Significance of the Apolipoprotein E ε2 Allele in Alzheimer's Patients' Memory Functioning

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Introduction

•It has been reported that in AD patients, the presence of an apolipoprotein E ε2 allele is associated with reduced neuritic plaques (Tiraboschi et al., 2004), reduced load of hyperphosphoylated tau protein (Thaker et al., 2003) and less neurofibrillary tangle pathology (in patients younger than 80; Ohm et al., 1999). Martins et al. (2005), in a study of 218 AD patients (of all genotypes) found that ε2 carriers exhibited slower cognitive decline than non-ε2 carriers.

•Among non-demented elderly persons, the presence of an ε2 allele has been associated with lower cholesterol levels (Lin et al., 2000), reduced risk of coronary artery disease in men (Kulminski et al., 2008), and reduced risk of major depression (Fan et al., 2006). In the largest study examining the relationship with cognitive functioning, Wilson et al. (2002), as part of the Religious Orders study, followed 669 elderly persons who were dementia-free at baseline for an average of 6 years, and found that the 86 ε2 carriers showed less decline in episodic memory functioning than non-carriers, but that the groups did not differ in other cognitive domains.

•In the present study, we investigated baseline cognitive functioning in a large sample (N=940) of probable AD patients, 74 of whom were ε2 carriers, and examined whether the possible effects on memory and other cognitive functions of having an ε2 allele (versus having an ε3 allele) depends on whether the patient's second allele is an ε3 or ε4 allele.

Participants

• Participants in this study (N=940) were selected from a larger database of patients from the Baylor College of Medicine Alzheimer's Disease Center (see Doody et al., 2005).

• Inclusion criteria included meeting NINCDS-ADRDA criteria for probable AD and completion of a comprehensive neuropsychological evaluation at entry into a longitudinal study of AD.

Method

• We compared the memory and other cognitive abilities of probable AD patients with 1) ε2ε3 (n=42) versus ε3ε3 (n=347) genotypes; and 2) ε2ε4 (n=32) versus ε3ε4 (n=519) genotypes, in order to contrast the effects of having an ε2 or ε3 allele paired with an ε3 or ε4 allele. Thus, ε4ε4 patients were not examined in these analyses.

•These patient subgroups did not differ in age, gender distribution, education, MMSE scores (all means 19-20), or ADAS error scores (all means 23.5-24.5).

Results

•As shown in Table 1, the ε2ε3 group obtained significantly better scores than the ε3ε3 group on WMS-R Logical Memory Immediate and Delayed Recall and on WMS-R Visual Reproduction Delayed Recall. The ε2ε3 patients also had significantly higher percent retention performances on both Logical Memory and Visual Reproduction. The groups did not differ on ADAS Word Recall or Word Recognition memory error scores.

•Table 1 also shows that the ε2ε4 and ε3ε4 groups did not differ significantly on any of the memory measures, and generally performed worse than the ε2ε3 and ε3ε3 groups (as expected).

Table 1: Memory Functioning in the Four APOE Subgroups (Means)

	ε2ε3 (n=42)	ε3ε3 (n=347)	ε2ε4 (n=32)	ε3ε4 (n=519)
Log Mem-Immed	10.5**	7.4	7.0	6.8
Log Mem-Delay	4.4**	2.3	1.9	1.7
Vis Rep-Immed	15.3	14.2	10.5	13.3
Vis Rep-Delay	5.9**	2.9	1.5	2.5
ADAS Recall (errors)	6.7	6.9	6.9	7.1
ADAS Recog (errors)	5.9	5.9	6.1	6.1

**Significant ($p < .01$) difference between the ε2ε3 and ε3ε3 groups

•The subgroups were also compared on non-memory cognitive measures, including WAIS-R Verbal and Performance IQ scores, the Verbal Series Attention Test (VSAT; time and error scores), the Boston Naming Test, Animal fluency, and Rey-Osterrieth copy scores.

•There were no significant differences between the ε2ε3 and ε3ε3 groups. The ε2ε4 group had significantly worse ($p<.05$) Performance IQ scores and made more VSAT errors than the ε3ε4 group.

•Interestingly, the ε2ε3 group had the *best* scores and the ε2ε4 group had the *worst* scores on all these measures.

Conclusions

•ε2ε3 patients performed better than ε3ε3 patients on WMS-R Logical Memory (immediate and delayed recall) and Visual Reproduction (delayed recall). However, ε2ε4 patients' memory performances did *not* differ from those of ε3ε4 patients. Thus, the presence of an ε2 allele (compared to the presence of an ε3 allele) was associated with better memory performance, but only when the patient's other allele was ε3 (not ε4).

•Thus, the negative effects of having an ε4 allele appeared to overwhelm any benefit of also having an ε2 allele. In fact, ε2ε4 patients actually performed significantly *worse* than ε3ε4 patients on several non-memory cognitive measures.

•The ε2ε3 and ε3ε3 groups did *not* differ on any of the non-memory cognitive measures, suggesting that the beneficial effect of having an ε2 allele (when paired with an ε3 allele) is limited to the memory domain. This specificity of the ε2 benefit is consistent with the findings of Wilson et al. (2002), who reported that normal elderly ε2 carriers exhibited less decline in episodic memory functioning over time than did non-carriers.

•We are currently examining long-term follow-up data to investigate rates of change in memory and other cognitive domains in these APOE subgroups, and seek to determine how long the ε2ε3 patients' better memory performances persist.