

## Context-specific memory and apolipoprotein E (ApoE) $\epsilon$ 4: Cognitive evidence from the NIMH prospective study of risk for Alzheimer's disease

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### Abstract

The aim of the study was to determine whether the  $\epsilon$ 4 allele of the apolipoprotein E (ApoE) gene was associated primarily with context-specific memory among individuals at genetic risk for developing Alzheimer's disease. The effect of ApoE status on comprehensive neuropsychological results was examined in 176 healthy adults during baseline cognitive testing in the NIMH Prospective Study of Biomarkers for Older Controls at Risk for Alzheimer's Disease (NIMH Prospective BIOCARD Study). The presence of the  $\epsilon$ 4 allele was associated with significantly lower total scores on the Logical Memory II subtest of the Wechsler Memory Scale–Revised and percent of information retained after delay. Further analysis indicated the prose recall and retention effect was partially explained by a small subgroup of  $\epsilon$ 4 homozygotes, suggesting a gradually progressive process that may be presaged with specific cognitive measures. The current results may represent an  $\epsilon$ 4-associated breakdown between gist-related information and context-bound veridical recall. This relative disconnection may be understood in light of putative  $\epsilon$ 4-related preclinical accumulation of Alzheimer pathology (tangles and plaques) in the entorhinal cortex (EC) and among frontal networks, as well as the possibility of less-efficient compensatory strategies. (*JINS*, 2004, *10*, 362–370.)

**Keywords:** Alzheimer risk, Context-specific memory, Apolipoprotein E

### INTRODUCTION

The  $\epsilon$ 4 isoform of the apolipoprotein E (ApoE) gene is a well-established risk factor for early development of Alzheimer's disease (AD; Blacker et al., 1997; Corder et al., 1993; Farrer et al., 1997; Saunders et al., 1993; Strittmatter et al., 1993). Although a recent meta-analysis has established an association between relatively deficient new learning ability and the  $\epsilon$ 4 allele in healthy older individuals (B.J. Small et al., 2003), the qualitative nature of this association remains unspecified. A useful phenomenological distinction in memory research is between content or actual item information and associated source or contextual material (Van Petten et al., 2000). In general, healthy older adults

are able to process context-related aspects of learning as effectively as younger adults; however, older persons require increased cognitive support when content and context are not intrinsically related (Gilsky et al., 2001; Spencer & Raz, 1995). In marked contrast, AD patients do not benefit from the inherent coupling of content and context on tasks of episodic and incidental learning (Balota et al., 1999; Simon et al., 1994; J.A. Smith & Knight, 2002). Is there a similar dissociation between content and intrinsic context in healthy older adults at risk for AD by virtue of the presence of the  $\epsilon$ 4 allele? This question has not been explored systematically in the extant literature.

Before examining the relevant findings in some detail, another content *versus* context dichotomy is that of gist-based learning and veridical response, which respectively are defined as abstract representation of semantic content and actual recall or recognition that preserves surface detail (Brainerd & Reyna, 1990). Standardized neuropsycholog-

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ical measures of learning and memory use material that vary in the amount of inherent gist information, from narrative prose and semantically organizable word lists to lists of unrelated words and some visual stimuli (i.e., those that can be reasonably associated with semantics, such as recognizable faces). Because most stories in western cultures are organized around a central theme, measures of prose recall are arguably among the most context-bound of standardized neuropsychological measures. However, most neuropsychological tests of learning and memory require verbatim recall. Consequently, standardized measures of semantic learning and memory may assess a hybrid of veridical process and gist-based representation, which may confer greater sensitivity for detecting an  $\epsilon 4$ -related effect. For the purposes of the current study, context-specific memory is defined as veridical recall or recognition of material with inherent gist.

A review of the neuropsychology literature suggests that the ApoE  $\epsilon 4$  allele primarily impedes the learning of context-specific information among healthy older adults at genetic risk for AD. For instance, whereas there is little or no relationship between the  $\epsilon 4$  allele and memorization of abstract designs in at-risk individuals (e.g., Bondi et al., 1999), there is longitudinal evidence of a relationship between the  $\epsilon 4$  allele and a reduced ability to discriminate pictorial information (i.e., faces of famous persons) that is context driven (B.J. Small et al., 1998). Similarly, no connection has been found between learning semantically unrelated words and presence of the  $\epsilon 4$  allele in healthy adults (Berr et al., 1996; Bookheimer et al., 2000; Caselli et al., 1999, 2001; Dik et al., 2000; Kantarci et al., 2002; G.E. Smith et al., 1998). In contrast, individuals possessing at least one  $\epsilon 4$  allele perform worse when learning and recalling items from word lists that can be actively organized by semantic categories, when studied either cross sectionally (Bondi et al., 1995, 1999; J.G. Chen et al., 2002) or longitudinally (de Leon et al., 2001; B.J. Small et al., 1998), (although cf. B.J. Small et al., 2000).

Diminished prose recall associated with  $\epsilon 4$  among healthy older adults has been documented in cross-sectional studies (Bookheimer et al., 2000; Schmidt et al., 1996; Schiffman et al., 2002; Wilson et al., 2002) and in one longitudinal study (O'Hara et al., 1998). Delayed prose recall also differentiates between controls and AD patients (Howieson et al., 1997; Marquis et al., 2002; Rubin et al., 1998; Storandt et al., 1984; Storandt & Hill, 1989). In addition, there is evidence that context-specific memory might decline early in the AD prodrome (Albert et al., 2001; Elias et al., 2000; Lange et al., 2002; Linn et al., 1995). For example, story recall has been shown to discriminate between preclinical AD and non-dementing controls, whereas prose recall was not able to differentiate between eventual AD converters and full-blown Alzheimer's disease (P. Chen et al., 2001). Moreover, Lange et al. (2002) found that the absence of the  $\epsilon 4$  allele was associated with better recall (immediate and delayed) of prose material as compared with a categorical word list in a subgroup of individuals who subsequently

developed AD, suggesting that story learning might be particularly sensitive to the presence of at least one  $\epsilon 4$  isoform.

Additionally,  $\epsilon 4$  presence is associated with lower scores on tasks of rote learning by selective reminding in healthy older persons (Helkala et al., 1995, 1996; Mayeux et al., 2001; O'Hara et al., 1998). Because selective reminding typically uses semantically unrelated words, the relationship between selective reminding and  $\epsilon 4$  appears more attributable to attentional and executive problems than contextual factors. For example, the presence of the  $\epsilon 4$  allele has been shown to be associated with relative decrements on standard neuropsychological measures of processing speed, attention, and executive functioning (e.g., Yaffe et al., 1997) as well as on cognitive paradigms of visuospatial attention and working memory (Greenwood et al., 2000; Parasuraman et al., 2002; Rosen et al., 2002).

The current study reports on data at baseline from the NIMH Study of Biomarkers in Older Controls at Risk for Alzheimer's Disease (NIMH Prospective BIOCARD study). Baseline cognitive data were examined to determine whether a relationship exists between the presence of the ApoE  $\epsilon 4$  allele and context-specific learning in asymptomatic older adults. Genetic risk for Alzheimer's disease was defined as possession of at least one ApoE  $\epsilon 4$  allele. A comprehensive neuropsychological battery was used, including measures of episodic learning, language functioning, and visuospatial ability. Tasks employing stories, a list of unrelated words (on which selective reminding was used), and designs constituted episodic learning. Because of the unique gist-related nature of the story learning task in our testing battery, we expected to find an association between presence of the  $\epsilon 4$  allele and reduced prose recall, but not with design recall or noncategorical word-list learning. Although measures of language and visuospatial ability are predictive of conversion to AD (Arnaiz et al., 2001; Bozoki et al., 2001), these neurocognitive domains were not expected to be effected early in the disease process, especially as accumulation of neurofibrillary tangles is largely confined to medial temporal lobe structures in the earliest stages (Braak & Braak, 1991).

## METHOD

### Research Participants

The entire group of participants consisted of 176 persons with a mean age of 59 years ( $SD = 8.6$ ) with a range of 42–86 years. The group was further subdivided into 115 without the  $\epsilon 4$  allele ( $\epsilon 4$ -absent) and 61 with the  $\epsilon 4$  allele ( $\epsilon 4$ -present). For the overall group and genetic subgroups, mean age, years of education, estimated verbal intelligence quotient (IQ) on the National Adult Reading Test (NART; Blair & Spreen, 1989), and gender distribution are shown in Table 1. As expected, ApoE allele groups did not differ significantly by age ( $p = .93$ ), education ( $p = .87$ ), NART IQ ( $p = .24$ ), or by gender,  $\chi^2 = 1.90$ ,  $p = .17$ . In

**Table 1.** Participant characteristics (means + standard deviations) for the entire sample and ApoE genotype subgroups

Characteristic	Group		
	Entire sample	$\epsilon 4$ -present	$\epsilon 4$ -absent
Number	176	61	115
Gender (F:M)	112:64	43:18	69:46
Age (years)	59.4 $\pm$ 8.6	59.3 $\pm$ 7.5	59.4 $\pm$ 9.2
Education (years)	16.8 $\pm$ 2.4	16.9 $\pm$ 2.3	16.7 $\pm$ 2.5
NART IQ	120.4 $\pm$ 7.4	121.2 $\pm$ 6.0	120.0 $\pm$ 8.1

Note.  $\epsilon 4$  = epsilon 4 allele of the apolipoprotein E gene; F = female; M = male; NART IQ = National Adult Reading Test Intelligence Quotient.

addition, 10 individuals from the  $\epsilon 4$ -present group were homozygotes; neither age, education, nor NART IQ scores differed as a function of the number of  $\epsilon 4$  alleles (0, 1, 2).

These 176 volunteer participants were evaluated as part of a longitudinal study of people at risk for developing AD by virtue of genetics, age, or positive family history. All participants were community-dwelling residents who responded to either printed advertisements in local media or national media sources, informational lectures, or word-of-mouth recruitment by friends or family members. For the purposes of the present study, genetic risk of Alzheimer's disease was defined as the presence of at least one  $\epsilon 4$  isoform. The majority of participants (79%) had a positive family history of AD, which was documented by careful review of the medical records of the first-degree relative with the illness.\* Certainty of diagnosis was determined in approximately 30% of familial history participants who provided autopsy records with definitive pathological evidence of AD in a parent or sibling. In the absence of autopsy confirmation, a firm case of AD in first-degree relatives was established through the preponderance of clinical evidence, including reports, neuropsychological evaluation, documentation of a slowly progressive downhill clinical course consistent with AD, and a medical evaluation excluding other known dementia etiologies. Participants whose first-degree relatives had only sparse records supporting a diagnosis of AD were not included in the study.

## Clinical Evaluation

The NIMH Geriatric Psychiatry Branch (GPB) evaluated participants during a brief inpatient stay at the NIH Clinical Center. The evaluation included a thorough medical screening, neurocognitive profiling, neuroimaging, ApoE genotyping, collection of biologic samples (cerebrospinal fluid, blood, and plasma), and behavioral observations. Medical evaluations consisted of a physical examination, electro-

cardiograph, and routine blood tests to eliminate other known contributors to memory and general cognitive impairment. Routine magnetic resonance imaging (MRI) or computer tomography (CT) scan was obtained and blood tests assessed venereal disease research laboratory (VDRL), complete blood count (CBC), Vitamin B12 level, thyroid function, and ApoE genotype.

## Measures

Neuropsychological functioning was assessed across five domains: story learning, word learning, design learning, language, and visuospatial functioning. *Story learning* was assessed with the Logical Memory I & II subsets from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987). *Word learning* was assessed with the Selective Reminding Test (SRT; Buschke, 1973) and Verbal Paired Associations I & II subtests from the WMS-R. Tests of *design learning* consisted of WMS-R Visual Reproduction I & II subtests and 3-min recall from the Complex Figure Test (CFT; Meyers & Meyers, 1995). For logical memory, visual reproduction, and the SRT, percent of information retained from immediate to delayed recall was determined; percent retained was calculated by dividing the delayed recall score by the immediate recall score. *Language* testing included letter fluency (either A or C), category fluency (body parts or countries; Batting & Montague, 1969), and a modified version of the Boston Naming Test (BNT; Kaplan et al., 1983). Three 20-item versions were created by starting with pictures one, two, or three and then using every third item in sequence. Participants were administered one of the three versions. Measures of *visuospatial functioning* were the copy phase of the CFT and the Block Design as well as Digit Symbol subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981).

## Procedure

The majority of participants enrolled in the NIMH Prospective BIOCARD Study were admitted to the GPB inpatient unit for a two-night stay at baseline. Medical procedures and biologic measures were performed upon waking on days 2 and 3. Cognitive testing was administered in 1.0–1.5 hr sessions over the entire admission and generally was conducted in a combination of late morning and early- to mid-afternoon sessions.

ApoE genotyping was done by one of two assaying methods, either polymerase chain reaction (PCR) or fragment length polymorphism (RFLP) by gel electrophoresis. In PCR, restriction endonuclease digestion was employed (performed by Athena Diagnostics, Worcester, MA). RFLP involved quantitation of restriction endonuclease patterns with image analysis (Wu et al., 2000).

## Data Analyses

Two-tailed unpaired *t* tests were used to determine statistical significance between groups ( $\epsilon 4$ -present vs.  $\epsilon 4$ -absent).

\*Participants with a positive family history of AD were on average significantly older as compared with individuals without a known family history of AD ( $p < .001$ ). However after covarying for age, family history of AD was not related to any of the neuropsychological measures.

Bonferroni corrections were used to preserve familywise alpha across the five-neurocognitive domains at  $p < .01$ . Although multiple measures were administered within each domain, within domain measures were highly intracorrelated, thereby reducing the need for further correction. Satterthwaite adjusted  $t$  test and degrees of freedom are reported when the group variances were unequal (Winer, 1991). Significant  $t$ -test results were followed with one-way ANOVA (number of  $\epsilon 4$  alleles: 0,1,2) and pair-wise Bonferroni comparisons. In addition for significant interdomain findings between the  $\epsilon 4$  absent and present groups, linear regression was conducted to determine if demographic variables (age, education, gender, and estimated IQ) mediated putative association between cognition and ApoE  $\epsilon 4$  status.

## RESULTS

### $\epsilon 4$ Presence Versus Absence

Mean values on all neuropsychological measures as a function of  $\epsilon 4$  allele status are shown in Table 2. Participants

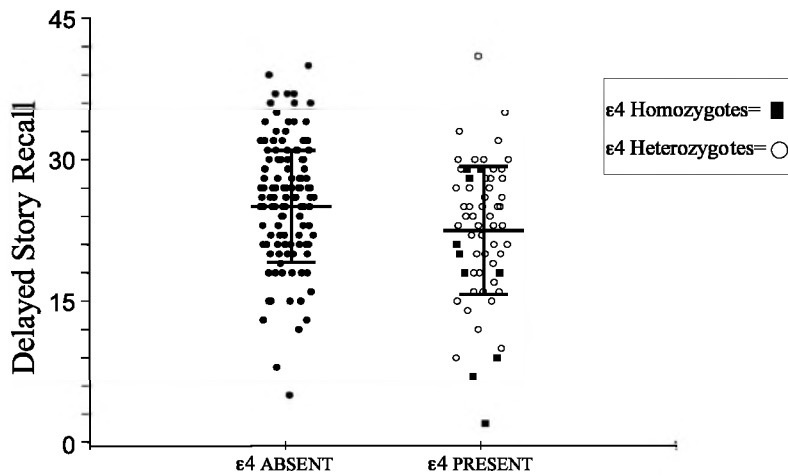
with the  $\epsilon 4$  allele recalled significantly fewer story elements after a 30-min delay on Logical Memory II ( $M = 22.6$ ,  $SD = 7.2$ ) as compared with the  $\epsilon 4$ -absent group ( $M = 25.7$ ,  $SD = 6.5$ ),  $t(174) = 2.90$ ,  $p < .01$  (see Figure 1). Correspondingly, the amount of story information retained from Logical Memory after the delay interval was approximately 10% lower for  $\epsilon 4$ -present individuals,  $t(174) = 2.85$ ,  $p < .01$ . Of note, measures of word and design learning were not influenced by presence of the  $\epsilon 4$  allele. Additionally, the groups did not differ on measures of language and visuospatial ability.

The distribution of Logical Memory II scores met the assumptions of homogeneity of variance between groups and that of normality across groups,  $W = .99$ ,  $p < .07$ . However, because the assumption for the normal distribution of prose recall scores was relatively marginal, one-sided nonparametric testing of Logical Memory II ( $\epsilon 4$  presence vs. absence) was conducted and was confirmatory,  $z = -2.63$ ,  $p < .01$ . In contrast, Logical Memory percent retained scores deviated significantly from a normal distribution as most participants exhibited consistent levels

**Table 2.** Neuropsychologic test scores of  $\epsilon 4$ -present and  $\epsilon 4$ -absent groups

Variable	ApoE genotype				$t$	$p$
	$\epsilon 4$ -present		$\epsilon 4$ -absent			
	$M$	$SD$	$M$	$SD$		
Prose Recall						
Logical Memory I	27.5	6.1	29.2	4.9	1.79	.07
Logical Memory II	22.6	7.2	25.7	6.5	2.90	<.01
LM percent retained	80.7	16.9	87.5	13.9	2.85	<.01
Word Recall						
SRT avg. immediate recall	8.9	1.3	9.2	1.2	1.26	.21
SRT consistency	.72	.16	.76	.14	1.56	.12
SRT delayed recall	8.4	2.2	8.6	2.6	.66	.51
SRT percent retained	92.8	.22	93.1	.18	-.10	.92
SRT recognition hits	11.6	.61	11.4	.99	-1.62	.11
Verbal Paired Associates I	20.4	3.0	20.5	3.3	.02	.99
Verbal Paired Associates II	7.9	2.0	7.6	1.4	-.90	.37
Design Recall						
Visual Reproduction I	34.2	4.8	33.8	4.5	-.65	.52
Visual Reproduction II	27.8	8.1	28.7	6.4	.76	.45
VR percent retained	81	.19	85	.17	1.54	.12
CFT 3-minute recall	17.8	7.1	17.4	7.1	-.40	.69
Visuospatial Ability						
CFT copy	33.7	2.4	33.6	2.3	-.37	.71
Block Design	32.5	9.3	31.4	9.0	-.80	.42
Digit Symbol	52.8	10.5	54.0	11.3	.67	.50
Language						
Letter fluency	15.1	5.2	15.7	4.8	.72	.47
Semantic fluency	28.6	7.9	26.9	7.9	-1.36	.18
BNT (20 items)	19.3	.90	19.2	1.1	-.54	.59

*Note.* ApoE = apolipoprotein E gene;  $\epsilon 4$  = epsilon 4 allele of the ApoE gene; LM = Logical Memory from the Wechsler Memory Scale-Revised; SRT = Selective Reminding Test; SRT avg. immediate recall = average of recall across SRT learning trials; SRT consistency = average of the total number of words consistently recalled on any two consecutive SRT trials; VR = Visual Reproduction from the Wechsler Memory Scale-Revised; CFT = Complex Figure Test; BNT = Boston Naming Test. Familywise alpha was set at .01 to accommodate Bonferroni corrections.



**Fig. 1.** Scatter plot of delayed story recall (raw score from Logical Memory II) across apolipoprotein E  $\epsilon 4$  status.  $\epsilon 4$ -present = presence of the  $\epsilon 4$  allele ( $n = 61$ ).  $\epsilon 4$ -absent = absence of the  $\epsilon 4$  allele ( $n = 115$ ).  $\epsilon 4$  Homozygotes = individuals with two  $\epsilon 4$  alleles ( $n = 10$ ).  $\epsilon 4$  Heterozygotes = individuals with one  $\epsilon 4$  allele ( $n = 51$ ). Lines represent mean values  $\pm$  one standard deviation.

of recall between immediate and delayed recall,  $W = .93$ ,  $p < .01$ . However, one-sided nonparametric testing of Logical Memory percent retained also was supportive of the parametric result,  $z = -2.28$ ,  $p < .05$ .

### Number of $\epsilon 4$ Alleles

The overall effect of the  $\epsilon 4$  allele was significant on Logical Memory II,  $F = 6.24$ ,  $p < .01$ . Even though the only significant *post-hoc* comparison was between  $\epsilon 4$  homozygotes and the  $\epsilon 4$ -absent group,  $t(173) = 3.17$ ,  $p < .01$ , there was a clear downward trend in scores between absence of the  $\epsilon 4$  allele ( $M = 25.6$ ),  $\epsilon 4$  heterozygotes ( $M = 23.3$ ), and  $\epsilon 4$  homozygotes ( $M = 18.6$ ), as depicted for all participants in Figure 1. The omnibus allele effect for Logical Memory percent retained also was significant,  $F = 7.37$ ,  $p < .001$ . In contrast with delayed prose recall, retention of story information for the  $\epsilon 4$ -absent group ( $M = .87$ ) as compared with  $\epsilon 4$  heterozygotes ( $M = .83$ ) was significant,  $t(173) = 2.58$ ,  $p < .05$ , as was the contrast between the  $\epsilon 4$ -absent group and  $\epsilon 4$  homozygotes ( $M = .70$ ),  $t(173) = 3.63$ ,  $p < .01$ , suggesting that some but not all of the  $\epsilon 4$ -related effect on prose learning is due to a double  $\epsilon 4$  dose.

### Linear Modeling of Context-Specific Memory

The presence of the ApoE  $\epsilon 4$  allele emerged as the primary predictor of reduced Logical Memory II scores ( $r = -.24$ ,  $p < .01$ ) in the overall linear model of prose retention,  $R^2 = .10$ . Neither age, education, nor gender was significantly related to delayed prose recall. In contrast, estimated verbal IQ was significantly related to prose recall in a positive direction ( $r = .17$ ,  $p < .05$ ), which follows from the established relationship between generalized verbal ability and related areas, such as verbal learning. Although the model predicted a relatively small amount of the variance in delayed story recall, the presence of the  $\epsilon 4$  allele none-

theless accounted for twice the amount of variance as compared with generalized verbal ability (5.6% vs. 2.8%).

### DISCUSSION

As predicted, we noted a statistically significant  $\epsilon 4$  allele effect at baseline only on delayed prose recall and retention in the NIMH Prospective Study of Biomarkers for Older Controls at Risk for Alzheimer's Disease. This finding corroborates previously published data on the effects of  $\epsilon 4$  in at-risk populations on contextual learning assessed either by recall of story material (e.g., Schmidt et al., 1996) or semantically organizable word lists (e.g., Bondi et al., 1999). It should be noted, however, that although participants possessing at least one  $\epsilon 4$  allele scored significantly lower on prose recall and retention, their scores were well within the range of normal functioning; in fact, a young adult (between the ages of 20 and 30) with the same score as the mean of our  $\epsilon 4$ -present group would be within normal limits on prose recall. Hence, the effect of  $\epsilon 4$  on context-bound learning and memory is subtle and likely is undetectable on the vast majority of daily tasks and interactions. Even so, the  $\epsilon 4$ -related reduction in context-specific memory is possibly suggestive of a biology-driven behavioral decrement. In addition, our finding of reduced story recall and retention in the  $\epsilon 4$ -present group might be consistent with findings that Logical Memory has greater power to predict conversion from cognitively intact to mild cognitive impairment (MCI) than from MCI to AD (e.g., Tierney et al., 1996).

A small group of  $\epsilon 4$  homozygotes explained some but not all of the ApoE  $\epsilon 4$  effect on delayed prose recall and retention. As shown in Figure 1,  $\epsilon 4$  homozygotes were clustered in three groups within the overall  $\epsilon 4$ -present group, including three individuals between the mean and one standard deviation above the mean, four individuals between the mean and one standard deviation below the mean, and three individuals less than one standard deviation below the mean. This spread in the distribution of  $\epsilon 4$  homozygotes

may represent a cross-sectional snapshot of a longitudinal process. However, interpretation of putative  $\epsilon 4$  dose-dependent effects is limited by the relatively small number of  $\epsilon 4$  homozygotes in the current participant sample.

The best explanation for the observed reduction in contextual memory may be an  $\epsilon 4$ -associated relative dissociation between gist and verbatim recall, wherein gist is a type of context defined as abstract representation of semantic content. There is evidence of intact recall of gist information (for prose) in the normal aging process (B.J. Small et al., 1999) and in AD (Johnson et al., 2003). However, gist does not facilitate recall for AD patients to the same degree as for older controls (cf. Budson et al., 2002 vs. Tun et al., 1998). We believe that gist and nonsemantic contextual information in general also provide less support during episodic learning tasks for older controls at genetic risk of AD by possession of the  $\epsilon 4$  allele. Moreover, the variability in the existing literature on the effect of  $\epsilon 4$  on learning among healthy controls may be largely attributable to whether or not contextual learning paradigms were used (cf. Bondi et al., 1995 vs. G.E. Smith et al., 1998). Accordingly in our study, the ApoE  $\epsilon 4$  allele may have partially blocked the integration of gist (context) and veridical recall (content) for prose material that is inherently contextual in nature, whereas learning of noncontextual material (i.e., non-categorical word lists and abstract designs) was not affected by the  $\epsilon 4$  allele.

The interaction between the  $\epsilon 4$  allele and the pathogenesis of AD may help explain the hypothesized disconnection between gist and recall of story details. More specifically, the  $\epsilon 4$  effect on context-specific memory might result from a relationship between the allele and extensive damage to the EC among medial temporal lobe structures that occurs relatively early in the AD prodrome (Braak & Braak, 1991; de Leon et al., 2001; De Santi et al., 2001; Gomez-Isla et al., 1996; Hyman et al., 1984, 1986; Killiany et al., 2000, 2002; Kordower et al., 2001) and a more direct association between the ApoE  $\epsilon 4$  allele and EC pathology (Ghebremedhin et al., 1998; Juottonen et al., 1998). In addition, nascent findings on the functional role of the EC relative to the hippocampus from animal paradigms (Frank et al., 2000; Suzuki et al., 1997) and functional neuroimaging studies on humans (Fernandez et al., 1999; Haist et al., 2001) suggest that the EC may play a specialized role in learning and consolidating information that can be organized based on prior learning. Consequently, putative  $\epsilon 4$ -related damage to the EC might interfere with the bidirectional flow of information between neocortical association cortex (fund of gist-related knowledge) and the hippocampus (item-specific encoding and consolidation).

In addition to serving as a repository for contextual information, frontal networks (i.e., the frontal lobes and fronto-cortical as well as fronto-subcortical pathways) in particular play an active role in integrating content with context during encoding and retrieval processes (Gilsky et al., 2001; Janowsky et al., 1989; Van Petten et al., 2000). Similar to the effect of the  $\epsilon 4$  on contextual episodic learning, recent

data suggest that the  $\epsilon 4$  allele also has an adverse impact on frontally mediated executive functions, such as working memory (Parasuraman et al., 2002; Rosen et al., 2002). Bolstering these behavioral findings, studies of resting glucose metabolism in older controls possessing the  $\epsilon 4$  allele have indicated reduced metabolic rate in similar prefrontal and cingulate areas as observed in AD (Reiman et al., 1996, 2001; G.W. Small et al., 2000). Though interestingly when cognitive processes are imaged *in vivo*, increased signal intensity has been detected in frontal areas (Bookheimer et al., 2000) and among putative frontal connections (Bondi et al., 2003; C.D. Smith et al., 1999). As these fMRI findings were based on relatively basic measures of learning and recall, increased signal intensity in cortical areas beyond the medial temporal lobes (MTL) may be a biological correlate of behavioral compensation as a result of degraded MTL functioning. Yet because frontal networks also appear to be compromised by the presence of the  $\epsilon 4$  allele, recruitment of frontally mediated compensatory strategies may further compound the effects of damage to the EC. Consequently,  $\epsilon 4$ -mediated degradation of frontal networks (diffuse accumulation of neuritic plaques) and to the EC (focal deposition of plaques and neurofibrillary tangles) may have interacted in the present study to result in relatively defective integration of gist (context) and veridical story recall and retention (content).

In conclusion, the presence of the ApoE  $\epsilon 4$  allele was associated with decreased recall and retention of context-specific prose among healthy older participants at genetic risk for Alzheimer's disease. Although it is theoretically plausible that this effect is due to extensive and selective damage to the EC early in the AD prodrome and exacerbated by more diffuse damage to frontal networks, verification with prospective follow-up data and functional imaging (and other developing *in vivo* techniques) is still necessary. Nonetheless, the current study may have clinical applications especially as more is learned about the pathogenesis of Alzheimer's disease and new pharmacological interventions are designed to arrest the disease process as early in the prodrome as possible. Therefore it is important to understand the qualitative nature of progressive memory impairment. For instance, mnemonic aides such as rehearsal and repetition that are of limited utility in Alzheimer cases would be expected to be helpful and at least partially restorative in this hypothetical preclinical stage (Backman & Small, 1998). Although contextual learning is less efficient in a hypothetical phase prior to extant memory impairment, context-specific memory is still intact and contextual memory aids (e.g., semantic or thematic cueing) would be of expected benefit. In addition, it remains to be determined if the reported effect of the  $\epsilon 4$  allele on context-specific memory in healthy at-risk individuals is also related to the development of objective memory impairment and DAT conversion (see Lange et al., 2002). These and other related questions are being explored in the longitudinal cognitive platform of the NIMH Prospective BIOCARD Study.

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