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The Influence of Apolipoprotein E Genotype on Visuospatial Attention dissipates After Age 80

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Abstract

Although it is established that the apolipoprotein E (APOE) e4 allele increases the risk of Alzheimer's disease (AD), epidemiological studies indicate that genetic risk decreases late in life. This raises the question of whether the effects of APOE on cognition which are seen in midlife arise from a cognitive phenotype of APOE or from the presence of early AD in some APOE-e4 carriers. We addressed this question by comparing the cognitive consequences of variation in the APOE gene between individuals over the age of 80 (old-old) and middle-aged and young-old individuals. A spatially cued discrimination paradigm – previously shown to be sensitive to AD and to APOE genotype – required a speeded categorization of a target letter following cues that were valid, invalid, or neutral in predicting target location. Results revealed greater costs of invalid cues in the APOE-e4 carriers of middle-aged and young-old, but not old-old, groups. The dissipation of the APOE effect in old-old individuals at lower risk of AD suggests that visuospatial attention impairments seen as early as midlife in APOE-e4 carriers may be a preclinical marker of AD.

Keywords

attention; APOE; phenotype; old-old

Introduction

It has become well established that the e4 allele of the Apolipoprotein E (APOE) gene increases risk of Alzheimer's disease (AD) in a gene-dose manner (Corder et al., 1993). This gene, however, is not used clinically to establish AD risk because it has limited predictive value (Henderson et al., 1995). Nevertheless, there are subtle though reliable cognitive deficits in non-demented carriers of the APOE-e4 allele – even in midlife (Bondi et al., 1995; Greenwood et al., 2000). Accompanying and probably presaging the changes in cognition are changes in brain integrity. Individuals with at least one e4 allele show shrinkage in hippocampal volume in midlife (Plassman et al., 1997) which correlates with reduced recognition memory performance (Lind et al., 2006). APOE-e4 carriers also show cerebral hypometabolism even in young adulthood in the absence of cognitive deficits (Reiman et al., 2004; Scarmeas and Stern, 2006).

Therefore, although the influence of APOE genotype on AD and cognitive functioning has been established, the nature of this influence remains a source of debate. Currently, there are two main competing views on how APOE genotype might influence cognition. The first is that the APOE gene produces a cognitive phenotype (Greenwood et al., 2005a). Cognitive phenotypes have been described in other heritable disorders, such as Williams syndrome (Donnai and Karmiloff-Smith, 2000) and Fragile X syndrome (Kaufmann et al., 1999). The cognitive phenotype hypothesis (Greenwood et al., 2005a) views cognitive variation with APOE genotype as arising from direct effects of this specific APOE polymorphism on efficiency of neuronal response to insult (Greenwood and Parasuraman, 2003). Within this hypothesis, APOE-e4 carriers uniformly show cognitive deficits on sensitive cognitive assays in a manner that is independent of eventual development of AD. By this view the association from genotype to neuronal response to cognitive function is direct and ubiquitous.

In contrast, an alternative “prodrome hypothesis” proposes that APOE serves merely as a marker for sub-populations with increased risk of developing AD or more rapidly advancing AD (Smith et al., 1998). By this view, as there is more preclinical AD among ostensibly normal APOE-e4 carriers than in non-carriers, mean differences between the two groups on sensitive cognitive measures are driven by a larger sub-population in the APOE-e4 group who are in the process of developing AD or who have as yet undiagnosed AD. The effects of APOE genotype on cognition are thus indirect; APOE-e4 marks increased risk for AD, and AD in turn affects cognitive function in a subset of APOE-e4 carriers. However, in the absence of preclinical AD, APOE-e4 carriers do not differ cognitively from other APOE genotypes. A critical corollary of this view is that the sensitive cognitive assays are detecting very early signs of the disease, at least in APOE-e4 carriers.

The purpose of the present study was to decide between these two competing theories using a sensitive cognitive assay of visuospatial attention administered to healthy old-old (80 years and above) individuals grouped by APOE genotype. This approach is undertaken because research indicates that after roughly this age, APOE-e4 status no longer seems to confer greater risk for dementia (Breitner et al., 1999). Based on this evidence, the prodrome hypothesis would predict no cognitive differences related APOE genotype in a group above age 80, as such a group is less likely to have more incipient AD cases in one genotype group relative to another. In contrast, the cognitive phenotype hypothesis would predict genotype differences to persist even in this old-old age group because APOE-e4 carriers uniformly show cognitive deficits independent of eventual development of AD.

A cued discrimination task was used to direct visuospatial attention in advance to regions of space containing letter targets. Cognitive assays that are targeted at specific components of cognitive processes have advantages over global assessment of cognition because they are aimed at specific networks whose brain mediation and innervation are well understood. Consequently, they are likely to be more sensitive to subtle but distinct cognitive changes that are not detected by standard neuropsychological tests (Greenwood et al., 2000). As cognitive deficits at an early stage of aging are likely to be small and subtle, such sensitive or specific tests can be useful, and may be combined with genotype to improve ability to predict which individuals progress to AD years later. In the cued discrimination task (adapted from Posner, 1980), following a fixation cross, a symbolic location cue appears centered in the screen. Cues were valid, invalid, or neutral in predicting the location of the target letter. The central finding from studies using such paradigm is that target processing is speeded by valid cues (benefits) but slowed by invalid cues (costs) (e.g., Posner, 1980). This ability to shift visuospatial attention appears to be mediated by cholinergic innervation of intraparietal sulcus (Corbetta et al., 2000; Davidson and Marrocco, 2000; Nobre et al., 1997) and is therefore selectively vulnerable to the reduced cholinergic integrity in aging and AD (Bartus et al., 1982; Gallagher and Colombo, 1995; Rogers et al., 1998). Speed of disengaging attention when location cues are

invalid is selectively slowed in aging (Greenwood et al., 1993), in AD (Parasuraman et al., 1992, and in APOE-e4 carriers (Greenwood et al., 2000). Further, studies with middle-aged participants have found APOE-e4 carriers who were unimpaired on standard neuropsychological tests nevertheless showed subtle but significant deficiencies in component processing tasks of spatial attention (Flory et al., 2000; Greenwood et al., 2000). In the present study we compared performance of old-old participants grouped by APOE genotype against middle-aged (41–59 years) and young-old (60–79 years) individuals. If the effect of the e4 allele on cognition earlier in life is due to phenotypic effects of the allele, then those cognitive effects should persist late in life, even after the risk of AD itself has diminished. Specifically, this cognitive phenotype view predicts greater costs in e4 carriers (Greenwood et al., 2005a) than in non-carriers in all age groups. Alternatively, if the effect of the e4 allele is prodromal then the cognitive effects should be reduced late in life. Therefore, the prodromal view predicts greater costs in e4 carriers only in the younger groups and not after age 80.

Methods

Participants

30 old-old participants (mean age: 83.2, range: 81–87 years) were compared with 30 middle-aged (mean age: 53.3, range: 41–59 years) and 30 young-old (mean age: 66.9, range: 60–75 years) individuals. Half of the participants in each age group were APOE-e4 allele carriers while the remaining half were APOE-e4 allele non-carriers. Participants were selected for age and gender, and their characteristics are shown in Table 1. Informed consent was obtained. Vision was tested with a Snellen Eye Chart and Rosenbaum pocket screener and all participants had vision corrected at least to 20/30. The old-old participants were recruited through the Mayo Alzheimer's Disease Patient Registry (ADPR) at the Mayo Clinic, Rochester, MN. Individuals participating in the ADPR are evaluated by a behavioral neurologist who obtains a medical history from an informant, completes a short test mental status examination (Kokmen et al., 1987), the Hachinski Ischemic Scale (Rosen et al., 1980), and performs a neurologic examination. Laboratory tests include CBC count, thyroid function tests, Vitamin B-12, folic acid levels, sensitive thyroid stimulating hormone level, and syphilis serology. Participants undergo brain imaging (computed tomography or magnetic resonance imaging). Diagnoses are established via a consensus meeting of behavioral neurologists, neuropsychologists, geriatricians, neuropsychiatrists, and nurses. Healthy individuals are those who: 1) are independently functioning community dwellers, 2) do not have active neurological or psychiatric conditions, 3) have no cognitive complaints, 4) have a normal neurological exam, 5) are not taking any psychoactive medications in doses that would impact cognition (Ivnik et al., 1992).

Participants in the middle-aged and young-old groups were those who volunteered to participate in the National Institute of Mental Health's Prospective Study of Biomarkers for Older Controls at Risk for Alzheimer's Disease (known as BIOCARD), which is double-blind and longitudinal. Individuals were excluded from participation if their performance did not fall within the normal age-related range of scores on a battery of standardized neuropsychological test batteries, including the Mattis Dementia Rating Scale, the Buschke Selective Reminding Test (Buschke, 1973), and the Wechsler Memory Scale—Revised WMS-R (Wechsler, 1987). Other criteria for exclusion were significant medical problems, including diabetes mellitus, hypertension, cerebrovascular disorder, autoimmune disorder, vitamin B-12 deficiency, or thyroid disorder. Exclusion of individuals for cerebrovascular disease was made on the basis of history of strokes and hypertension and on review of MRI scans. Thus, all participants in the study were cognitively healthy individuals.

APOE genotypes

For the old-old participants recruited at the Mayo clinic, a DNA extractor (Model 340A, Applied Biosystems, Foster City, CA) extracted high-molecular weight DNA from peripheral blood leukocytes (buffy coat). A polymerase chain reaction thermal cyclor then amplified DNA (Perkin Elmer Cetus, Norwalk, CT). For the middle-aged and young-old participants, APOE genotypes were determined by restriction endonuclease digestion of polymerase chain reaction amplified genomic DNA (performed by Athena Diagnostics, Worcester, Massachusetts). Participants with genotypes E2/E4, E3/E4, or E4/E4 were classified as APOE-e4 allele carriers, whereas those with genotypes E2/E2, E2/E3, or E3/E3 were classified as APOE-e4 allele non-carriers. There were insufficient numbers of homozygotes to analyze data by “gene dose” of the e4 allele.

All procedures were approved by the institutional review boards, and informed consent was obtained from all participants.

Stimuli and procedures

A spatially cued letter discrimination task, developed in our previous study of APOE-e4 carriers (Greenwood et al., 2000), was used. Following a fixation point (displayed for 1000 ms), a symbolic location cue – an arrow or asterisk – appeared centered in the screen (Figure 1). A valid arrow cue accurately indicated future location of the target letter, whereas an invalid cue indicated the opposite location. Asterisks represented neutral trials. The cue was valid in predicting the subsequent target location on 60% of the trials, invalid on 20%, and neutral on 20%. There were 60 valid trials at each SOA and 20 invalid and neutral trials. The centered location cue appeared for a variable cue–target stimulus onset asynchrony (SOA) of 200, 500, or 2,000 ms, following which a letter target appeared 6.7° to the right or left of fixation. Participants were required to make a speeded categorization of the target as either a consonant or a vowel by pressing one of two response buttons. The inter-trial interval was varied randomly (2,200, 2,500 or 2,800 ms). The range of SOAs was selected to assess the development of cue validity effects. Based on previous investigations with this task (Parasuraman et al., 1992; Greenwood et al., 2000), we predicted the effects of cue validity would increase with SOA. Also, based on that work, we predicted the strongest group effects would be seen at the longest SOA where cue validity effects are best developed.

Results

All statistical tests were performed at the .05 level of significance, with results meeting the .10 level reported as marginal. Significance tests were always two-tailed. RT was the measure of interest, but accuracy was also analyzed.

Accuracy

Accuracy of target categorization as consonant or vowel was analyzed as ratios (number correct: number presented) for each condition. These were subjected to a repeated measures ANOVA, with Age and APOE status as between-subjects factors and cue validity and cue–target SOA as within-subjects factors. Accuracy varied with cue validity, $F(2, 168) = 3.32$, $p < .04$, eta-squared = .01, but not with SOA. Accuracy also varied with Age, $F(2, 84) = 10.51$, $p < .0001$, eta-squared = .19 (Figure 2), being lowest in the old-old (.927) and highest in the middle-aged (.988). There were no significant interactions involving Age, although Validity $\times$ SOA $\times$ Age was a non-significant trend, $F(8, 336) = 1.84$, $p = .07$. The main effect of APOE genotype was not significant although there was a marginally significant interaction with SOA (APOE $\times$ SOA, $F(2, 168) = 3.01$, $p = .052$). This was, however, the only effect of APOE status observed for the accuracy measure, and no other interactions concerning APOE were significant.

RT

Median RTs were computed for correct letter discriminations. RTs below 200 ms and above 2 s were excluded from analysis. RT data were subjected to a mixed-effects omnibus ANOVA, with Age Group (middle-aged, young-old, and old-old) and APOE genotype (APOE e4 carriers and APOE e4 non-carriers) as the between-subjects factors and Cue Validity (valid, neutral, or invalid) and SOA (200, 500, and 2,000 ms) as within-subjects factors.

As can be seen in Figure 3, RT overall was fastest following valid cues, slowest following invalid cues, and intermediate following neutral cues [Cue Validity, $F(2, 168) = 52.58$, $p < .0001$, $\eta^2 = .11$]. Further, RT was fastest for middle-aged, intermediate for young-old, and slowest for old-old groups [Age, $F(2, 84) = 18.12$, $p < .0001$, $\eta^2 = .30$]. Effects of cue validity developed as cue-target SOA increased from 200 to 2,000 ms [SOA, $F(2, 168) = 7.82$, $p < .001$, $\eta^2 = .18$], with RT benefits of valid cues evident at a shorter SOA than were RT costs of invalid cues [Validity $\times$ SOA, $F(4, 336) = 24.04$, $p < .0001$, $\eta^2 = .09$]. There was no main effect of APOE genotype on overall RT. However, there were APOE $\times$ Cue Validity [$F(2, 168) = 4.74$, $p < .01$, $\eta^2 = .01$] and APOE $\times$ Age $\times$ Cue Validity [$F(4, 168) = 4.99$, $p < .001$, $\eta^2 = .17$] interactions, which suggested that the effect of cue validity on RT varied as a function of Age and APOE genotype. These interactions justified follow-up analyses on summary measures of costs of invalid cues (invalid cue – neutral cue RT) and benefits of valid cues (neutral cue – valid cue RT). Based on previous work (Greenwood et al., 2005a; Greenwood et al., 2000), the strongest effects are predicted at the longest SOA where cue validity effects are best developed. Thus, while we analyzed RT at all SOAs, we only report costs and benefits at the longest SOA.

Costs and benefits

Figure 4a shows RT costs of invalid cues at the longest SOA for each age group as a function of APOE genotype. APOE-e4 carriers in both middle-aged and young-old groups showed greater costs of invalid cues than non-carriers. The old-old group, by contrast, did not show differences in costs as a function of APOE genotype. Consistent with these observations, an Age (middle-aged vs. young-old vs. old-old) $\times$ APOE (e4 carriers vs. e4 non-carriers) ANOVA on costs revealed a significant main effect of APOE [$F(1, 84) = 10.93$, $p < .002$, $\eta^2 = .11$] and an APOE $\times$ Age interaction, [$F(2, 84) = 3.05$, $p < .05$, $\eta^2 = .06$]. Subsequent pair-wise comparisons of the age groups showed an APOE $\times$ Age interaction on costs when comparing the old-old group to both middle-aged [$F(1, 56) = 5.65$, $p < .02$, $\eta^2 = .10$] and young-old [$F(1, 56) = 3.03$, $p < .05$, $\eta^2 = .05$] groups, suggesting that the old-old group differed from both of these groups as a function of APOE genotype. In contrast, the middle-aged and young-old groups did not differ in costs as a function of APOE genotype; the APOE $\times$ Age interaction comparing these two age groups was not significant, [$F(1, 56) = .48$, $p = .49$]. Further, separate ANOVAs on each age group showed greater costs of invalid cues for APOE-e4 allele carriers than non-carriers in both middle-aged [$F(1, 28) = 10.29$, $p < .003$, $\eta^2 = .37$] and young-old [$F(1, 28) = 5.88$, $p < .02$, $\eta^2 = .21$] groups. In contrast, the old-old group did not show group differences in costs as a function of APOE genotype [$F(2, 98) = .001$, $p = .98$], suggesting a weakened effect of the APOE-e4 allele on invalidity cost in the old-old group. One reviewer questioned whether apparently reduced effects of genotype in the old-old group were actually due to absent effects of cue validity in that group. We assessed effects of genotype and cue validity in the old-old group only. We observed a main effect of cue validity (valid = 732.4, neutral = 756.7, invalid = 792.4, $F(2, 116) = 34.85$, $p < .0001$). There was no effect of APOE genotype [$F(2, 58) = .07$, $p = .79$]. This indicates that cue validity effects – both costs and benefits -- are present in the old-old group despite the absence of genotype effects.

RT benefits of valid cues at the longest SOA are shown in Figure 4b. While there was a trend for greater benefits of valid cues for APOE-e4 non-carriers than carriers in middle-aged and young-old groups, no significant group differences were observed on this component. Therefore, the interaction of cue validity and genotype could be attributed to greater costs of invalid cues rather than to a change in benefits of valid cues.

The editor pointed out that the prodrome hypothesis predicts the old-old e4 carrier group would show less variability in performance than the younger carrier groups. If so, then there should be greater variability among the younger e4 carriers compared to the oldest e4 carriers. Standard deviations of costs decreased with age, being highest in the middle-aged (67.6) and lowest in the old-old (53.2) and were higher overall in the e4 carrier compared to non-carrier groups (62.9 and 51.4, respectively). This was seen in the middle-aged (carriers = 60.6; non-carriers = 57.0) and old-old groups (carriers = 63.7; non-carriers = 42.4), but not the young-old group (carriers = 52.2; non-carriers = 56.3). A p test of differences in variation across the groups was not significant.

Discussion

The present study investigated whether the effects of the APOE-e4 allele on cognition are linked with effects of the allele on risk of AD. Although the e4 allele is an established risk factor for AD late in life, it has not been known whether those effects are phenotypic or prodromal. As a group, e4 carriers – particularly the homozygotes – show cognitive changes even in midlife (Cohen et al., 2001; Flory et al., 2000; Greenwood et al., 2005a; Greenwood et al., 2000; Parasuraman et al., 2002) and show brain changes as early as young adulthood (Lind et al., 2006; Reiman et al., 2004). This suggests either that AD pathology develops very early in some e4 carriers (prodrome), or that the e4 allele somehow produces characteristic cognitive traits (phenotype), or both. That effects of the e4 allele on risk of AD are apparently diminished after about age 80 (Breitner et al., 1999; Corder et al., 1993) makes it possible to investigate the role of the e4 allele in people presumably at lower risk of AD. We here report that cognitive effects of the e4 allele are reduced in cognitively normal individuals over age 80 compared to younger individuals. This finding suggests that the cognitive deficits which have been associated with the e4 allele as early as midlife (Flory et al., 2000; Greenwood et al., 2005a) may be attributed to the subset of APOE-e4 carriers in the AD prodrome. Although the natural history of the AD prodrome is not known, researchers have estimated that symptoms precede diagnosis by 4–6 years in those who develop the disease (Backman et al., 2002; Linn et al., 1995; Small et al., 2000). Thus, it is likely that the oldest e4 carriers in our study are part of a subset of e4 carriers who will not develop AD, consistent with findings that only about half of e4 homozygotes have developed AD by age 90 (Henderson et al., 1995). Although our oldest group of e4 carriers had the lowest mean accuracy, they nevertheless performed at or above 90% accuracy (Figure 2). The old-old e4 carriers also had the slowest RTs (Figure 3), which does not suggest they were slowing down to increase accuracy. This 90% accuracy performance by the old-old suggests that the slight increase in coronary heart disease among e4 carriers (1.06 odds ratio in a recent meta-analysis of large-scale studies, Bennet et al., 2007) is not a likely explanation for our results.

Others have found evidence that effects of APOE-e4 on cognition decline with age. In a metaanalysis of effects of APOE on cognition, Small et al. (2004) concluded that the e4 allele had a greater effect on the cognitive performance of younger than older individuals. Consistent with this conclusion, Lind et al. (2006) reported that reductions in right hippocampal volume were more pronounced in those e4 carriers who were younger than age 65. Also consistent is an interaction we recently reported between APOE and a nicotinic receptor gene (CHRNA4) in a population different from the one reported here. Individuals with a combination of at least one APOE-e4 allele and two copies of the CHRNA4 T allele showed heightened effects of

invalid cues on discrimination performance. Moreover, this effect was stronger in middle-aged than in older individuals (Espeseth et al., 2006). Considered together, these studies suggest that the effect of APOE on cognition is weaker in those individuals who remain non-demented in old age. It is also possible that the heightened effect of the APOE-e4 allele is strongest in midlife and declines thereafter. That possibility will be considered below.

The present result raises interesting questions about the AD prodrome. The existence of a prodrome only in some e4 carriers implies that the cognitive and brain changes observed in *groups* of younger e4 carriers (e.g., Flory et al., 2000; Greenwood et al., 2005a; 2000) reflect the existence of an AD prodrome only in *some* members of the group. The challenge will be to determine ways of distinguishing which cognitively normal APOE e4 carriers are more likely to eventually develop AD and which are less likely. Moreover, efforts to identify subgroups should not be limited to carriers of the APOE-e4 allele, as non-carriers also develop AD.

The present cross-sectional analysis cannot directly address the question of whether our poorest performing APOE-e4 carriers in all groups will progress to AD. However, by extension, these results suggest that patterns of longitudinal cognitive change might predict which e4 carriers will eventually develop AD. Previous studies have reported faster longitudinal change in e4 carriers in measures of as brain (Moffat et al., 2000; Reiman et al., 2001) and cognition (Bretsky et al., 2003; Feskens et al., 1994), but have not looked at individual trajectories of change. The NIMH BIOCARD study (Greenwood et al., 2005a) was designed in part to investigate patterns of cognitive longitudinal change as a function of APOE-e4 genotype. As part of that study, we examined performance on a cued visual search task over 3 years. That task manipulated the size of rectangular precues (500 ms in advance) to target location in a search array (Greenwood et al., 1997). In healthy young and old, we previously reported a cross-sectional increase in effect of precue size on search speed (Greenwood and Parasuraman, 2004), suggesting an increase with age. In the BIOCARD study, we found that middleaged participants without the APOE-e4 allele also showed a pattern of longitudinally increasing attentional scaling effects on search speed (Greenwood et al., 2005b). However, APOE-e4 carriers deviated from that apparently normal pattern of longitudinal increase in effect of precue size by showing a longitudinal decrease in effect of precue size on search. Of particular relevance to the question of subgroups, of the 8 people who subsequently converted to MCI and/or AD, all but 1 (APOE e2/4) showed the decreasing longitudinal pattern. Of those who did not convert, only a subset showed the decreasing pattern – 4 of the 7 e4/4 (average of 6.8 years in the study without converting). In contrast, 31% of the non-carriers and 36% of the e3/4 heterozygotes showed the decreasing pattern. We interpreted these data as indicating this pattern of longitudinal decline in the effect of cue size on attentional scaling in a subset of e4 carriers might predict which e4 carriers will later convert to MCI and/or AD.

Results from the present cross-sectional study on attentional shifting are consistent with those longitudinal findings on attentional scaling. In Figure 4, costs of invalid location cues in non-carriers of the e4 allele are similar over the 3 age groups, consistent with longitudinal stability. In contrast, costs in e4 carriers are greater than in non-carriers in the two younger groups, consistent with our previous report that costs are greater in e4 carriers in midlife (Greenwood et al., 2000; 2005). Although this data indicates that non-carriers remain stable over time, it is less informative about the e4 carriers. It is possible that the cross-sectional reduction in costs in e4 carriers is due to (1) a longitudinal decline in costs only in e4 carriers, (2) the selective conversion of e4 carriers who showed heightened costs to MCI and/or AD, or (3) both. We have unpublished longitudinal data from this task. Initial analyses suggest that costs remained stable over the first 3 years of testing in non-carriers. In e4/4 homozygotes costs declined over 3 years in 11 (M age 57.6) and increased in 2 (M age 56.1). In e3/4 heterozygotes costs declined in 19 (M age 59.5) and increased in 27 (M age 57.5). Considered together, this suggests a

different longitudinal course in about half of the e4 carriers, consistent with previous reports that only about 50% of e4 carriers develop AD by age 90 (Henderson et al., 1995).

If the subset of e4 carriers showing heightened costs relative to non-carriers in midlife are at increased risk of converting to AD, then the lack of group differences in the oldest group in the present study suggests that e4 carriers with heightened costs are not well represented among older, healthy individuals. Consistent with that interpretation, the APOE-e4 allele is associated with greater risk of death among older people, an association which is partially mediated by AD (Hayden et al., 2005). It may be that in e4 carriers who have survived to age 80 without apparent dementia, the negative effects of the allele have been mitigated, delayed, or otherwise avoided. Relevant to that possibility is a substantial literature implicating APOE in neuronal repair and plasticity (e.g. (Mauch et al., 2001; Poirier, 1994). Transgenic mice with the human e4 compared to the e3 allele show reduced clearance of lipid debris and axonal sprouting (White et al., 2001a; White et al., 2001b) and reduced rates of synaptogenesis (Teter and Ashford, 2002) following lesions to entorhinal cortex. In humans, the APOE-e4 allele is associated with faster rate of progression in ALS (Drory et al., 2001), multiple sclerosis (Fazekas et al., 2001), and recovery after traumatic brain injury (Lichtman et al., 2000; Teasdale et al., 2005) (see review in (Greenwood and Parasuraman, 2003). Nevertheless, the present results suggest that a subgroup of e4 carriers are spared the consequences of the apparently inefficient neuronal repair and plasticity mechanisms associated with the allele. Therefore, heightened costs in midlife might reflect inefficient neuronal repair which could potentially allow future cognitive decline. Longitudinal studies will be needed to determine the relation between heightened costs, longitudinal decline in costs, and eventual stability or conversion to AD in the context of APOE.

The different cross-sectional age pattern of costs in e4 carriers compared to non-carriers in the present study suggests a negative influence of the e4 allele on the attention system in midlife. Previous work has shown that RT costs of invalid cues are a sensitive index of brain damage. Heightened costs of invalid cues have been reported in parietal patients (Posner et al., 1984), in patients in the early stage of AD (Parasuraman et al., 1992), and in APOE-e4 carriers even in midlife (Greenwood et al., 2000; 2005). This was interpreted by Posner et al. as slowed 'disengagement' of the attentional focus from invalidly cued space. It is important to note that costs of invalid cues, and not benefits of valid cues, were affected by APOE in light of evidence that slowed RT following invalid cues is specifically dependent on muscarinic cholinergic neurotransmission. Infusion of the muscarinic antagonist scopolamine into intraparietal sulcus in rhesus monkeys slowed responding particularly following invalid cues (Davidson and Marrocco, 2000). Also relevant to the present findings are links between APOE and cholinergic function. In two studies, Sunderland and colleagues have reported evidence of alteration in the muscarinic cholinergic system in e4 carriers, viz, greater muscarinic-2 receptor binding attributed to lower acetylcholine concentration in the synapses of older APOE-e4 carriers (Cohen et al., 2003) and altered in responsiveness to physostigmine in the cholinergic pathway in APOE-e4 carriers in the 30s and 40s (Cohen et al., 2006). Such altered muscarinic cholinergic function in younger e4 carriers could contribute to the greater costs we observed in the younger groups of APOE-e4 carriers. Furthermore, there is recent evidence that recovery from experimental cortical injury is dependent on an intact basal forebrain cholinergic system (Conner et al., 2005). If so, then the cholinergic dysfunction seen in association with the e4 allele by Sunderland and colleagues could add to the inefficient neuronal repair functions associated with the e4 allele and contribute to functional deficits.

In summary, the present study used a cued letter discrimination task to examine the effect of APOE-e4 allele on visuospatial attention and found greater costs of invalid cues in the APOE-e4 carriers composed of middle-aged and young-old, but not old-old, groups. To the best of our knowledge, we are unaware of similar studies comparing APOE-e4 carriers and non-

carriers across three age groups. Our findings suggest that the effect of the APOE-e4 allele on cognition is weaker in individuals remaining non-demented beyond age 80, consistent with epidemiological evidence of no increased risk of AD in this age group (Breitner et al., 1999). The findings also implicate the utility of the visuospatial attention paradigm at detecting very early signs of Alzheimer's disease, and suggest that cognitive deficits in APOE-e4 carriers could be used as a predictor of individual future decline or stability. Longitudinal studies are required to confirm these findings.

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Figure 1.
Illustration of CUED LETTER DISCRIMINATION task.

Figure 2. ACCURACY plotted as a function of CUE VALIDITY for APOE-e4 CARRIERS and APOE-e4 NON-CARRIERS at each of three Age Groups.

Figure 3. REACTION TIME (RT) plotted as a function of CUE VALIDITY for APOE-e4 CARRIERS (filled-in symbols) and APOE-e4 NON-CARRIERS (open symbols) of MIDDLE-AGED (triangles), YOUNG-OLD (squares), and OLD-OLD (circles) groups [*a*: 2000 ms cue-target stimulus onset asynchrony (SOA), *b*: 500 ms SOA. *c*: 200 ms SOA]. Error bars represent standard errors.

Figure 4. Calculated COSTS of invalid cues (a) and BENEFITS of valid cues (b) at 2000 SOA plotted as a function of APOE genotype group for MIDDLE-AGED, YOUNG-OLD, and OLD-OLD groups. Error bars represent standard errors.

Table 1

Mean participant characteristics.

	Middle-Aged	Young-Old	Old-Old
Age (in years)	53.3 (4.7, 41–59)	66.9 (5.0, 60–75)	83.2 (1.9, 81–87)
APOE Group (e4+/e4–)	15/15	15/15	15/15
Gender (F/M)	20/10	20/10	20/10
Age in each APOE group	e4+:53.3 (4.5) e4–:53.2 (5.1)	e4+:66.4 (5.1) e4–:67.3 (5.1)	e4+:83.2 (2.1) e4–:83.3 (1.7)
Gender in each APOE group (F/M)	e4+:10/5 e4–:10/5	e4+:10/5 e4–:10/5	e4+:10/5 e4–:10/5

Note: Standard deviations and range are indicated in parentheses.