Published in final edited form as:

Am J Geriatr Psychiatry. 2012 July ; 20(7): . doi:10.1097/JGP.0b013e3182107e6a.

Influence of Alzheimer Disease Family History and Genetic Risk on Cognitive Performance in Healthy Middle-Aged and Older People

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Abstract

Objectives—Identification of risk factors for Alzheimer disease (AD) is critical for establishing effective diagnostic and therapeutic strategies. Carrying the $\epsilon 4$ allele of the apolipoprotein E gene (APOE4) and having a family history of the disease are two such factors, with family history risk reflecting additional yet unknown or rarely studied genetic and perhaps nongenetic risks. Our aim was to determine the influence of APOE genotype and family history status on cognitive performance in healthy individuals.

Design—Longitudinal study.

Setting—Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles.

Participants—Seventy-two cognitively healthy middle-aged and older people (mean age $\pm$ SD: 62 ± 9 years).

Measurements—Neuropsychological examinations at baseline and after 2 years.

Results—Subjects with a family history of AD had lower baseline scores in processing speed, executive functioning, memory encoding, and delayed memory when compared with those without a family history. The family history risk factor did not influence degree of cognitive decline over time. By contrast, baseline cognitive performance did not vary according to APOE4 carrier status. Non-APOE4 carriers showed improved cognitive performance in the memory domains at follow-up, while performance of APOE4 carriers did not change.

Conclusions—Our data highlight the unique contributions of each risk factor to cognitive performance in healthy people. Both factors should be modeled in neuropsychological assessments of people at risk for AD.

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Keywords

Alzheimer disease; family history; APOE genotype

Alzheimer disease (AD) is the most common cause of dementia in an aging society.¹ The allele of the apolipoprotein E gene (APOE4), the major known genetic risk factor for late-onset sporadic AD, contributes to familial clustering of the disease.² However, a family history of AD may also reflect other unknown or rarely studied genetic, and possibly nongenetic, risks. Although it is a clinical standard to evaluate multiple risk factors before making diagnostic or therapeutic decisions, it is important to know how a given risk factor pattern affects brain structure and function, as this may influence the way we monitor or treat our patients.

Modeling family history as a unique risk factor has been used to account for yet unknown AD risk factors in neuroimaging studies investigating healthy people at APOE4 genetic risk for AD.^{3,4} Overall, studies suggest that both APOE4 and family history risk are associated with distinct characteristics in brain anatomy that may render subjects at higher risk for developing AD.^{5,6} For example, APOE4 carriers demonstrate a thinner entorhinal cortex,^{7,8} a brain region preferentially susceptible to AD pathology.⁹ Functional neuroimaging studies also suggest specific differences between APOE4 allele carriers and noncarriers among cognitively healthy younger and elderly people.^{10,11} We recently demonstrated that family history of AD is associated with reduced cortical thickness among medial temporal lobe subregions in healthy people, independent of APOE4 carrier status.³ Lunetta and coworkers¹² also suggest that family history risk is associated with structural brain characteristics that cannot be explained by APOE status alone, such as general and local atrophy patterns, white matter hyperintensities, and overall cerebrovascular status. These widespread effects associated with family history risk are in line with recent data presented by van Exel and colleagues.¹³ The authors highlight APOE4-independent associations of hypertension and inflammatory markers with family history risk. Because both risk factors overlap clinically, it remains controversial whether and how APOE4 and family history risk interact or whether they additively contribute to AD risk.^{14,15} However, it becomes obvious that modeling both risk factors could help explain inconsistencies among imaging studies.^{3,4}

Modeling both factors may be equally important in neuropsychological investigations. Studies aimed at investigating APOE effects on cognitive abilities in healthy subjects have produced mixed results. Carrying the APOE4 genotype might be associated with even superior memory in young adults,¹⁶ possibly reflecting the allele's antagonistically pleiotropic effects at different stages of the life span. Most studies suggest decreased cognitive performance associated with the APOE4 allele later in life. In a meta-analysis of 77 cross-sectional studies investigating APOE4 effects on cognitive functioning in healthy subjects (baseline data were used in the few studies that also performed follow-up investigations), Wisdom and colleagues¹⁷ revealed poorer cognitive performance among APOE4 carriers in episodic memory, executive functioning, perceptual speed, and global cognitive measures. Whereas a previous meta-analysis found that age masked APOE4 effects,¹⁸ Wisdom and colleagues¹⁷ demonstrated that older age exacerbated reduced cognitive functioning among APOE4 carriers. Longitudinal investigations aimed at detecting cognitive decline often focus on people who already have cognitive impairment. Fewer studies have examined longitudinal APOE4 effects in cognitively healthy people. Those have shown greater decline associated with the allele, although there is variability in the cognitive domains found to be affected^{19,20} and not all studies revealed a longitudinal APOE4 effect.²¹ It is possible, however, that unknown risk factors contribute to mixed findings among studies investigating APOE-related differences in cognitive performance.

Modeling family history of AD as a unique risk factor could be helpful to better determine effects more closely associated with the APOE genotype.

Studies investigating the effects of a family history of AD on cognition while accounting for APOE genotype are rare and focus on single neuropsychological tests or global measures. La Rue and colleagues²² showed that family history of AD was associated with greater reliance on immediate memory when compared with subjects without this risk factor in a word list learning task. In a large-scale longitudinal investigation using a modified Mini-Mental State Exam, Hayden and coworkers²³ did not find a family history or APOE4 effect for cognitive decline and suggest that decline was mainly driven by incipient disease.

The variability across studies investigating the influence of genetic risk for AD on cognitive performance in healthy people may be largely explained by the participants' varying age, or inclusion of subjects with preclinical dementia.¹⁸ Studies also use different neuropsychological tests when investigating a particular cognitive domain. Furthermore, a family history of AD could reflect yet unidentified AD risks that might have even greater influences than the known APOE4 allele.²⁴ It is therefore likely that there is an APOE-independent contribution of family history risk on cognitive performance. Family history risk may also include variables less specific for AD, ranging from vascular and inflammatory processes affecting cognition¹³ to nongenetic risk factors, such as socioeconomic status or dietary habits.²⁵ Family history effects on cognitive abilities may reflect this diversity and could be associated with performance changes not restricted to a particular cognitive domain.

In this longitudinal study, we investigated the effects of family history and APOE4 risk on cognitive performance in a healthy nonimpaired older population. Rather than focusing on individual test performance, we combined data across several tests measuring similar cognitive domains, which should both add power and decrease error variance. We examined the following cognitive domains: processing speed, executive functioning, memory encoding, and delayed memory. These domains are associated with different anatomical substrates that are often affected in aging and dementia. A critical relationship between memory processes and the medial temporal lobe, specifically hippocampal functioning, is well established.²⁶ In AD, early evidence of memory deterioration is reflected by large number of studies examining medial temporal lobe structure and function. In contrast, performance in cognitive domains such as processing speed and executive functioning is closely associated with frontal cortices.^{27,28} Prior studies have found evidence for subtle differences in cognitive performance associated with APOE4 genetic risk for AD in executive functioning, perceptual (processing) speed, and episodic memory.^{17,18} Bäckman and colleagues²⁹ highlight that these three domains are most effective at identifying people at risk for AD and that they are implicated in normal cognitive aging as well as preclinical AD. However, because changes in delayed memory have been shown to predict AD in nondemented individuals,^{30,31} we decided to model memory encoding and delayed memory as separate domains. This is in line with Wisdom and colleagues¹⁷ suggestion that future research should examine which areas of episodic memory are most impacted by APOE genotype. The domains we used allowed us to investigate whether APOE4 and family history risk would differ in their contribution to cognitive processes that are possibly more or less closely related to AD. We did not expect onset of dementia over the 2-year time frame in healthy individuals, but specific contributions of each risk AD risk factor to changes in cognitive performance within the normal range. We hypothesized that APOE4 genetic risk for AD would be associated with reduced performance in the memory domains, whereas having a family history of AD would be associated with more general cognitive deficits.

METHODS

Subjects

After complete description of the study to the subjects, written informed consent was obtained in accordance with the UCLA Human Subjects Protection Committee procedures. Participants were drawn from a population of 794 subjects, recruited through advertisements for investigations aimed at examining brain structure and function using different neuroimaging techniques in cognitively healthy people, subjects with mild cognitive impairment (MCI) and AD. As of the beginning of 2010, 190 subjects have received a follow-up neuropsychological assessment. Seventy-three middle-aged and older subjects (aged 47--82) were cognitively normal at baseline, according to NINCDSADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) criteria,³² and scoring 27 or more points in the Mini-Mental State Exam.³³ Because we were specifically interested in the effects of AD risk factors on cognitive performance and performance change over time in healthy people, one subject that met MCI criteria at follow-up was not included in the study. General exclusion criteria were a history of psychiatric or neurological disorder, or major systemic disease affecting brain function. All participants underwent standard laboratory testing including APOE genotyping, structural magnetic resonance imaging, and neurological and psychiatric evaluations. These evaluations included an interview with a physician to rule out existing acute or chronic medical conditions, for example, a present depressive episode, a history of major depression, or other diseases that could affect cognitive functioning. Physical and neurological examinations were also performed by the physician to possibly reveal yet undiagnosed medical conditions, such as Parkinson disease, that could also be associated with cognitive dysfunction. Thus, neurological and psychiatric evaluations complemented structural MRI scans and laboratory testing aimed at detecting medical conditions that could be associated with cognitive dysfunction. The 72 final study participants (mean age $\pm$ standard deviation: 62 ± 9 years) received follow-up assessments after 24 ± 8 months. Among the 42 participants, not carrying the APOE4 allele were 41 APOE 3/3 subjects and one individual with the APOE 2/3 genotype. Among the 30 APOE4 carriers were three homozygous APOE4 subjects. The study sample did not include subjects with the APOE 2/2 or 2/4 genotype. Family history of AD was defined as having at least one first-degree relative diagnosed with AD. To obtain this information, study participants were asked whether a physician had established the diagnosis of AD in a first-degree relative following diagnostic evaluation. All participants with a family history of AD reported parental family history only.

Neuropsychological Testing

Neuropsychological testing was performed using a standard battery³⁴ investigating the following domains of cognitive functioning: processing speed (Wechsler adult intelligence scale-III Digit Symbol; Trailmaking test part A; Stroop test, word reading), executive functioning (Verbal fluency FAS and Animal naming tests; Trailmaking test part B; Stroop test, interference), memory encoding (Wechsler Memory Scale III, Logical Memory I and Verbal Paired Associates I; Buschke-Fuld selective reminding test, consistent long-term retrieval), and delayed memory (Rey Osterrieth Complex Figure, delayed recall; Wechsler Memory Scale III, Logical Memory II, and Verbal Paired Associates II; Buschke-Fuld selective reminding test, delayed recall). Cronbach's alpha values---processing speed: 0.71; executive functioning: 0.80; memory encoding: 0.70; delayed memory: 0.71.

Statistical Analyses

To determine whether APOE4 genotype and family history of AD were associated with poorer cognitive performance at baseline or greater decline, we estimated general linear

models, with APOE genotype and family history as between-group factors. We also examined the interaction between these factors. Gender and education were modeled as covariates.

We combined the individual tests measuring similar aspects of neurocognitive performance into domain scores by averaging the individual tests' scores. We did not use the individual tests' raw scores but rather corrected values based on age norms, calculating the z-score difference between each subject's performance and the age norm, to which we refer as "z-scores." Whereas a score of 0 indicates average age-adjusted performance, a score of +1 or -1 would reflect subjects' performance at one standard deviation above or below age average, respectively. The domain approach is less affected by performance variability on individual tests, allows for reliable combination of scores across different ages, and reduces the number of comparisons performed. Z-scores were averaged separately at each time point for each of the four domains. *Longitudinal change* was defined as a difference of these z-scores. Domain z-scores at baseline and changes in domain z-scores were used as dependent variables in two separate multivariate models. To investigate longitudinal change, we used a measure of baseline performance as an additional covariate. We constructed an overall measure of baseline performance by averaging the baseline z-scores of the four cognitive domains. We additionally investigated whether using the four baseline domain scores as separate covariates would yield a different finding than using the combined measure, which was not the case.

Because we are investigating four cognitive domains, we used a multivariate approach, with the domain scores as the dependent variables, and we conducted post-hoc univariate tests only after significance was established by the multivariate *F*-test, to determine the domains that contributed to the significant finding. Thus, we conducted four univariate post-hoc tests for the baseline scores and for the change scores. Within-group analyses were also only conducted if the multivariate between-group analysis yielded a significant finding. All analyses used a significance level of $p < 0.05$, two-tailed.

RESULTS

For demographic and clinical characteristics, see Table 1. At baseline, we found a significant main effect for family history (multivariate $F_{[4, 63]} = 3.4$, $p = 0.01$). Post-hoc analyses showed poorer performance associated with having a family history of AD in processing speed ($F_{[1, 66]} = 8.43$, $p = 0.005$), executive functioning ($F_{[1, 66]} = 4.45$, $p = 0.04$), memory encoding ($F_{[1, 66]} = 7.6$, $p = 0.008$), and delayed memory ($F_{[1, 66]} = 4.53$, $p = 0.04$). APOE genotype did not contribute to baseline cognitive performance differences (Figure 1).

In contrast, family history of AD did not contribute to greater decline in performance over time in any domain. However, we found a significant effect of APOE genotype for longitudinal change overall (multivariate $F_{[4, 62]} = 3.78$, $p = 0.008$) and posthoc analyses revealed significant group differences in change in the memory encoding ($F_{[1, 65]} = 5.7$, $p = 0.02$) and delayed memory ($F_{[1, 65]} = 9.0$, $p = 0.004$) domains (Figure 1). Within group-analysis showed that this effect was due to improved performance among non-APOE4 carriers in these domains (paired samples *t*-tests: memory encoding: $t(41) = -4.96$, $p < 0.001$; delayed memory: $t(41) = -4.04$, $p < 0.001$), likely reflecting a benefit from repeated test presentation (practice effect). APOE4 carriers did not show greater decline over time in any domain within group.

There was no significant finding for the interaction between the factors APOE genotype and family history for both baseline and change scores.

DISCUSSION

We found differential contributions of APOE4 genetic risk for AD and a family history of AD on cognitive functioning in healthy middle-aged and older people. Having a family history of AD was associated with poorer baseline performance in processing speed, executive functioning, memory encoding, and delayed memory, but not greater decline over time. APOE carrier status did not explain baseline group differences but was associated with a longitudinal effect in the memory encoding and delayed memory domains. However, this was due to non-APOE4 carriers performing better at follow-up rather than decline among APOE4 carriers. Because the same tests were used at baseline and follow-up, we would expect subjects to show evidence of practice. Particularly, the memory domains may be susceptible to APOE-associated practice effect differences.^{35,36} The memory encoding and delayed memory measures are also dependent upon each other. Specifically, to recall information after a delay, information must be initially encoded. Indeed, we found that the measures were correlated; nonetheless, they represent distinct cognitive processes, perhaps differentially susceptible to the influence of AD risk factors. Our data suggest that subjects without the APOE4 allele showed typical practice-related effects while those carrying the AD risk gene failed to show improvement at re-test. APOE effects on cognition are most consistently associated with differential memory performance.^{17,19} Failure to show practice effects especially on delayed memory tasks suggests subtle differences in memory consolidation systems in APOE4 allele carriers. Zehnder and coworkers³⁵ also found that the APOE4 allele had a negative impact on cognitive performance in healthy people, especially episodic memory, and that APOE4 carriers showed smaller practice effects when compared with noncarriers of the allele. Whereas practice effects have traditionally been viewed as a study bias, they may yield diagnostic and prognostic information in people at risk for developing dementia.³⁷

In contrast, at baseline, family history of AD, which may reflect a wide range of risk variables that may interact in complex ways,³⁸ was associated with more general cognitive deficits and particularly frontal cortical functions. This suggests that APOE4 genetic risk and family history risk for AD contribute in unique ways to cognition during aging. These unique effects on cognition may ultimately reflect different underlying neuroanatomic substrates and mechanisms contributing to AD risk. For instance, family history risk may include factors less specific for AD, reflecting genetic variables linked to one's overall cognitive abilities or contributing to vascular and inflammatory processes affecting cognition.¹³ However, this must be examined directly in future studies.

Compared to genetic factors such as APOE genotype, nongenetic variables affecting cognition and AD risk have received less attention. In addition to known and yet unknown genetic factors, a family history of AD could also reflect nongenetic variables, such as socioeconomic status, social interaction patterns, or dietary habits that run in families, likely being passed to the next generation.²⁵ It has been shown in infants that parent-child relationships and maternal sensitivity affect later school performance.³⁹ Nutritional habits, for example, having a regular breakfast, can improve cognitive function in children and adolescents,⁴⁰ and diet quality is also associated with cognitive performance in aging people.⁴¹ There is a growing awareness that factors ranging from intellectual stimulation in infancy to nutrition late in life may be able to modulate AD onset and progression within a framework of factors more closely related to AD pathology itself, and factors related to the clinical expression of cognitive impairment.^{25,42} Therefore, the family history effect on cognition could reflect developmental and/or environmental influences that may either attenuate or maintain neuronal integrity once a neurodegenerative process starts.

Although some of the unknown factors contributing to family history risk may be able to cause longitudinal changes, the diversity of genetic and nongenetic variables involved could mask this effect. Alternatively, the follow-up period we used could have been too short to allow detection of effects on how a diverse risk factor pattern would contribute to cognitive decline, and it is certainly possible that family history effects are expressed later in life than APOE genotype effects. To test the hypothesis whether our subjects' mixed age range could have prevented detection of a longitudinal effect associated with family history risk, we divided subjects along the median age into two groups, hypothesizing that a zero relationship in younger subjects might have obscured a greater relationship in older subjects. Among the older subjects, we still did not find an effect of family history on longitudinal change in the cognitive domains investigated, which makes it rather unlikely that the lack of effect is power related. Despite the mixed age range, we did have sufficient power to detect a longitudinal APOE genotype effect. However, we did not observe cognitive *decline* over this brief time period associated with the APOE4 genotype (except in one subject, who developed MCI and was not included in the analysis). Some studies reported greater memory decline associated with carrying the APOE4 allele, although there have been mixed findings.¹⁹⁻⁻²¹ Caselli and colleagues¹⁹ found greater cognitive decline among homozygous APOE4 carriers when compared with heterozygous APOE4 carriers and noncarriers. In their study, the authors identified participants by using advertisements requesting for healthy individuals with a first-degree relative with AD. In contrast, we emphasize that family history risk could be considered a unique risk factor itself. Furthermore, only three homozygous APOE4 subjects participated in our study, and we therefore could not use APOE4 allele dose as a variable. The findings of Bretsky and coworkers²⁰ suggest that a longer follow-up period could be necessary to detect longitudinal changes. The issue of whether both risk factors interact also remains controversial: whereas recent multi-institutional investigations show family history effects on AD risk regardless of APOE genotype,⁴³ Huang and coworkers⁴⁴ revealed that family history of AD was associated with increased AD risk only among APOE4 carriers.

This study has several limitations. Family history status was reported by study participants, and we did not examine the relatives' medical records ourselves. Although participants were asked whether a physician had established the diagnosis, there were no autopsy data available for definite confirmation of AD diagnosis. Furthermore, yet healthy relatives could develop AD in the future. It is also not possible to determine clinically whether an APOE4 allele carrier would have a family history of AD because of the APOE4 allele or would carry additional risk factors contributing to family history. APOE and family history effects in healthy people are generally very subtle, and limited statistical power due to small sample sizes could prevent detection of group differences.^{18,45} Our subject sample covers an age range that may imply heterogeneous susceptibility to longitudinal decline in neuropsychological performance. However, age ranges were similar for all four groups. That we were able to detect a longitudinal APOE genotype effect also tends to strengthen our results, because increased age variance should mark against seeing significance. Jarvik and colleagues³⁸ reviewed in detail that it is difficult to isolate the specific contributions of AD risk factors (such as age, family history, or APOE genotype) to future cognitive decline, as they interact in various and often yet unknown ways. Finally, we did not directly investigate the association between AD risk and specific laboratory parameters linked to inflammation or vascular disease, which has been demonstrated elsewhere.¹³

In summary, the family history risk factor is a possibility to account for yet unknown or rarely studied genetic and possibly nongenetic risks for AD. Whereas APOE effects can be detected in memory domains, family history of AD is associated with a more general decrease in cognitive performance. It becomes increasingly evident that modeling both risk factors is important in neuropsychological studies aimed at investigating AD risk.

Acknowledgments

The authors thank Ms. Andrea Kaplan and Ms. Debbie Dorsey for help in subject recruitment, data management, and study coordination.

Dr. Small reports having served as a consultant and/or having received lecture fees from Dakim, Eisai, Forest, Novartis, Pfizer, Radica, and Medivation. Dr. Small also reports having received stock options from Dakim. Dr. Ercoli reports having received lecture fees from the Alzheimer's Association Speakers Bureau and Keiro Senior Health Services. The investigators have no financial interests.

NIH grants P01-AG025831, R01-AG13308, P50-AG 16570, MH/AG58156, MH52453; AG10123; M01-RR00865, General Clinical Research Centers Program, the Fran and Ray Stark Foundation Fund for Alzheimer's Disease Research; the Larry L. Hillblom Foundation. Markus Donix was funded by the Max Kade Foundation.

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FIGURE 1.

Baseline and longitudinal test performance according to APOE and family history status. This figure visualizes baseline neuropsychological test performance (A) and longitudinal change (B) according to apolipoprotein E (APOE) genotype and family history status. Subjects with a family history of AD (FH+) show reduced baseline performance in all cognitive domains investigated when compared with subjects without family history risk (FH-). Asterisks indicate significant between-group differences (baseline: multivariate $F_{[4, 63]}$ and post-hoc univariate $F_{[1, 66]}$). APOE genotype did not contribute to baseline differences but noncarriers of the APOE4 allele showed improved memory performance

over time when compared with APOE4 allele carriers. Asterisks indicate significant between-group differences (follow-up: multivariate $F_{[4, 62]}$ and posthoc univariate $F_{[1, 65]}$).

Demographic and clinical characteristics

Table 1

Characteristic	APOE4 FH+	APOE4 FH-	non-APOE4 FH+	non-APOE4 FH-	Statistics ^I
Number of Subjects	16	14	23	19	
Age (mean ± sd, range)	60.8 ± 9.6, 47–76	61.7 ± 11.2, 47–80	60.1 ± 8.4, 49–81	64.0 ± 8.9, 52–82	F(3,68)=0.64, p=0.59
Female sex (no. / %)	9 / 56	5 / 36	20 / 87	10 / 53	² (3)=11.09, p=0.01
Education (years, mean ± sd)	16.3 ± 3.1	16.1 ± 2.2	17.1 ± 3.0	17.5 ± 3.0	F(3,68)=0.93, p=0.43
MMSE baseline (mean ± sd)	29.4 ± 0.8	29.6 ± 0.6	29.2 ± 1.0	29.6 ± 0.6	F(3,68)=1.25, p=0.3
MMSE change (mean ± sd)	−0.1 ± 0.7	−0.4 ± 1.3	0.0 ± 1.0	−0.4 ± 1.1	F(3,68)=0.8, p=0.5
Assessment interval (months, mean ± sd)	24.8 ± 7.1	23.5 ± 7.2	26.3 ± 9.2	21.5 ± 7.8	F(3,68)=1.34, p=0.27

FH+/FH−: positive/no family history of Alzheimer's disease, MMSE: Mini Mental State Examination, APOE: apolipoprotein E

^I univariate ANOVAs except for 'female sex' (²)