 40,* 2226–2233.

Rosen, V. M., Sunderland, T., Levy, J., Harwell, A., McGee, L., Hammond, C., et al. (2004). Apolipoprotein E and category fluency: Evidence for reduced semantic access in healthy normal controls at risk for developing Alzheimer's disease. *Neuropsychologia, 43,* 647–658.

Rubin, E. H., Storandt, M., Miller, J. P., Kinscherf, D. A., Grant, E. A., Morris, J. C., & Berg, L. (1998). A prospective study of cognitive function and onset of dementia in cognitively healthy elders. *Archives of Neurology, 55,* 395–401.

Salthouse, T. A., Berish, D. E., & Siedlecki, K. L. (2004). Construct validity and age sensitivity of prospective memory. *Memory & Cognition, 32,* 1133–1148.

Shimamura, A. P., & Jurica, P. J. (1994). Memory interference effects and aging: Findings from a test of frontal lobe function. *Neuropsychology, 8,* 408–412.

Sliwinski, M. J., Hofer, S. M., Hall, C., Buschke, H., & Lipton, R. B. (2003). Modeling memory decline in older adults: The importance of preclinical dementia, attrition, and chronological age. *Psychology and Aging, 18,* 658–671.

Sliwinski, M. J., Lipton, R. B., Buschke, H., & Stewart, W. F. (1996). The effect of preclinical dementia on estimates of normal cognitive function in aging. *Journal of Gerontology: Psychological Sciences, 51B,* P217–P225.

Small, B. J., Basun, H., & Backman, L. (1998). Three years change in cognitive performance as a function of apolipoprotein E genotype: Evidence from very old adults without dementia. *Psychology and Aging, 13,* 80–87.

Small, B. J., Graves, A. B., McEvoy, C. L., Crawford, F. C., Mullan, M., & Mortimer, J. A. (2000). Is APOE-e-4 a risk factor for cognitive impairment in normal aging? *Neurology, 54,* 2082–2088.

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Backman, L. (2004). Apolipoprotein E and cognitive performance: A meta-analysis. *Psychology and Aging, 19,* 592–600.

Smith, G. E., Bohac, D. L., Waring, S. C., Kokmen, E., Tangalos, E. G., Invik, R. J., et al. (1998). Apolipoprotein E genotype influences cognitive "phenotype" in patients with Alzheimer's disease but not in healthy control subjects. *Neurology, 50,* 355–362.

Storandt, M., Grant, E. A., Miller, J. P., & Morris, J. C. (2002). Rates of progression in mild cognitive impairment and early Alzheimer's disease. *Neurology, 59,* 1034–1041.

Storandt, M., Grant, E. A., Miller, J. P., & Morris, J. C. (in press). Longitudinal course and neuropathological outcomes in original vs. revised MCI and PreMCI. *Neurology*.

Storandt, M., & Hill, R. D. (1989). Very mild senile dementia of the Alzheimer type. II. Psychometric test performance. *Archives of Neurology, 46,* 383–386.

Teng, E. L., & Chui, H. C. (1987). The modified Mini-Mental State (3MS) Examination. *Journal of Clinical Psychiatry, 48,* 314–318.

Thurstone, L.L., & Thurstone, L.G. (1949). *Examiner manual for the SRA Primary Mental Abilities Test.* Chicago: Science Research Associates.

Wechsler, D. (1955). *Wechsler Adult Intelligence Scale* [Manual]. San Antonio, TX: Psychological Corporation.

Wechsler, D., & Stone, C. P. (1973). *Wechsler Memory Scale* [Manual]. San Antonio, TX: Psychological Corp.

West, R. (2005). The neural basis of age-related declines in prospective memory. In R. Cabeza, L. Nyberg, & D. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 246–264). London: University Press.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120,* 272–292.

Wilson, R. S., Schneider, J. A., Barnes, L. L., Beckett, L. A., Aggarwal, N. T., Cochran, E. J., et al. (2002). The apolipoprotein E e4 allele and decline in different cognitive systems during a 6-year period. *Archives of Neurology, 59,* 1154–1160.

Wolf-Klein, G. P., Silverstone, F. A., Levy, A. P., & Brod, M. S. (1989). Screening for Alzheimer's disease by clock drawing. *Journal of the American Geriatric Society, 37,* 730–736.

Yaffe, K., Cauley, J., Sands, L., & Browner, W. (1997). Apolipoprotein E phenotype and cognitive decline in a prospective study of elderly community women. *Archives of Neurology, 54,* 1110–1114.

Received January 31, 2006
Revision received June 26, 2006
Accepted July 6, 2006 ■