

Memory performance in healthy elderly without Alzheimer's disease: effects of time and apolipoprotein-E[☆]

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Abstract

Transgenic mice expressing human APOE- ϵ 4 develop an age-dependent decline in memory without pathological features of Alzheimer's disease (AD). This implicates APOE in the maintenance of memory during normal senescence, but parallel human studies are limited because longitudinal investigations of memory usually do not exclude patients with AD or "questionable" AD (QD). The current study examined the effect of APOE on cognitive function over time in elderly without dementia. We hypothesized that, compared to other APOE alleles memory decline even in healthy elderly would be greater among those with an APOE- ϵ 4.

The results of neuropsychological tests, grouped into domains of memory, language and visuospatial/cognitive function by factor analysis, were examined at three intervals over a seven-year period in 563 healthy elderly without AD or QD using generalized estimating equations. Memory performance declined over time, while scores on the visuospatial/cognitive and language factors did not change. Increased age was associated with lower scores, and higher education with higher scores on all factors at each interval. No APOE allele was associated with performance on a specific cognitive factor at any interval, but the presence of an APOE- ϵ 4 allele was associated with a more rapid decline in the memory factor over the follow-up period. The effect was most pronounced among individuals with less than 10 years of formal education. There was no similar time-dependent relationship between APOE- ϵ 4 and the language or visuospatial/cognitive factors.

Transgenic mice and elderly humans without AD or QD expressing APOE- ϵ 4 show a decline in memory performance over time. These observations provide evidence for an APOE-specific effect on memory during senescence. © 2001 Elsevier Science Inc. All rights reserved.

1. Introduction

APOE- ϵ 4 is the major known genetic risk factor for late-onset familial and sporadic AD. Several mechanisms have been proposed to explain how APOE- ϵ 4 increases AD risk. APOE may be an active participant in β -amyloid clearance [25,30,40]. APOE deficient mice expressing the APP₇₁₇ mutation that causes an early-onset, autosomal

dominant form of AD deposit a greater number of amyloid plaques [1] and show more pronounced memory impairment than wildtype mice [16]. A direct role for APOE, independent of an interaction with β -amyloid, involving both biochemical and neuronal integrity has been suggested in animal models with impaired memory [16,20]. Compared with intact mice, APOE deficient mice have decreased synaptic density in cholinergic, noradrenergic and serotonergic projections to relevant brain regions [13] and perform worse in several types of memory tasks [8,16,42,43]. These proposed mechanisms have been supported, in part, by parallel studies in humans. APOE- ϵ 4 is associated with greater β -amyloid plaque density than other APOE alleles among patients with AD [24,49]. Compared to individuals with

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other APOE genotypes, individuals with an APOE- ϵ 4 allele develop hippocampal atrophy [31,33,35,44,50,65] and are more likely to have cognitive impairment [2,5,6,11,12,15,18,21,22,29,39,50,53,68]. Whether APOE- ϵ 4 has a direct effect on memory in the absence of disease, or acts only through its association with AD, remains unknown because the majority of studies have been either cross-sectional or have not excluded individuals with QD. The few longitudinal studies have provided divergent results [15,29,56]. We designed a series of analyses of data collected in a longitudinal study to determine whether or not APOE influences memory and other cognitive functions in individuals who are free of dementia or cognitive impairment.

2. Methods

2.1. Subjects and Setting

Data were included from individuals participating in a prospective study of 2,126 Medicare recipients, 65 years and older, residing in a single community in Northern Manhattan. Each person received the same medical, neurological and neuropsychological evaluations at regular intervals. The cohort was followed over a 7-year period beginning in 1992. Three follow-up examinations took place at 20-month intervals after the baseline interview. Over the study period, the annual mortality rate has been 8.1%, the overall refusal rate has been 10% and the annual incidence rate of AD has been 3% [63].

In order to address the study hypothesis, we included data only from 563 individuals without dementia (AD or other forms), QD [Clinical Dementia Rating Scale score of 0.5, [26]], stroke, Parkinson's disease or other major neurological disorders at all follow-up intervals (Fig. 1). Blood was obtained for APOE genotypes at the baseline visit.

2.2. Clinical evaluation

Data included medical, neurological, and neuropsychological evaluations [41,58]. Past medical history was recorded with specific attention to stroke, trauma, medications, and recreational drug use. All subjects underwent a standardized neuropsychological battery that tested multiple domains [58]. Orientation was evaluated using items from the modified Mini-Mental State Examination [17]. Language was evaluated using the Boston Naming Test [32], the Controlled Word Association test [3], category naming, the Complex Ideational Material Subtest and the repetition of phrases from the Boston Diagnostic Aphasia Evaluation [19]. Abstract reasoning was evaluated using WAIS-R Similarities subtest [66], and the non-verbal Identities and Oddities subtest of the Mattis Dementia Rating Scale [37]. Visuospatial ability was evaluated using the Rosen Drawing Test [45], and a matching version of the Benton Visual Retention Test [4]. Memory was evaluated using the mul-

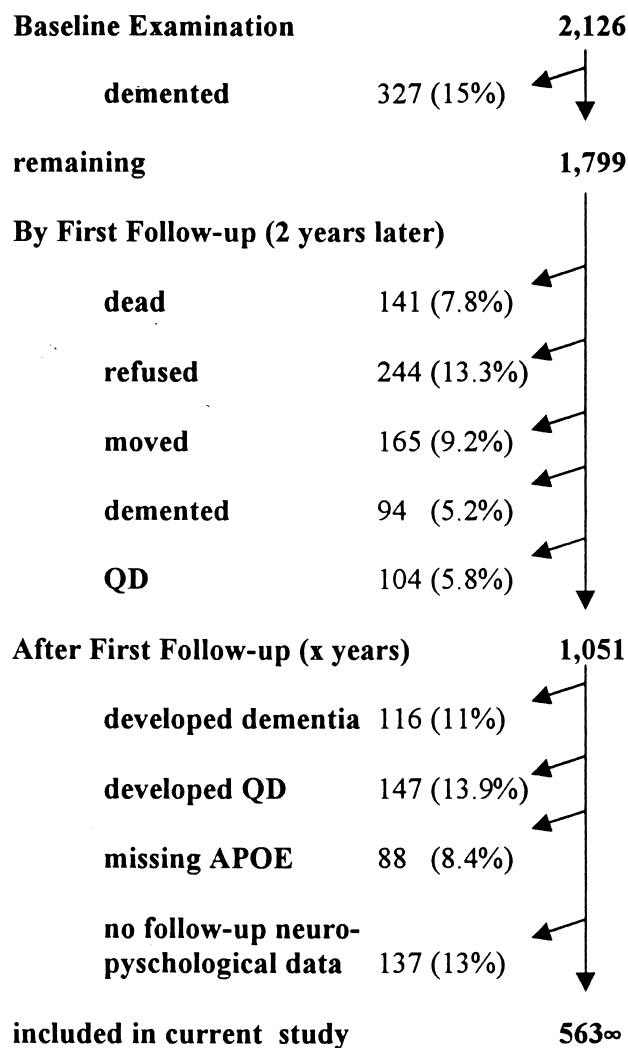


Fig. 1. [∞] individuals without dementia or questionable dementia.

iple choice version of the Benton Visual Retention Test [4] and the seven subtests of the Selective Reminding Test [7]: total recall, long term recall, long term storage, continuous long term storage, words recalled on last trial, delayed recall, and delayed recognition. The neuropsychological test battery has established norms for the community [60].

Information from the neurological, psychiatric and neuropsychological assessments were reviewed in a consensus conference comprised of neurologists, psychiatrists, and neuropsychologists. Based on this review all participants were assigned to one of three categories: dementia, cognitive impairment or normal cognitive function.

2.3. Data analysis

A factor analysis performed using data from the entire cohort with the 15 neuropsychological measures using a principal component analysis with varimax rotation and Kaiser normalization [34]. This analysis yielded three fac-

tors (Table 1): (1) A memory factor, where the seven subtests of the Selective Reminding Test [7] were the main contributors. (2) A visuospatial/cognitive factor, in which visuospatial and tests of reasoning were the main contributors. These included the Rosen Drawing Test [45], matching and recognition components of the Benton Visual Retention Test [4] and the Identities and Oddities of the Mattis Dementia Rating Scale [37]. (3) A language factor, where language measures were the main contributors. The Boston Naming Test [32], the Controlled Oral Word Association test [3] and the WAIS-R Similarities [66]. Component scores for each subject at each visit were calculated by adding the scores of the measures that contributed most to each factor. Each factor score was normally distributed (skewness: memory 0.8, language -0.6 , visuospatial factor 0.7).

Generalized Estimated Equations (GEE) [69] were used to examine changes in each cognitive domain over time. The dependent variables were the factor scores, and the independent variables were APOE- $\epsilon 4$ status (one or more $\epsilon 4$ alleles versus none), time, included as a continuous variable, and the interaction of APOE- $\epsilon 4$ by time. Gender, age, education, and ethnic background were included as covariates in subsequent analyses.

The GEE analyses yields beta values which represent associations between a factor score and variables included in the model. A significant group effect would indicate a difference between two groups at the baseline or at any subsequent interval. A positive value for beta values indicates that the group with a specific variable performed better than the group without that variable. A significant time effect would indicate a change in a factor score over the total duration of follow-up. A significant interaction effect would indicate a difference in the rate of change in a factor score between the two APOE groups.

3. Results

The demographic characteristics of the 563 healthy elderly are shown in Table 2. There were 390 (69%) women. Twenty-five percent were White, 31% were Black and the remaining were Caribbean Hispanics. The number of women in each ethnic group did not differ significantly. There was a difference in APOE- $\epsilon 4$ allele frequency by ethnic group consistent with published genotype frequencies [36] (African American 18%, Hispanic 12%, White 13%, $P = 0.05$). Years of education also differed significantly by ethnic group (African-American 10.7 yrs, Caribbean Hispanic 6.9 yrs, White 12.6 yrs; $P = 0.001$). Compared with the group, from which they were selected, these 563 individuals were younger and had more years of education.

GEE analysis indicated that memory performance decreased significantly over time (Fig. 2), whereas visuospatial/cognitive and language performance did not change over the study period. We calculated the slope of perfor-

Table 1
Rotated component matrix from factor analysis of neuropsychological tests

Neuropsychological test	Components		
	Factor 1 memory	Factor 2 visuospatial/ cognitive	Factor 3 language
Total recall (7)	.895	.288	.185
Long-term recall (7)	.946	.191	.126
Delayed recall (7)	.823	.236	.144
Long-term storage (7)	.925	.178	.134
Cued long-term recall (7)	.904	.209	.091
Total recall over 6 trials (7)	.733	.205	.117
Benton recognition (4)	.275	.728	.133
Similarities (WAIS)	.312	.634	.296
Identities/oddities (37)	.130	.692	.013
Rosen drawing (45)	.103	.718	.102
Benton matching (4)	.182	.762	.123
Naming total (32)	.195	.226	.929
Naming, uncued (32)	.178	.267	.921
Verbal fluency (3)	.328	.570	.294
Comprehension (18)	.143	.582	.326

Please note. The cut-off for inclusion was 0.5; items included within a specific factor are shown in gray.

mance for each individual and the majority, 67%, had a slope less than 0 indicating a decline in memory function over time. Increased age at baseline was associated with lower scores at each interval in all three domains of memory, visuospatial/cognitive ability and language, while higher education was associated with higher scores in all domains at each interval.

There was also no association between the presence of an APOE- $\epsilon 4$ allele and performance on any of the three cognitive factors at a specific interval. However, for the memory factor score there was a statistically significant APOE- $\epsilon 4$ allele*time (duration of follow-up) interaction indicating that memory declined at a faster rate among individuals with an APOE- $\epsilon 4$ allele compared to other al-

Table 2
Demographic characteristics of study population

Variable	Health elderly	Questionable dementia (CDR = 0.5)	Alzheimer's disease (CDR ≥ 1)
N	563	178	228
Age*	75.9 [sd] 5.0	78.5 [sd] 5.6	80.5 [sd] 6.4
Percent women	69%	71.3%	71.5%
Years of education*	9.5 [sd] 4.5	7.4 [sd] 4.3	6.4 [sd] 4.4
Ethnic group*			
African-American	32%	33%	36%
Hispanic	43%	51%	54%
White	25%	16%	10%
APOE- $\epsilon 4$ allele frequency +	14.2%	17.1%	18.4%

* $P = 0.001$, + $P = 0.05$.

Table 3
Relationship of Time of Follow-up and APOE- ϵ 4 to Memory, Visuospatial and Language Performance in Healthy Elderly Over 7 years*

Variable	Estimated β	Standard error	Robust z	Significance
Memory Factor				
Time	-4.9	1.3	-3.9	0.0001
Time*APOE- ϵ 4	-4.4	2.2	-1.9	0.02
Visuospatial Factor				
Time	-0.3	0.1	-0.3	0.8
Time*APOE- ϵ 4	-0.1	0.2	-0.6	0.5
Language Factor				
Time	0.1	0.2	0.1	0.9
Time*APOE- ϵ 4	-0.3	0.2	-1.5	0.2
Education	2.3	0.4	6.4	0.0001
Age	-1.9	0.3	-6.5	0.0001
Ethnic Group (White vs. African-American and Hispanic)	11.9	4.1	2.9	0.004

* All 3 models included the following variables age, education, ethnic group, APOE- ϵ 4, Time and Time*APOE- ϵ 4. APOE- ϵ 4 was not associated with performance on any factor.

◀ Time*APOE- ϵ 4 is an interaction term see text for explanation. Time is the duration of follow-up after the baseline interview.

les (Table 2, Fig. 2). The association remained significant when adjusted for sex, age, education and ethnic group.

There was no similar relationship between APOE- ϵ 4 allele*time and the language or visuospatial/cognitive factors. Mean scores on both of these factors represented the 50th percentile at each follow-up interval indicating that there was a normal distribution of performance and that the lack of an APOE- ϵ 4 allele*time effect was not the result of a ceiling or floor effect.

Analyses stratified by ethnic group revealed a weaker association between memory performance and the interaction term (APOE- ϵ 4 allele*time) in Whites, but a stronger association in Blacks and Hispanics. This difference was related to difference in years of education between the

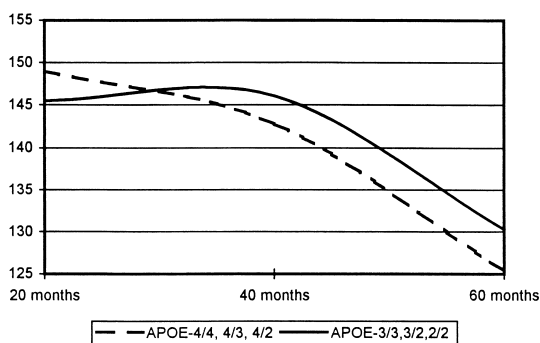


Fig. 2. Comparison of rate of decline in memory factor over time among individuals with and without an APOE- ϵ 4 allele. Please note. The intervals on the X axis represent the average time of follow-up assessments after baseline. These are smoothed regression lines that depict the differences in the slope of performance over time. There was no statistically significant difference at a particular interval

ethnic groups. We repeated the analysis stratifying by the median years of education (10 years) and including individuals of all ethnic groups. In those with less than 10 years of education, the APOE- ϵ 4 allele*time interaction remained statistically significant indicating that memory declined at a faster rate among individuals with an APOE- ϵ 4 allele compared to other alleles ($\beta = -6.7$, $P = 0.01$). The APOE- ϵ 4 allele*time interaction was not statistically significant among those with more than 10 years of education ($\beta = -1.5$, $P = 0.6$), but the number of subjects was small. Memory performance still declined significantly over time in the better educated group, however ($\beta = -6.7$, $P = 0.001$).

The same analyses were conducted among 228 individuals from the cohort (see Table 2 for demographics) who had clinically diagnosed AD over the same follow-up period (from the first follow-up interval), had neuropsychological testing at subsequent intervals and had been genotyped. In these individuals there was a statistically significant decline in memory ($\beta = -9.6$, $P = 0.0001$), visuospatial/cognitive ($\beta = -1.2$, $P = 0.001$) and language ($\beta = -0.6$, $P = 0.002$) performance over time. There was no association between the performance on any cognitive factor and the interaction term (APOE- ϵ 4 allele*duration of follow-up) among individuals with AD.

We also analyzed data over the same time period from 178 individuals with QD (CDR = 0.5) at the baseline interval who had genotype data and for whom neuropsychological testing data was available at subsequent intervals (Table 2 for demographics). The pattern of performance was similar to that observed for AD. From the first follow-up period both memory ($\beta = -12.1$, $P = 0.0001$), and to a lesser extent, visuospatial/cognitive ($\beta = -0.7$, $P = 0.001$) performance declined over time. There was no significant change in language performance over time ($\beta = -0.3$, $P = 0.2$). The presence or absence of an APOE- ϵ 4 allele was not associated with performance on any cognitive factor at any interval nor was there an association with the interaction term (APOE- ϵ 4 allele*duration of follow-up).

4. Discussion

In this study memory performance declined over time in healthy elderly individuals without AD or QD, but other cognitive skills remained stable. Increased age was associated with lower scores in all cognitive domains while increased education was associated with higher scores. APOE- ϵ 4 was not associated with poor performance in any cognitive domain at any specific time interval. However, there was a statistically significant relationship between APOE- ϵ 4 and change in memory performance over time in the healthy elderly group. No such interaction was observed for the visuospatial/cognitive or language factors in the healthy elderly group. Those individuals with either AD or QD showed a decline not only in memory but also in

visuospatial/cognitive and language performance over time. Performance in neither of these two groups over time was related to the presence of an APOE- ϵ 4 allele. It has been previously established that APOE variability is not associated with the rate of progression of Alzheimer's disease [51,59,67].

The study was designed to address a specific question regarding the role of APOE- ϵ 4 in memory. As a prerequisite, we excluded data from individuals that had developed clinical evidence of AD or QD. Therefore, the observed effect of APOE- ϵ 4 on memory over time can not be attributed to the onset of either AD or QD in these individuals. In fact, the healthy elderly showed no decline in visuospatial/cognitive function or language over time. The results of our study parallel those in transgenic mice, indicating that APOE influences the maintenance of memory function during human senescence.

Compared to individuals with less education, individuals with 10 or more years of formal education, regardless of ethnic group, did not show the effect of APOE- ϵ 4 on memory over the study period. Though the beta score indicated that the decline in memory remained statistically significant over time, there was no additive effect of APOE- ϵ 4. This modifying effect of education is consistent with the "cognitive reserve" hypothesis that posits educational experience as means to lessen the impact of brain disease on cognitive function [14,47,48,57].

The relationship between allelic variability at the APOE gene and cognitive function in elderly individuals has been previously examined with inconsistent results [2,5,6,11,15,22,27,29,39,50,52,53,56,68]. Many studies were cross-sectional and lacked longitudinal data using only a single time-point for analysis [2,18,21,22,27,50]. Most of the longitudinal studies included individuals who developed AD or those with QD and did not include methods to limit the inclusion of such individuals [5,6,12,53]. Change in performance over time is a more accurate and less biased measure of cognitive function, and can identify individuals who developed early manifestations of AD. Furthermore in animal models the effect of APOE on memory appears to be both age and time-dependent which requires longitudinal analysis of data in humans for comparison [8,42,43]. Structural changes in the hippocampus of healthy individuals with an APOE- ϵ 4 may also implicate a direct effect of this gene on memory [31,33,35,54,65].

Influenced by the results in APOE transgenic mice, we designed the current study to incorporate performance in several cognitive domains assessed by formal neuropsychological testing as dependent variables, and to explicitly incorporate time as measured by duration of follow-up and both age and education as independent variables. The use of generalized estimated equations to evaluate the longitudinal data set is an added technical advantage because this statistical method provides the ability to measure the slope of performance as an indication of change in each cognitive domain over the study period [69].

Despite the careful selection of data from subjects without clinical evidence of AD or QD, it is possible that some, with or without APOE- ϵ 4, may have still had been in a prodromal stage of AD. The fact that the decline was observed selectively for memory weighs against this argument [28]. AD is characterized by decline in multiple cognitive domains, memory impairment may be most pronounced early on because the disease process targets the hippocampal formation [55]. Nonetheless, it is unlikely that the decline in memory performance observed here simply reflects incipient AD because performance in the visuospatial/cognitive and language factors remained stable over time.

Previously, researchers [23,38,46] [36,61,62] have found APOE- ϵ 4 to be a weaker genetic risk factor for AD among African-Americans and Caribbean Hispanics in comparison to Whites. Thus, the current findings concerning memory performance might seem contradictory because the effect on memory occurred in all three of these ethnic groups. APOE is known to have many biological effects. It is conceivable that the role of APOE and its isoforms in AD may be distinct from its activity in the maintenance of memory. In AD, APOE is a critical component in a complex biological interaction with β -amyloid [25,49]. It is unclear whether variations in other genes contribute to, or facilitate this process. Most importantly, the explanation for ethnic variability in APOE-related AD risk remains unknown.

APOE transgenic mice do not develop AD pathology. Thus, memory decline observed in this healthy elderly population may be the direct effect of APOE- ϵ 4 on hippocampal-based memory systems. The ϵ 4 variant of APOE has been shown to cause a decrease in synapse per neuron ratio [10], developmental defects within the dentate gyrus [64] and increased vulnerability to exogenous neurotoxins [9]. Any one of these, or other mechanisms as yet unidentified, may explain the decrease in memory over time among in humans with the APOE- ϵ 4 allele.

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