Published in final edited form as:

Am J Geriatr Psychiatry. 2008 May ; 16(5): 366–374. doi:10.1097/JGP.0b013e3181629957.

Cognitive Discrepancies Versus APOE Genotype as Predictors of Cognitive Decline in Normal-Functioning Elderly Individuals: A Longitudinal Study

Eric M. Fine, Ph. D, Dean C. Delis, Ph. D, Spencer R. Wetter, Ph. D, Mark W. Jacobson, Ph. D, Amy J. Jak, Ph. D, Carrie R. McDonald, Ph. D, Jodessa C. Braga, B.A, Leon J. Thal, M.D[†], David P. Salmon, Ph. D, and Mark W. Bondi, Ph. D.

Veterans Affairs San Diego Healthcare System (EMF, DCD, SRW, MWJ, AJJ, JCB, MWB); Departments of Psychiatry (DCD, SRW, MWJ, CRM, MWB) and Neurosciences (LJT, DPS), School of Medicine, University of California, San Diego, CA

Abstract

Objectives—Cognitive-discrepancy analysis has been shown to be a useful technique for detecting subtle cognitive deficits in normal-functioning elderly individuals who are genetically at-risk for Alzheimer disease (AD). However, studies that have used cognitive-discrepancy measures to date have used retrospective or cross-sectional designs, and the utility of this approach to predict cognitive decline has not been examined in a prospective investigation.

Design—Longitudinal study.

Setting—San Diego, CA, Veterans Administration Hospital.

Participants—Twenty-four normal-functioning elderly individuals participated in the study, with 16 subjects exhibiting no change in their Dementia Rating Scale (DRS) scores over an 1-year period (Stable Group), and 8 subjects exhibiting a decline in DRS scores over the 1-year period (Decline group).

Measurements—A cognitive-discrepancy measure isolating cognitive switching was computed that contrasted performance on a new higher-level task of executive functioning (a Stroop/Switching measure) relative to a composite measure of lower-level Stroop conditions.

Results—a) In the year before their cognitive changes, the Decline group exhibited a significantly larger cognitive-discrepancy (Stroop/Switching versus lower-level Stroop conditions) score compared with a control (Stable) group; and b) the cognitive-discrepancy measure was superior to APOE genotype in predicting DRS decline.

Conclusion—Cognitive-discrepancy analysis isolating a component executive function ability not only seems to be a useful tool for identifying individuals at risk for cognitive deficits, but also shows promise in predicting individuals who may show subtle cognitive decline over time.

Keywords

Cognitive discrepancies; aging; Alzheimer disease; executive functioning

Send correspondence and reprint requests to Eric Fine, Ph. D., Psychology Service (116B)—Delis Lab, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161. efine@ucsd.com.

[†]Deceased.

There is a great need for efficient, cost-effective methods that can differentiate between the significant cognitive decline associated with normal aging and the superimposed subtle cognitive changes that may signal the earliest preclinical stage of Alzheimer disease (AD). An important breakthrough in this area of research was the discovery of a genetic risk factor for AD. Specifically, individuals with the Apolipoprotein E (APOE) e4 genotype have an increased risk for AD.¹ However, recent estimates of the percentages of individuals with the e4 allele who eventually develop AD are much lower than initially thought,² and APOE genotyping provides no information about *when* the neuropathologic changes of AD may initially manifest. In addition, approximately half of all individuals diagnosed with AD do not have the e4 allele.³ In light of these findings, a recent National Institute of Health task force has recommended against relying exclusively on large-scale genetic testing for predicting development of AD.⁴

Based on the limited predictive utility of AD by the presence of the e4 allele, it has been suggested that a combination of APOE genotyping and neuropsychological testing may improve the prediction of the development of AD relative to genotyping alone.^{5,6} For example, Bondi et al.⁵ demonstrated that episodic memory changes were associated with the APOE e4 allele in nondemented older adults. They also found that significantly more of the e4 individuals developed AD over time and that changes in episodic memory were a significant predictor, above and beyond the APOE e4 allele, of conversion to AD. Such results underscore that the earliest detection of AD may be enhanced if risk factors such as APOE genotype are considered in conjunction with performance on neuropsychological measures. Based on these and other findings,^{6–9} a number of neuropsychological studies have examined whether normal-functioning elderly individuals with the e4 genotype exhibit cognitive deficits relative to matched none4 subjects. However, the results of these investigations have been mixed, with some studies reporting mild cognitive deficits in elderly individuals with the e4 genotype^{5–7,10–16} and other studies failing to detect differences in cognitive performance between e4 and none4 groups.^{17–20}

There are at least two possible reasons for the inconsistent evidence of cognitive decline in elderly individuals with the APOE-e4 allele relative to matched subjects without the e4 allele. First, a genetic risk model predicts that only a *subgroup* of e4 subjects will develop AD, and this subgroup's early subtle changes may be masked by analyses of central tendencies (i.e., group means on individual cognitive tests) in the entire APOE-e4 sample. In support of this possibility, a retrospective study of Bondi et al.⁵ revealed that only a subgroup of the at-risk e4 individuals went on to develop AD, and when these individuals who later converted to AD were removed from the analysis, there were no longer any significant group differences on any of the neuropsychological measures. Second, individuals in a pre-clinical stage of AD (with or without an e4 allele) may exhibit only subtle cognitive abnormalities (for reviews, see Refs. ^{21,22}) that do not reach the level of "impairment" as traditionally defined by neuropsychological assessment techniques (e.g., their test scores still fall within one SD of the mean for their age group).

Several recent studies have attempted to overcome these problems by analyzing neuropsychological test performance in a manner that enhances the detection of subtle cognitive changes in a subgroup of a larger sample of individuals at risk for AD (for example, see Refs. ^{23–26}). This method utilizes a discrepancy analysis of cognitive-test performance. The traditional method for characterizing group differences involves analyses of subject groups' overall mean score on individual cognitive tasks, whereas a cognitive-discrepancy analysis involves the subtraction of each subject's standardized score on one cognitive task from that of another. The two contrasted cognitive tests are selected a priori based on existing evidence that one of the tasks is likely to be more affected than the other in early AD. For example, early AD is often characterized by asymmetric hemispheric

neuropathology that results in disproportionate compromise to either verbal or spatial abilities.^{3,27–30} It follows that a preclinical stage of AD would also be associated with greater impairment on either verbal or nonverbal tasks. To detect these subtle differential deficits in a subgroup of a larger sample, a cognitive-discrepancy analysis examines whether a higher frequency of individuals in the at-risk group exhibits significantly greater impairment on a verbal measure relative to a nonverbal measure or vice versa.

In a retrospective study, Jacobson et al.²³ investigated the utility of this approach by contrasting performance on a verbal task (Boston Naming Test) with that of a nonverbal test (Block Design) in normal-functioning elderly individuals the year before they converted to an AD diagnosis. Subjects in the pre-clinical phase did not differ from control subjects when the overall group means on the naming or block-construction tests were directly contrasted. However, there was a significantly higher frequency of verbal-nonverbal discrepancies (as measured by a difference of one SD or more between the two tasks) in the preclinical AD subjects relative to the control subjects.²³ Since this initial study, higher frequencies of cognitive discrepancies have also been reported in normal-functioning elderly individuals with the e4 allele relative to matched subjects without the e4 allele when contrasting performance on pairs of other lateralized cognitive measures, including spatial span versus auditory span,²⁴ global versus local visual processing,²⁵ and verbal versus nonverbal fluency.²⁶

There is also accumulating evidence indicating that alterations in executive functioning may be among the earliest signals of a preclinical phase of AD (for review, see Ref. ³¹). As an example, in a retrospective study, Albert et al.³² found that tests of set-shifting (Trail Making Test, Part B³³) and sequencing (Self Ordering Test³⁴) were predictive of onset of AD. Chen et al.³⁵ conducted a retrospective study of individuals who later developed AD and also found that deficits on Part B of the Trail Making Tests predicted onset in this group. In addition, Rosen et al.¹⁵ reported deficits on a central executive or divided-attention task for nondemented elderly e4 positive individuals. Importantly, the early declines in executive functioning are consistent with the evidence from recent structural and functional neuroimaging studies documenting alterations in frontal brain systems in normal functioning elderly carriers of the e4 allele.^{17,36–46}

Accordingly, the subgroup of at-risk individuals who have subtle deficits in frontal-mediated “executive functions” might be identifiable based on a discrepancy between performance on a higher-level executive-function task and a more fundamental cognitive-skill measure (see also Refs. ^{15,32,35}). In contrast to the discrepancies between verbal and nonverbal measures discussed above, it would be expected that the discrepancy between higher-level or executive and lower-level or fundamental cognitive ability would be unidirectional (i.e., stable lower-level or fundamental cognitive abilities in the context of subtle declines in higher-level or executive functions).

In the present study, therefore, we examined the utility of performance on the Color-Word Interference Test (CWIT^{47,48}), a recently developed modification of the Stroop Test,⁴⁹ to predict cognitive decline on the DRS (Mattis⁵⁰) across a 1-year period in a group of normal-functioning elderly individuals who were being followed in a prospective, longitudinal study. Like the original Stroop Test, a widely used measure for assessing selective attention and response inhibition, the CWIT includes two baseline conditions (i.e., basic color naming and word-reading speed) and a higher-level task with an interference condition requiring examinees to name the ink color of color words that are printed in an incongruent ink (e.g., say “green” when the word is *red* is printed in green ink). In addition to the three traditional Stroop conditions, the CWIT includes a fourth condition called Inhibition/Switching.⁴⁷ The stimuli in this new condition are the same as in the traditional interference condition with the

exception that half of the words are printed inside a small box. This condition requires the examinee to name the dissonant ink color for words not in a box, and to switch set and read the printed word (rather than the dissonant ink color) for items within a box. This fourth condition is considered a dual executive-function task because it is dependent on both inhibitory and cognitive-shifting abilities; for this reason, it is more challenging and places greater burden on executive abilities.⁴⁷ Therefore, the task design of the CWIT affords the opportunity to isolate cognitive switching abilities by calculating a cognitive discrepancy between the Inhibition/Switching condition and a composite score for the three other conditions.

Specific emphasis in our analysis was given to the new Inhibition/Switching task for the following reasons: *a*) this instrument was found in a cross-sectional study to be particularly sensitive to the subtle executive functions changes in the at-risk e4 elderly individuals relative to matched none4 subjects;⁵¹ *b*) past retrospective studies have found evidence of deficits on other types of cognitive-switching tasks in nondemented individuals who later converted to AD;^{15,32,35} and *c*) an array of evidence from neuro-imaging studies implicates changes in frontal brain systems in at-risk e4 elderly individuals.^{17,36–46} Given evidence of subtle changes in executive functions during a preclinical phase of AD (for reviews, see Refs. 22,31), we hypothesized that individuals who declined on the DRS across a 1-year span (the Decline group) would, in their previous year of testing, display a significant cognitive discrepancy between the higher-level Stroop/Switching measure and the lower-level composite measure relative to subjects whose DRS scores remained generally unchanged (the Stable group). We also predicted that the magnitude of the initial cognitive-discrepancy score would significantly predict decline on DRS subscale scores over the 1-year period in the Decline group but not in the Stable group. Finally, given that the APOE-e4 genotype has been found to be a significant predictor of both mild cognitive impairment (MCI)^{52,53} and AD,¹ we compared the relative utility of the Inhibition/Switching measure versus the APOE-e4 genotype in predicting cognitive decline across the 1-year period.

METHODS

Participants

As part of an on-going longitudinal study by this laboratory, eight individuals were identified as being in the Decline Group by demonstrating a decrease in DRS score in a 1-year period as defined by either *a*) at least a 1-SD decline on one of the two subscales that are most sensitive to AD (i.e., the Memory or Initiation/Perseveration subscales;^{54,55} [N = 6]); or *b*) by at least a 2-SD decline on any of the other subscales of the DRS (N = 2; Table 1 for demographics and DRS scores). The more conservative threshold of a 2-SD decline cutoff for the other DRS subscales (i.e., attention, visuoconstruction, conceptualization) was applied because these subscales are less reliable indicators of AD.^{54,55} Sixteen individuals who did not show evidence of cognitive decline on the DRS served as the comparison group (Stable group). The two groups were similar in terms of their age, gender, and education (Table 1). Subjects were genotyped for the APOE e4 allele according to the methods described by Saunders et al.¹ Of the 24 individuals participating in the study, 13 were APOE-e4 allele positive (all e3/e4) and 11 were APOE-e4 negative (all e3/e3). Four of the eight individuals in the Decline group and 9 of the 16 subjects in the Stable group were e4 positive. All subjects were examined by a staff neurologist and received medical and laboratory tests to rule out any metabolic, endocrine, or nutritional deficiencies. None of the participants had a history of alcohol or drug abuse, learning disability, head injury with loss of consciousness, stroke or other significant cerebrovascular disease, a current psychiatric illness, or other neurologic disorder. Subjects were selected without regard to gender, ethnicity, or race, and written informed consent was obtained in all cases.

Materials and Procedure

The CWIT⁴⁷ and the DRS⁵⁰ were administered to each subject individually by a trained psychometrist. The CWIT is a new, expanded version of the Stroop task that includes four conditions. As in the traditional instrument, there are two baseline conditions for evaluating key component skills of the higher-level conditions: naming color patches (Color Naming; Condition 1) and reading words that denote colors printed in black ink (Word Reading; Condition 2). There is also the traditional Stroop condition (Inhibition; Condition 3) in which the subject must inhibit reading words denoting colors to name the dissonant ink colors in which those words are printed (e.g., the word “red” printed in blue ink). In addition, the CWIT test also includes a new dual-level executive-function task (Inhibition/Switching; Condition 4) that requires the subject to switch back and forth between naming the dissonant ink colors and reading the conflicting words. By simultaneously requiring both inhibition and cognitive switching, this condition places greater demands than the traditional Stroop inhibition condition on executive functioning.^{47,56}

The DRS is a 144-point cognitive-screening instrument that has subscales assessing attention, initiation and perseveration, construction, conceptualization, and memory. The total score provides a general index of an individual’s level of global cognitive functioning.

Statistical Analyses

Scores on the CWIT were examined during the year before the decline in cognitive functioning (Year A). Performance was analyzed using a mixed-model analysis of variance (ANOVA), with subject group (Decline, Stable) as the between-subjects factor and condition (CWIT Conditions 1, 2, 3, and 4) as the within-subjects factor. The dependent variable was the total time to completion on each of the four conditions of the CWIT (higher completion times reflect slower or worse performance). The analyses were performed using age- and gender-corrected scaled scores obtained from the CWIT national normative study.⁴⁸

In addition to examining mean group differences, we also conducted a discrepancy analyses to isolate the specific effect of cognitive switching after controlling for performance on the other three task conditions included in the CWIT. Specifically, the cognitive discrepancy between performance on the Inhibition/Switching condition of the CWIT versus a composite measure of the other three conditions was analyzed by subtracting the averaged scaled scores of the lower-level measures (Color Naming, Word Reading, and Inhibition) from the scaled score of the higher-level Inhibition/Switching condition. This discrepancy measure yielded a continuous variable indicating the degree of standard-score difference between the Inhibition/Switching condition and the composite measure of the lower-level conditions. Group differences (Decline versus Stable groups) on this discrepancy measure were assessed using a one-way ANOVA. These analyses investigated differences in cognitive functioning between the Decline and Stable groups at Year A. In addition, we conducted logistic regression analysis to compare the relative utility of the cognitive-discrepancy measure on the CWIT at Year A versus APOE-e4 genotyping in predicting DRS decline from Year A to Year B in the Decline group.

RESULTS

Table 1 shows demographic and DRS results for the Decline and Stable groups. The two groups were similar in terms of age, gender, education level, and APOE allelic frequencies. The 2 subject groups were also comparable on overall DRS score in Year A; however, as expected, the Decline group’s overall DRS score at Year B, although still in the low-average

range (T score = 45), was significantly lower than that of the Stable group ($t_{[22]} = 4.7$, $p < 0.001$; Table 1).

In terms of times to complete the different conditions of the CWIT at Year A, results demonstrated significant main effects of subject group ($F_{[1,22]} = 7.5$, $p = 0.01$) and condition ($F_{[3,66]} = 3.2$, $p = 0.03$). A significant interaction effect was also found ($F_{[3,66]} = 3.9$, $p = 0.01$), with the Decline group performing significantly worse than the Stable group only on the Inhibition/Switching condition. This interaction effect is illustrated in Fig. 1.

The cognitive-discrepancy measure, which contrasts performance on the Inhibition/Switching condition versus the composite score of the lower-level conditions, also yielded significant results. The Decline group had a significantly larger mean cognitive-discrepancy score than the Stable group ($t_{[22]} = 2.3$, $p = 0.03$).

Logistic regression analyses (Dichotomous variables: Stable and Decline) investigated the ability of the cognitive-discrepancy measure at Year A and APOE status to predict cognitive decline over the subsequent year. Analysis revealed that APOE status alone did not significantly predict decline ($\chi^2_{[1]} = 0.08$, $p = 0.77$, 67% correct classification rate [CCR]). However, the CWIT cognitive-discrepancy measure at Year A significantly predicted cognitive decline from Year A to Year B ($\chi^2_{[1]} = 5.0$, $p = 0.025$, 75% CCR). The inclusion of both cognitive discrepancy and APOE status did not improve the model further ($\chi^2_{[2]} = 5.0$, $p = 0.08$; 75% CCR), as would be expected given that the APOE status alone did not significantly predict decline.

DISCUSSION

The results of the present study revealed that, as predicted, individuals who after a 1-year period exhibited evidence of cognitive decline on the DRS, displayed a significantly larger cognitive discrepancy on the Stroop/Switching task the year before their decline. At Year A, the Decline group performed significantly worse compared with the Stable group on the Inhibition/Switching condition of the Stroop task (CWIT), but not on the other three lower-level conditions of this measure. In addition, a logistic regression analysis correctly classified 75% of individuals into either the Decline or Stable groups at Year B based on their cognitive-discrepancy score at Year A. This high rate of correctly classifying individuals either in the Decline or Stable group based on their prior discrepancy scores is noteworthy, because individuals in the Decline group, while exhibiting a significant decline on the DRS over the 1-year period, nevertheless obtained a total mean score on the DRS at Year B that fell within the lower end of the average range (mean raw DRS score for the Decline group at Year B was 133.3, T score = 45). Importantly, APOE status alone failed to significantly predict cognitive decline, and the combination of the cognitive-discrepancy measure at Year A and APOE status did not improve the prediction of cognitive decline at Year B over the cognitive-discrepancy measure alone. Taken together, these findings suggest that cognitive-discrepancy analyses that isolate cognitive switching abilities may have greater utility than APOE status in predicting cognitive decline over time.

The Stroop/Switching measure (and its contrast with the three lower-level conditions) used in the present study has been found to be particularly sensitive to frontal dysfunction,⁵⁶ likely because it requires subjects to execute two executive-function operations—verbal inhibition and cognitive switching—within the same procedure. Specifically, subjects are presented with color words printed in conflicting ink color (e.g., the word “red” printed in green ink), and they must switch between naming the dissonant ink color and reading the conflicting word.⁴⁷ Whether the increased sensitivity of this measure reflects simply an associated increase in processing demands or specifically the required switching component

remains unclear. In any case, the detection of deficits in the Decline group by this dual-level executive-function task is consistent with several structural and functional neuroimaging studies of early AD patients and healthy e4 carriers that have documented subtle changes in subcortical-frontal regions, including the anterior cingulate, prefrontal cortex, and basal forebrain-regions.^{17,36–46} These findings support a growing body of evidence indicating the presence of executive-function deficits before AD onset.^{15,26,32,35} Although the extent to which executive-function deficits may predate the development of AD is unclear, recent reviews suggest that these and other impairments may signal preclinical AD several years before a formal diagnosis of AD (for review, see^{22,31}).

For the current study, we did not formally consider the diagnostic entity of MCI for a few reasons. First, there has been a great deal of change in the definition of MCI itself recently (see Ref. ⁵⁷ for discussion). Second, there is no generally accepted consensus regarding the specific cognitive domains or tests that should be used in diagnosing MCI, nor are there any generally accepted cutoff scores for designating impairment. Third, the focus of our study was limited to identifying predictors of decline in cognitive functioning, and at this point, there is limited information regarding the expected slope of change in individuals with MCI.⁵⁸ In any case, our results accord with recent suggestions that the diagnostic category of MCI should be expanded to include a variety of nonamnestic subtypes, not simply amnestic MCI.^{57,58} Although individuals in the decline group for the most part did not score in the impaired range on the Inhibition/Switching condition of the CWIT, the current study nevertheless indicates that cognitive discrepancy measures that parse out more fundamental abilities from a targeted higher-level cognitive ability may enhance *a*) the detection of subtle executive-function deficits in subgroups of patients; and *b*) the prediction of cognitive decline. Thus, the application of this type methodology may be valuable in the clinical assessment of normal-functioning elderly individuals presenting with cognitive complaints.

A limitation in the present study concerns our sample size. Although this investigation is one of the first to conduct a prospective, longitudinal study of cognitive discrepancies in normal-functioning elderly individuals, the sample size was relatively small. However, the current sample size is generally consistent with those of other prospective studies examining cognitive change during the preclinical period of AD (e.g., Bäckman et al.⁵⁹ [N = 15 converters of 105 initially nondemented elderly individuals studied over a 6-year period]). Another limitation in the present study is that, at this point, it is unclear whether the individuals in the Decline group will continue to exhibit further cognitive deterioration over time and eventually convert to an AD diagnosis. Nevertheless, our findings (i.e., a cognitive-discrepancy measure using an executive-function task predicted a subsequent, more global cognitive decline) concur with the literature implicating early changes in executive functions in individuals with AD (for review, see Refs. ^{22,31}). Moreover, the magnitude of the decline on the DRS, a global cognitive screen that is robust to changes associated with normal cognitive aging,⁶⁰ is further suggestive that the observed decline represent a pathologic change and not normal age-related cognitive decline. However, to address this question further, we continue to pursue longitudinal follow-up of the current sample with the hopes of investigating the utility of cognitive-discrepancy measures in predicting cognitive decline in general and conversion to an AD diagnosis in particular.

Acknowledgments

This work was supported in part by a Veterans Administration Merit Review grant (to DCD), a Veterans Administration Career Development award (to MWJ), and National Institute on Aging grants RO1 AG12674 (to MWB) and P50 AG05131 (to LJT). Dr. Delis is a coauthor of the D-KEFS Color-Word Interference Test and receives royalties from the test.

References

1. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467–1472. [PubMed: 8350998]
2. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–923. [PubMed: 8346443]
3. Rebeck GW, Perls TT, West HL, et al. Reduced apolipoprotein epsilon 4 allele frequency in the oldest old Alzheimer's patients and cognitively normal individuals. *Neurology* 1994;44:1513–1516. [PubMed: 8058160]
4. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). *Neurology* 2001;56:1143–1153. [PubMed: 11342678]
5. Bondi MW, Salmon DP, Galasko D, et al. Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. *Psychol Aging* 1999;14:295–303. [PubMed: 10403716]
6. Linn RT, Wolf PA, Bachman DL, et al. The 'preclinical phase' of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. *Arch Neurol* 1995;52:485–490. [PubMed: 7733843]
7. Bondi MW, Salmon DP, Monsch AU, et al. Episodic memory changes are associated with the APOE-epsilon 4 allele in nondemented older adults. *Neurology* 1995;45:2203–2206. [PubMed: 8848194]
8. Elias MF, Beiser A, Wolf P, et al. The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort. *Arch Neurol* 2000;57:808–813. [PubMed: 10867777]
9. Jacobs DM, Sano M, Dooneief G, et al. Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology* 1995;45:957–962. [PubMed: 7746414]
10. Caselli RJ, Osborne D, Reiman EM, et al. Preclinical cognitive decline in late middle-aged asymptomatic apolipoprotein E-e4/4 homozygotes: a replication study. *J Neurol Sci* 2000;189:93–98. [PubMed: 11535238]
11. Driscoll I, McDaniel MA, Guynn MJ. Apolipoprotein E and prospective memory in normally aging adults. *Neuropsychology* 2005;19:28–34. [PubMed: 15656760]
12. Greenwood PM, Sunderland T, Friz JL, et al. Genetics and visual attention: selective deficits in healthy adult carriers of the epsilon 4 allele of the apolipoprotein E gene. *Proc Natl Acad Sci USA* 2000;97:11661–11666. [PubMed: 11027364]
13. Negash S, Petersen LE, Geda YE, et al. Effects of ApoE genotype and mild cognitive impairment on implicit learning. *Neurobiol Aging* 2007;28:885–893. [PubMed: 16701920]
14. Nilsson LG, Adolfsson R, Bäckman L, et al. The influence of APOE status on episodic and semantic memory: data from a population-based study. *Neuropsychology* 2006;20:645–657. [PubMed: 17100509]
15. Rosen VM, Bergeson JL, Putnam K, et al. Working memory and apolipoprotein E: what's the connection? *Neuropsychologia* 2002;40:2226–2233. [PubMed: 12417453]
16. Wilson RS, Bennett DA, Bienias JL, et al. Cognitive activity and incident AD in a population-based sample of older persons. *Neurology* 2002;59:1910–1914. [PubMed: 12499482]
17. Reiman EM, Caselli RJ, Chen K, et al. Declining brain activity in cognitively normal apolipoprotein E epsilon 4 heterozygotes: a foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease. *Proc Natl Acad Sci USA* 2001;98:3334–3339. [PubMed: 11248079]
18. Duchek JM, Balota DA, Cortese M. Prospective memory and apolipoprotein E in healthy aging and early stage Alzheimer's disease. *Neuropsychology* 2006;20:633–644. [PubMed: 17100508]
19. Small GW, Mazziotta JC, Collins MT, et al. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. *JAMA* 1995;273:942–947. [PubMed: 7884953]
20. Smith GE, Bohac DL, Waring SC, et al. Apolipoprotein E genotype influences cognitive 'phenotype' in patients with Alzheimer's disease but not in healthy control subjects. *Neurology* 1998;50:355–362. [PubMed: 9484353]

21. Small BJ, Rosnick CB, Fratiglioni L, et al. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging* 2004;19:592–600. [PubMed: 15584785]
22. Twamley EW, Ropacki SA, Bondi MW. Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *J Int Neuropsychol Soc* 2006;12:707–735. [PubMed: 16961952]
23. Jacobson MW, Delis DC, Bondi M, et al. Do neuropsychological tests detect preclinical Alzheimer's disease: individual-test versus cognitive-discrepancy score analyses. *Neuropsychology* 2002;16:132–139. [PubMed: 11949704]
24. Jacobson MW, Delis DC, Bondi MW, et al. Asymmetry in auditory and spatial attention span in normal elderly genetically at risk for Alzheimer's disease. *J Clin Exp Neuropsychol* 2005;27:240–253. [PubMed: 15903153]
25. Jacobson MW, Delis DC, Lansing A, et al. Asymmetries in global-local processing ability in elderly people with the apolipoprotein e-epsilon4 allele. *Neuropsychology* 2005;19:822–829. [PubMed: 16351358]
26. Houston WS, Delis DC, Lansing A, et al. Executive function asymmetry in older adults genetically at-risk for Alzheimer's disease: verbal versus design fluency. *J Int Neuropsychol Soc* 2005;11:863–870. [PubMed: 16519265]
27. Delis DC, Massman PJ, Butters N, et al. Spatial cognition in Alzheimer's disease: subtypes of global-local impairment. *J Clin Exp Neuropsychol* 1992;14:463–477. [PubMed: 1400912]
28. Finton MJ, Lucas JA, Rippeth JD, et al. Cognitive asymmetries associated with apolipoprotein E genotype in patients with Alzheimer's disease. *J Int Neuropsychol Soc* 2003;9:751–759. [PubMed: 12901781]
29. Haxby JV, Duara R, Grady CL, et al. Relations between neuropsychological and cerebral metabolic asymmetries in early Alzheimer's disease. *J Cereb Blood Flow Metab* 1985;5:193–200. [PubMed: 3988821]
30. Martin, A. Neuropsychology of Alzheimer's disease: the case for subgroups. In: Schwartz, MR., editor. *Modular Deficits in Alzheimer-Type Dementia*. Cambridge, MA: The MIT Press; 1990. p. 143-175.
31. Bäckman L, Jones S, Berger AK, et al. Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology* 2005;19:520–531. [PubMed: 16060827]
32. Albert MS, Moss MB, Tanzi R, et al. Preclinical prediction of AD using neuropsychological tests. *J Int Neuropsychol Soc* 2001;7:631–639. [PubMed: 11459114]
33. Reitan RM. The relation of the trail making test to organic brain damage. *J Consult Psychol* 1955;19:393–394. [PubMed: 13263471]
34. Petrides M, Milner B. Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* 1982;20:249–262. [PubMed: 7121793]
35. Chen P, Ratcliff G, Belle SH, et al. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology* 2000;55:1847–1853. [PubMed: 11134384]
36. Bookheimer SY, Strojwas MH, Cohen MS, et al. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med* 2000;343:450–456. [PubMed: 10944562]
37. Bondi MW, Houston WS, Eyler LT, et al. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology* 2005;64:501–508. [PubMed: 15699382]
38. Fleisher AS, Houston WS, Eyler LT, et al. Alzheimer's disease risk and functional MRI in normal aging. *Arch Neurol* 2005;62:1881–1888. [PubMed: 16344346]
39. Han SD, Houston WS, Jak AJ, et al. Verbal paired-associate learning by APOE genotype in non-demented older adults: fMRI evidence of a right hemispheric compensatory response. *Neurobiol Aging* 2007;28:238–247. [PubMed: 16434125]
40. Johnson KA, Jones K, Holman BL, et al. Preclinical prediction of Alzheimer's disease using SPECT. *Neurology* 1998;50:1563–1571. [PubMed: 9633695]
41. Killiany RJ, Gomez-Isla T, Moss M, et al. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. *Ann Neurol* 2000;47:430–439. [PubMed: 10762153]
42. Lind J, Persson J, Ingvar M, et al. Reduced functional brain activity response in cognitively intact apolipoprotein E epsilon4 carriers. *Brain* 2006;129:1240–1248. [PubMed: 16537568]

43. Reiman EM, Chen K, Alexander GE, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci USA* 2004;101:284–289. [PubMed: 14688411]
44. Reiman EM, Chen K, Alexander GE, et al. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. *Proc Natl Acad Sci USA* 2005;102:8299–8302. [PubMed: 15932949]
45. Wishart HA, Saykin AJ, McAllister TW, et al. Regional brain atrophy in cognitively intact adults with a single APOE epsilon4 allele. *Neurology* 2006;67:1221–1224. [PubMed: 17030756]
46. Wishart HA, Saykin AJ, Rabin LA, et al. Increased brain activation during working memory in cognitively intact adults with the APOE epsilon4 allele. *Am J Psychiatry* 2006;163:1603–1610. [PubMed: 16946187]
47. Delis, DC.; Kaplan, E.; Kramer, JH. Delis-Kaplan Executive Function System (D-KEFS). San Antonio, TX: The Psychological Corporation; 2001.
48. Delis, DC.; Kaplan, E.; Kramer, JH. Delis-Kaplan Executive Function System (D-KEFS)—Technical Manual. San Antonio, TX: The Psychological Corporation; 2001.
49. Stroop JR. Studies of interference in serial verbal reaction. *J Exp Psychol* 1935;18:643–662.
50. Mattis, S. Dementia Rating Scale: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1973.
51. Wetter SR, Delis DC, Houston WS, et al. Deficits in inhibition and flexibility are associated with the APOE-E4 allele in nondemented older adults. *J Clin Exp Neuropsychol* 2005;27:943–952. [PubMed: 16207619]
52. Devanand DP, Pelton GH, Zamora D, et al. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Arch Neurol* 2005;62:975–980. [PubMed: 15956169]
53. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;352:2379–2388. [PubMed: 15829527]
54. Monsch AU, Bondi MW, Salmon DP, et al. Clinical validity of the Mattis Dementia Rating Scale in detecting Dementia of the Alzheimer type. A double cross-validation and application to a community-dwelling sample. *Arch Neurol* 1995;52:899–904. [PubMed: 7661728]
55. Marson DC, Dymek MP, Duke LW, et al. Subscale validity of the Mattis Dementia Rating Scale. *Arch Clin Neuropsychol* 1997;12:269–275. [PubMed: 14588419]
56. Cato MA, Delis DC, Abildskov TJ, et al. Assessing the elusive cognitive deficits associated with ventromedial prefrontal damage: a case of a modern-day Phineas Gage. *J Int Neuropsychol Soc* 2004;10:453–465. [PubMed: 15147602]
57. Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and a treatment target. *Arch Neurol* 2005;62:1160–1163. [PubMed: 16009779]
58. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004;256:240–246. [PubMed: 15324367]
59. Bäckman L, Small BJ, Fratiglioni L. Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain* 2004;124:96–102.
60. Salmon DP, Thal LJ, Butters N, et al. Longitudinal evaluation of dementia of the Alzheimer type: a comparison of 3 standardized mental status examinations. *Neurology* 1990;40:1225–1230. [PubMed: 2381530]

FIGURE 1.

Mean ($\pm$ 1 SE) Color-Word Interference Test Completion Times by Subject Group and Condition

Notes: Condition 1, Color Naming; Condition 2, Word Reading; Condition 3, Inhibition; Condition 4, Inhibition/Switching. Higher reaction times reflect slower (worse) performance.

TABLE 1

Demographics and DRS Scores (Means and Standard Deviations) for Decline and Stable Groups

Variable	Decline	Stable
N	8	16
Age	78.8 (5.4)	74.4 (9.6)
Education	14.6 (2.5)	14.1 (2.0)
% Female	63%	50%
% e4 positive	50%	56%
DRS (Year A)	137.3 (3.7)	140.1 (3.2)
<i>T</i> score	50	54
DRS (Year B)	133.3 (3.6)	139.9 (3.2) ^a
<i>T</i> score	45	52

^a
 $t[22] = 4.7, p < 0.001$.

DRS: Dementia Rating Scale.