Clinical Section

Gerontology

Gerontology 2009;55:32–40
DOI: 10.1159/000137666

Received: September 13, 2007
Accepted: February 27, 2008
Published online: June 5, 2008

Racial Differences in the Influence of the APOE Epsilon 4 Allele on Cognitive Decline in a Sample of Community-Dwelling Older Adults

Kathryn Sawyer[a] Natalie Sachs-Ericsson[a] Kristopher J. Preacher[b]
Dan G. Blazer[c]

[a]Department of Psychology, Florida State University, Tallahassee, Fla., [b]Department of Psychology, University of Kansas, Lawrence, Kans., and [c]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C., USA

Key Words
APOE genotype · Cognitive decline · Racial differences, APOE epsilon 4 allele

Abstract
Background: Most, but not all, past studies have suggested that the APOE genotype is a risk factor for dementia in whites but not African Americans. This paper first describes explanations as to why some studies may have failed to detect the effect of APOE genotype in African American samples. Briefly, studies have been limited by various methodological problems including small sample sizes, dichotomous measures of cognitive functioning (which tend to be less sensitive to change), and racial bias in assessing demented status. ***Objective:*** This paper suggests methods for increasing the likelihood that genuine racial differences will be identified when examining genetic risk factors. Further, we test our model of racial differences in the relationship of APOE genotype and cognitive decline (CD) in a large prospective community sample. ***Methods:*** Building on the work of Fillenbaum and colleagues [J Am Geriatr Soc 2001;49:1148–1155], we used data from the Duke EPESE study collected in four waves over a 10-year period (n = 2,076) to illustrate methods which may better assess racial differences in the influence of the APOE ε4 allele on CD. We used multilevel models for repeated measures to examine racial differences in participants' increase in errors on a continuous measure of cognitive functioning as they aged. ***Results:*** We found the APOE ε4 allele to predict CD for both African Americans and whites. Having at least one ε4 allele predicted more cognitive errors at wave 1 and a faster rate of decline for both African Americans and whites over time. While African Americans experienced a faster rate of CD than whites, there was no additional increase in CD from being both African American and a carrier of the ε4 allele. ***Conclusion:*** The study points to several common methodological issues that arise when examining racial differences in genetic influences on health-related outcomes. Further, the study's results highlight the importance of including both African Americans and Caucasians in research concerning the contribution of APOE genotype to CD.

Introduction

Many older adults demonstrate some degree of cognitive decline (CD) over time. Nonetheless, CD is a risk factor for developing mild cognitive impairment [1, 2] that may even progress to dementia [3, 4]. Among older adults, estimates of mild cognitive impairment range from 3 to 22% [4, 5] and researchers have estimated the rate of conversion from mild cognitive impairment to dementia

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/ger

Natalie Sachs-Ericsson, PhD
Department of Psychology
Florida State University
Tallahassee, FL 32306-1270 (USA)
Tel. +1 850 644 4576, Fax +1 850 645 1758, E-Mail sachs@psy.fsu.edu

over a 2- to 4-year period to range from 23 to 51% [5, 6]. Various factors, including genetic and environmental variables, have been identified as potentially contributing to this process of CD.

One demonstrated risk factor for developing Alzheimer's disease (AD), the most common type of dementia, is the ε4 allele of the apolipoprotein E (APOE) gene [7–9]. However, there is some evidence that the APOE genotype does not predict AD among African Americans, i.e., several studies have shown that the APOE ε4 allele is associated cross-sectionally with the presence of AD in whites but not in African Americans, and that longitudinally the APOE ε4 allele is predictive of change from nondemented to demented status in whites but not in African Americans. In the current paper we review studies examining racial differences in the influence of the APOE genotype on cognitive functioning, and identify methodological factors that may have obscured the effect of APOE genotype in African American populations. These methodological problems include inadequate sample size, the use of dichotomous rather than continuous measure of cognitive functioning, possible racial bias in measures of cognitive assessments, and statistical methods that are not suited to modeling racial differences in the rate of change over time.

Several studies have found APOE genotype to influence cognitive functioning in whites but not African Americans. In biracial samples, Tang et al. [10] and Evans et al. [11] used longitudinal designs in which they measured participants' change from nondemented to demented status as determined by a clinical interview and neurological examination, over the course of a 4.1- and a 5-year period, respectively. Tycko et al. [12] used a cross-sectional design in which they evaluated the incidence of AD among an elderly population of whites, Caribbean Hispanics, and African Americans. In all three studies, APOE genotype predicted developing AD for whites but not for African Americans.

Such studies detecting no effect of APOE genotype among African Americans were based on relatively smaller sample sizes (e.g., <1,000 African Americans). In contrast, studies finding APOE genotype to influence cognitive functioning in African Americans had relatively large samples of African American participants. For example, a study using a large biracial sample (the MIRAGE data set, n = 2,793 African American participants) [13] found APOE genotype to be a risk factor for AD among both whites and African Americans. A recent meta-analysis examining relationships between genotype and various genetic diseases [14] found that such large sample sizes may be required to detect the effect of genetic variants on any complex disease, and an even larger sample may be required where environmental or racial differences create heterogeneity among the patient population, or where misdiagnosis is a serious concern.

Apart from concerns of sample size, one additional explanation relates to measurement bias in the assessment of cognitive functioning. Measures of cognitive functioning have been, for the most part, normed using white samples and are strongly influenced by education [15, 16]. Researchers have found that false-positive rates for dementia on standardized screening tests are higher for African Americans than for whites when compared with a neurologist's rating of cognitive status [17, 18]. Thus, higher false-positive rates for diagnosis of AD among African Americans may have obscured the influence of APOE genotype.

The power to detect the influence of the APOE ε4 allele on CD to AD may be further reduced when using dichotomous rather than continuous measures, i.e., examining the presence or absence of dementia, or examining change from nondemented to demented status, may be a less sensitive measure of change than examining an increase in the number of errors on a cognitive measure over time (i.e., continuous measures). Whereas some studies have shown that the APOE ε4 allele is associated cross-sectionally with dementia for whites but not African Americans, and is predictive of change over time from nondemented to demented status in whites but not African Americans, few studies have examined racial difference in the influence of the APOE ε4 allele over time on continuous scores of cognitive functioning. Thus, possible explanations for the failure to identify an effect of the APOE ε4 allele on CD among African Americans, in the studies described above, include the relatively small samples, as well as possible racial bias in cognitive assessment coupled with the use of a dichotomous measure of cognitive functioning and consequently lower statistical power to detect change.

Additionally, there are other factors that may contribute to obscuring the influence of APOE genotype on cognitive functioning. There is some evidence that rates of cognitive impairment [19–21] and AD [3, 4] are greater in African Americans than in whites [22]. This may be related to the higher prevalence in African Americans, compared to whites, of some risk factors. Specifically, lower income, fewer years of education, less literacy, and physical functioning and health problems, including vascular or related diseases [23], are more common among

African Americans and influence CD [22]. Thus, the influence of lower socioeconomic status (SES) and greater health-related problems found in older African Americans compared to Caucasians may mask the predictive effect of APOE genotype by generally increasing the incidence of diagnosed AD in the African American population. Thus, it is important to control for such variables in analyses examining racial differences in the effect of APOE genotype on CD. Moreover, it is of interest to note that in cross-sectional studies restricted to African American samples (thus decreasing between-group variability on SES and health variables) researchers have been more likely to find an association of APOE genotype and AD [24–26].

Accordingly, in the current study, we employ several methods to increase our ability to detect the influence of APOE genotype on CD. These methods include the use of prospective data, a continuous measure of cognitive functioning, a large biracial sample of community-dwelling older adults in which African Americans were oversampled, multilevel growth curve models, the use of age (rather than arbitrary year of data collection) as our time metric, and controlling for variables that may influence racial differences in CD, including indices of SES and physical and health functioning variables.

Data for this study were derived from the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) [27], a population survey of persons 65 years and older. In the current study, we prospectively examined racial differences in the influence of the APOE ε4 allele on CD using a series of multilevel growth curve analyses. This allowed us to examine the influence of the APOE ε4 allele on CD with increasing age at four waves over a 10-year period, while controlling for indices of SES (income, education, literacy) as well as health functioning.

It is important to note that a previous study based on waves 3 and 4 of these data found APOE genotype to predict change from nondemented to demented status regardless of race [1]. The current study adds to these findings (1) by directly comparing racial differences in the rate of change in cognitive functioning over a 10-year period and (2) by examining the potential interactions of race and the APOE ε4 status on the rate of CD.

In this regard, multilevel growth curve analyses have several advantages over methods used to examine this phenomenon in past studies. First, they allow for the inclusion of participants with some missing data, resulting in a larger sample size than previous analyses using this data set. Moreover, multilevel growth curve analyses allow for an examination of the rate of change in cognitive functioning with each year of aging, among carriers and noncarriers of the APOE ε4 allele. This is a more fine-tuned measure of the effect of APOE genotype on CD than likelihood of change from nondemented to demented status between study waves. We predicted that APOE genotype would predict CD for both whites and African Americans.

Methods

Participants

Data were derived from the Duke EPESE [27], an epidemiologic investigation of physical, psychological, and social functioning of community-dwelling older adults. The North Carolina sample consisted of community residents selected from five contiguous counties. Data were collected in four in-person interviews over a 10-year period. The wave 1 study was conducted in 1986–1987 (n = 4,162, 54.3% African American), and follow-up interviews were conducted in 1989–1990 (wave 2, n = 3,559, 54.6% African American), 1992–1993 (wave 3, n = 2,840, 55% African American), and 1996–1997 (wave 4, n = 1,767, 53.5% African American). APOE genotype was obtained at wave 3 (see more detail below). The sampling design has been described in detail previously [27]. Briefly, the study used a probability sample of 4,162 community residents. African Americans were oversampled. We include in the current study only participants for whom we have data on race and genotype and at least one assessment of cognitive functioning. Even though individuals contributing only one data point cannot contribute information to change over time, their data nevertheless contribute to estimation of the intercept, and thus the results are more precise and comprehensive for their inclusion.

Control Variables

Several variables have been found to be associated with CD among the elderly; therefore, it was important to control for such variables in the analyses. These variables include demographic variables (age, gender), socioeconomic variables (income, education, literacy), health variables [e.g., diabetes, high blood pressure (HBP), heart attack, stroke], and physical functioning [22].

Measures

Demographics

A comprehensive demographic section assessed gender, years of education, family income, and race of participants.

Cognitive Functioning

Cognitive functioning was assessed by the 10-item Short Portable Mental Status Questionnaire (SPMSQ) [28] at wave 1 (Cronbach's $\alpha = 0.74$), wave 2 (Cronbach's $\alpha = 0.74$), wave 3 (Cronbach's $\alpha = 0.93$), and wave 4 (Cronbach's $\alpha = 0.96$). The SPMSQ is a brief (10-item) measure of global cognition. For example, items assessed knowledge of day, date, and current president.

Unlike some other studies that dichotomized the SPMSQ, in this study participants' errors across items were summed to form a continuous scale (0–10 errors) with higher scores indicating more difficulty.[1]

Physical Functioning

Three items from the Rosow-Breslau Functional Health Scale [29] were used at wave 1 to assess physical functioning. These items concerned participants' ability to do heavy housework, walk up and down stairs, and walk one-half mile (1 = 'no,' 2 = 'yes'). Responses were summed, with lower scores indicating poorer functioning (Cronbach's $\alpha = 0.79$).

Health Problems

Participants were asked at wave 1 whether a physician had informed them that they had certain health problems, including heart attack, diabetes, hypertension, stroke, and hip fracture. For each problem responses were coded: 1 = 'no', 2 = 'possibly', 3 = 'yes'.

Assessment of Genotype

At the third in-person interview (wave 3), 6 years after wave 1, blood was drawn from subjects who gave consent (1,999 of the 2,840 participants were genotyped at this time). Approximately 4 years later, cheek swabs were sought from survivors who had not undergone the blood draw (an additional 77 participants were genotyped at this time).

APOE genotype was determined by DNA extraction and polymerase chain reaction, as described previously and in specific detail by Fillenbaum et al. [1]: High-molecular-weight DNA was obtained from whole blood, and crude DNA extract was obtained from buccal cheek swabs. Genomic DNA was amplified by polymerase chain reaction. An initial denaturation was followed by 35 cycles of annealing in the final extension. After amplification, 5 U of *Hha* I was directly added to each well, and the plates were incubated for at least 3 h at 37°C. Type III stop dye was added to each well, and 3 μl of each reaction was loaded on a 6% nondenaturing polyacrylamide gel and electrophoresed for 1 h under constant current (45 mA). After electrophoresis, the DNA was visualized by staining with SyberGold (FMC) (Whittaker Bioproducts, Walkersville, Md., USA) followed by fluorography. Each fluorogram was read independently by two observers.

In the current study, participants were divided into two groups, those who had at least one APOE ε4 allele and those who had no ε4 allele. We included in the analyses all participants with information on genotype and race and at least one cognitive score. All participants with genotype information also had information on race and at least one cognitive score and were, therefore, included in the analyses. Thus, of those who participated at wave 3 (n = 2,840), 2,076 of the participants were included in the analyses (50.4% of those who participated at wave 1). As having an ε4 allele is associated with earlier age of mortality [30] and might, therefore, have caused differential attrition prior to genotyping, absence of genotype information was likely not random. We, therefore, performed additional analysis to address this issue.[2]

Assessment of Literacy

Our assessment of literacy has been described in detail previously [22]. Briefly, interviewers assessed participants' literacy based on their ability to read several pieces of written information given to them during the interview.

Table 1. Description of the sample by race at time 1

	Sample as a whole (n = 2,076)	White (n = 961)	African American (n = 1,115)	F statistic or χ^2	p
Race, %					
Caucasian	46.3	–	–	–	–
African American	53.7				
Gender, %					
Male	34.9	35	34.9	0.016	0.899
Female	65.1	65	65.1		
Age, years	71.6	71.4	71.81	0.283	0.595
Education, years	9.01	10.4	7.81	237.53	<0.001
Income, USD	11,487.22	15,825.90	7,747.78	342.83	<0.001
Literacy, %				139.17	<0.001
Literate	89.5	95.7	84.4		
Illiterate	10.5	4.3	15.6		
Heart attack, %				1.99	0.37
No	87.6	86.5	88.6		
Maybe	2.7	2.9	2.4		
Yes	9.7	10.5	9.0		
Stroke, %				13.37	0.001
No	94.8	96.1	93.7		
Maybe	0.6	0.9	0.4		
Yes	4.5	2.9	5.9		
Diabetes, %				46.57	<0.001
No	82.4	87.9	77.6		
Maybe	2.7	2.9	2.5		
Yes	14.9	9.2	19.9		
HBP, %				56.76	<0.001
No	43.1	51.8	35.6		
Maybe	3.2	3.2	3.2		
Yes	53.7	45.0	61.2		
Physical function problems	0.62	0.53	0.7	15.14	<0.001
APOE ε4 allele, %				53.32	<0.001
Absent	68	76.1	61.1		
Present	32	23.9	38.9		

[1] Racial differences in SPMSQ scores may be due in great part to racial bias in testing. To control for this bias, other studies have adjusted SPMSQ score by race. That is, in defining a cut score for probable dementia, different cut scores were identified for blacks and whites. While this racial bias in testing may explain initial differences on the SPMSQ for blacks and whites, examining change over time is not subject to the same problems of racial bias. As we examined each participant's change over time, rather than cross-sectional differences, baseline differences are already controlled in the design.

[2] To examine the influence of missing genotype data on the study's current findings, we reanalyzed the data with all participants missing a genotype characterized as having the ε4 allele. Consistent with our study's findings, results of these analyses showed that the ε4 allele predicted CD, and did so for both African Americans and whites.

Procedures for Analyses

First, the effect of age on growth of cognitive errors was examined. Second, race was added as a predictor in the analyses to examine the impact of race on growth of cognitive errors with increasing age. Finally, the effect of APOE genotype on growth of cognitive errors with increasing age was examined, controlling for demographics, health functioning, and SES (education, literacy, income), and we tested for an interaction of race and genotype on growth of cognitive errors.

Results

Planned Analyses

We first provide descriptive statistics for the sample as a whole and for African American and white participants on key variables (table 1). Then, we conducted multilevel growth curve analyses to examine the effect of race and genotype on growth of cognitive errors with increasing age.

Descriptive Analyses

Among the sample, 46.3% were white, 32.9% were male, and the average age at wave 1 was 71.6 years (SD = 6.7). Among the participants, 32% had at least one ε4 allele. In our sample African Americans were more likely than whites to carry the ε4 allele [38.9 vs. 23.9%; χ^2 (d.f. = 1, n = 2,076) = 53.32, $p < 0.01$]. The validity of the genotyping is indicated by the concordance of the allele frequency with Hardy-Weinberg equilibrium for the sample as a whole [χ^2 (d.f. = 3, n = 2,076) = 7.21, $p > 0.25$], for the white participants only [χ^2 (d.f. = 3, n = 961) = 4.83, $p > 0.25$], and for African American participants only [χ^2 (d.f. = 3, n = 1,115) = 5.97, $p > 0.25$].

African Americans, compared to whites, were also more likely to be illiterate [15.6 vs. 4.3%; χ^2 (d.f. = 1, n = 2,076) = 72.9, $p < 0.001$], to have fewer years of education [7.8 vs. 10.4; F(1,2075) = 237.53, $p < 0.001$], to have a lower income [USD 7,747 vs. USD 15,825; F(1,2075) = 342.83, $p < 0.001$], and to have more physical functioning problems [0.7 vs. 0.53; F(1,2069) = 15.14, $p < 0.001$], stroke [5.9 vs. 2.9%; χ^2 (d.f. = 2, n = 2,076) = 13.37, p = 0.001], diabetes [19.9 vs. 4.2%; χ^2 (d.f. = 2, n = 2,074) = 46.57, $p < 0.001$], and HBP [61.2 vs. 45%; χ^2 (d.f. = 2, n = 2,076) = 56.76, $p < 0.001$].[2]

Multilevel Growth Curve Analyses

Multilevel growth curve analyses were used to examine the growth in cognitive errors with increasing age (10 years with four data point collections). We used MLwiN 2.02 [31] to specify a multilevel model of change, treating wave as the level 1 unit nested within person as the level 2 unit [32]. This analysis permitted us to estimate individual differences in CD as a function of age and to assess whether variability in decline could be predicted by key variables while controlling for demographic variables. The influences of race and of APOE genotype on the growth of cognitive errors, controlling for age, were examined, as well as the interaction of race and genotype. In the first set of analyses, we fit a model that estimated linear change in CD for every person. The participants were included in the unconditional multilevel growth curve analyses if they had an APOE genotype, at least one score on the SPMSQ, and race and age information.

We first estimated a null model. The null model contains no predictors, and is intended only to partition variance in CD into between-person and within-person components. The level 2 covariance matrix, therefore, consists only of the intercept variance (τ_{00}), whereas the level 1 residual variance is denoted σ^2_e. We found that variability in number of errors was split almost evenly between levels, with an estimated within-person vari-

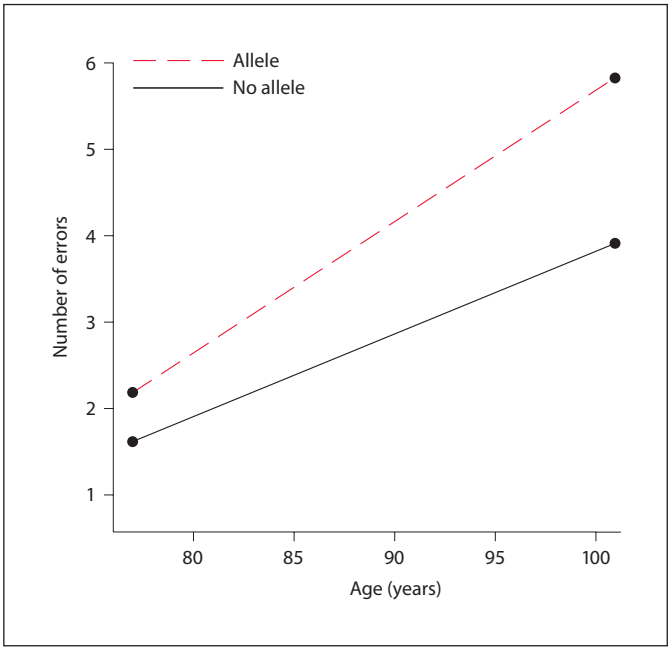

Fig. 1. Longitudinal change in SPMSQ errors with increasing age in participants with and without the APOE ε4 allele. As participants age, errors on the SPMSQ increase at a faster rate in those with the APOE ε4 allele than in those without the allele. Since there were no differences by race, separate curves by race are not included.

Table 2. Parameter estimates and significance tests for multilevel growth models

Model	Point estimate	SE	z	p
Null model				
Intercept	2.289	0.033	69.364	<0.0001
Intercept variance	2.364			
Residual variance	3.025			
Age as predictor (fixed slope)				
Intercept	2.367	0.032	73.969	<0.0001
Age	0.146	0.003	48.667	<0.0001
Intercept variance	3.046			
Residual variance	2.524			
Age as predictor (random slope)				
Intercept	2.336	0.033	70.788	<0.0001
Age	0.139	0.004	34.75	<0.0001
Intercept variance	3.223			
Slope variance	0.017			
Intercept-slope covariance	0.169			
Residual variance	2.101			
Age and race as predictors				
Intercept	1.783	0.045	39.622	<0.0001
Age	0.138	0.004	34.5	<0.0001
Race	0.993	0.057	17.421	<0.0001
Intercept variance	2.873			
Slope variance	0.017			
Intercept-slope covariance	0.16			
Residual variance	2.116			
Age and race as predictors, age × race interaction				
Intercept	1.724	0.048	35.917	<0.0001
Age	0.123	0.006	20.5	<0.0001
Race	1.104	0.065	16.985	<0.0001
Age × race	0.028	0.008	3.5	0.0005
Intercept variance	2.885			
Slope variance	0.017			
Intercept-slope covariance	0.16			
Residual variance	2.114			
Age and allele as predictors				
Intercept	1.675	0.042	39.881	<0.0001
Age	0.113	0.004	28.25	<0.0001
Allele	0.363	0.068	5.338	<0.0001
Intercept variance	2.019			
Slope variance	0.019			
Intercept-slope covariance	0.113			
Residual variance	1.354			
Age, allele, and race as predictors, allele × race interaction				
Intercept	1.231	0.053	23.226	<0.0001
Age	0.11	0.004	27.5	<0.0001
Allele	0.202	0.102	1.98	0.0477
Race	0.92	0.073	12.603	<0.0001
Allele × race	0.003	0.132	0.023	0.9819
Intercept variance	1.716			
Slope variance	0.018			
Intercept-slope covariance	0.104			
Residual variance	1.375			
Age, allele, and race as predictors, allele × race interaction				
Intercept	1.613	0.043	37.512	<0.0001
Age	0.095	0.005	19	<0.0001
Allele	0.582	0.077	7.558	<0.0001
Age × allele	0.056	0.009	6.222	<0.0001
Intercept variance	2.106			
Slope variance	0.018			
Intercept-slope covariance	0.11			
Residual variance	1.352			
Age, allele, and race as predictors, all two- and three-way interactions				
Intercept	1.095	0.057	19.211	<0.0001
Age	0.072	0.007	10.286	<0.0001
Allele	0.445	0.118	3.771	0.0002
Race	1.078	0.082	13.146	<0.0001
Age × allele	0.064	0.015	4.267	<0.0001
Age × race	0.044	0.01	4.4	<0.0001
Allele × race	–0.092	0.152	–0.605	0.545
Age × allele × race	–0.026	0.019	–1.368	0.1712
Intercept variance	1.718			
Slope variance	0.017			
Intercept-slope covariance	0.101			
Residual variance	1.372			

ability of $\hat{\sigma}_e^2 = 3.025$ and a between-person variability of $\hat{\tau}_{00} = 3.264$ (intraclass correlation = 0.519, indicating that 51.9% of the variability was between subjects). Age was entered as a predictor (grand mean centered at age = 77) in a random-intercept fixed-slope model. With no covariates, errors increased by an average of $\hat{\gamma}_{10} = 0.146$ (SE = 0.003, z = 48.67, $p < 0.0001$) per year of age. We then assessed the degree to which the rate of CD varied across individuals by freely estimating the slope variance ($\hat{\tau}_{11} = 0.017$) and the intercept-slope covariance [$\hat{\tau}_{21} = 0.169$, $\Delta\chi^2$ (d.f. = 2) = 796.94, $p < 0.0001$, i.e., there was a large amount of individual variability in CD]. Race was added as a level 2 predictor, yielding a significant slope ($\hat{\gamma}_{20} = 0.993$, SE = 0.057, z = 17.42, $p < 0.0001$), with African Americans making about one more error than whites on average at age = 77. Additionally, there was a significant interaction of age and race ($\hat{\gamma}_{20} = 0.028$, SE = 0.008, z = 3.50, p = 0.0005), meaning that the increase in errors was significantly steeper for African Americans than for whites. The gap in mean errors widened by 0.028 per year of age. African Americans made more errors on average and demonstrated more rapid CD.

APOE genotype was examined as a predictor of CD. Having the ε4 allele led to an average of ($\hat{\gamma}_{20}$ = 0.363, SE = 0.068, z = 5.34, $p < 0.0001$) more errors, controlling for age but not for race. We tested the interaction of APOE genotype and race (controlling for age). Race and genotype independently predicted errors, controlling for age, but there was no interaction of the two factors ($\hat{\gamma}_{40}$ = 0.003, SE = 0.132, z = 0.023, p = 0.982). We investigated the presence of a two-way age-by-APOE genotype interaction with CD and found it to be significant ($\hat{\gamma}_{30}$ = 0.056, SE = 0.009, z = 6.22, $p < 0.0001$), such that individuals with the APOE genotype suffer greater CD than those without it. Figure 1 illustrates the growth in cognitive errors over time by APOE genotype. Finally, we examined whether APOE genotype interacted with race to predict CD (essentially a three-way interaction of race, genotype, and age), but found no significant effect ($\hat{\gamma}_{70}$ = –0.026, SE = 0.019, z = –1.37, p = 0.171).

In a second step, indices of SES (literacy, years of education, and income), health variables (stroke, diabetes, HBP), and physical functioning were added as covariates in the model. The effects of APOE genotype and race remained significant, but were diminished when these factors were taken into account. The parameter estimates and significance tests for the multilevel growth models are summarized in table 2.

Discussion

Many scientists hold the belief that the APOE ε4 allele is a risk for CD and AD in whites but not African Americans. In the current study, building on the work of Fillenbaum et al. [1], we found that APOE genotype predicted CD for both African Americans and whites, with carriers of the ε4 allele making more cognitive errors on average. Importantly, we found no racial differences in the influence of APOE genotype on CD. African Americans did experience faster rates of CD, but there was no interaction of APOE genotype and race, and when indices of SES and health variables were controlled in the analyses, this discrepancy was diminished.

Our methods of analysis illustrate some improvements in methodology compared to past studies. First, by comparing growth in cognitive errors over time, rather than a dichotomous change in demented status, we used a more sensitive metric than many previous studies have used. Second, our analyses examined changes in cognitive errors by age rather than by wave; thus the time metric over which CD unfolds is age rather than arbitrary wave of study. Previous studies combined individuals of different ages into the same wave, introducing variance due to differing rates of decline at different ages. This, in combination with a large sample size in which African Americans were oversampled, made it possible to better detect the potential predictive effect of APOE genotype for each racial group and to examine the amount of CD expected with each year of age for carriers and noncarriers of the APOE ε4 allele.

The results of our study have clear implications for diagnosis and treatment of AD. By identifying persons who are at risk but have not yet developed AD, it would be possible to pinpoint the neurodegenerative processes that lead to the disease but occur in the preclinical phase [33]. Moreover, the APOE genotype, in combination with complaints of subjective memory impairment, is a reliable indicator of AD [34]. Thus, identifying both African American and white individuals with the APOE ε4 allele and subjective memory complaints offers a potential method of detecting persons at higher risk for AD.

Whereas there were no racial differences in the influence of the APOE genotype on CD, there are other environmental and behavior variables that may influence the racial differences in CD observed in this and other studies [see 22] and that may be modifiable. Exercise and diet are important environmental factors that can help to attenuate or delay the clinical manifestation of CD and dementia. For instance, engaging in leisure time physical activity in midlife has been shown to protect against later CD [35]. Some studies have found that African Americans engage in less leisure time physical activity than whites, although this relationship is mediated by level of education [36, 37]. Further, dietary differences between African Americans and whites have been demonstrated, which may also contribute to racial differences in conditions associated with vascular-related diseases – e.g., obesity [38] and diabetes [39] – that contribute to an increased risk for CD.

Thus, addressing exercise and dietary behaviors may be an important strategy in lowering risk factors for CD, especially for African Americans. In evaluating this study, several limitations should be considered:

First, this study used a brief measure of cognitive functioning, the SPMSQ, rather than a more comprehensive diagnostic interview. Whereas the SPMSQ has been shown to be a reliable and valid measure of cognitive functioning, it is a 10-point scale and has limited differentiation. Thus, the measure may have failed to detect more subtle cognitive difficulties, and instead may have detected only moderately advanced to severe impairment. Therefore, our measure may have obscured possi-

ble racial differences in the influence of the APOE genotype on cognitive functioning by failing to detect early and less severe CD. Additionally, this may limit the applicability of our study to populations of elders with moderately advanced to severe dementia.

Second, some participants already had a high number of errors at wave 1. For these participants our 10-point scale allowed only a limited increase in errors over time, as they already approached the maximum number of errors at wave 1. We fitted a parsimonious linear model to all participants, and those beginning with a high number of errors would have flatter slopes over time, due to this limitation of our measure rather than to lack of decline. Therefore, this might serve to obscure the effect of APOE genotype on CD. However, as less than 1% of the participants had >6 errors on the SPMSQ at baseline, the influence of these participants is limited.

Third, the participants' health status was measured using single-item self-report measures in which participants were asked whether a physician had informed them that they had certain health problems. This method depends upon the participant's ability to correctly remember that he or she has a particular health problem, and thus might lead to inaccuracies or underreporting of health problems among persons with memory deficits. Further, as the APOE ε4 allele may increase the risk of some health problems associated with CD, the relationship between APOE genotype and CD may be explained in part by unreported physical health problems. However, it is important to note that studies have found that objective measures are the strongest predictors of single-item self-report measures of health among the elderly [40] and that such single-item self-report measures have good reliability [41] and validity [42] in this population.

Further, some of the participants experiencing CD were probably doing so for reasons unrelated to APOE genotype (e.g., due to stroke or alcohol-related dementias), but were still included in the analyses. These participants would have experienced significant CD in the absence of the ε4 allele, and thus likely served to obscure the effect of APOE genotype on CD.

One further consideration is possible selection bias in our sample. We were only able to assess APOE genotype for participants who survived until wave 3. As there is some evidence that APOE genotype may affect health and mortality [43], it is possible that persons with the APOE ε4 allele were more likely to die prior to genotyping [44]. However, we examined this possibility in an analysis in which we assumed that all persons who died before genotyping were carriers of the ε4 allele. Findings continued to support the influence of APOE genotype on CD, regardless of race.

This study examined the effect of the APOE ε4 allele on CD over a 10-year period in a community-dwelling population of African American and white older adults. Using multilevel growth curve analyses to examine participants' increase in errors on a measure of cognitive functioning with increasing age, we found having at least one ε4 allele predicted more cognitive errors at baseline and a faster rate of decline for both African Americans and whites. The study's results highlight the importance of including both African American and Caucasian participants in studies of the relationship of APOE genotype and CD. Future studies of the causes and treatment of AD will likely target persons who are carriers of the APOE ε4 allele. It is vital that such studies include both African Americans and Caucasians in their sample.

Acknowledgment

This work was supported by grant 5R01 AG20614-02 from the National Institute on Aging (NIH, Bethesda, Md., USA).

References

1 Fillenbaum GG, Landerman LR, Blazer DG, Saunders AM, Harris TB, Launer LJ: The relationship of APOE genotype to cognitive functioning in older African-American and Caucasian community residents. J Am Geriatr Soc 2001;49:1148–1155.

2 Howieson DB, Camicioli R, Quinn J, Silbert LC, Care B, Moore MM, Dame A, Sexton G, Kaye JA: Natural history of cognitive decline in the old old. Neurology 2003;60:1489–1494.

3 Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST: Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–1142.

4 Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC: Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). Br J Psychiatry 2003;182:449–454.

5 Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, Breitner J, Lyketsos C, Jones B, Kawas C, Carlson M, Kuller LH: Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study. Part 1. Arch Neurol 2003;60:1385–1389.

6 Lopez OL, Kuller LH, Becker JT, Dulberg C, Sweet RA, Gach HM, DeKosky ST: Incidence of dementia in mild cognitive impairment in the Cardiovascular Health Study Cognition Study. Arch Neurol 2007;64:416–420.
7 Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–923.
8 Roses AD: Apolipoprotein E affects the rate of Alzheimer disease expression: beta-amyloid burden is a secondary consequence dependent on APOE genotype and duration of disease. J Neuropathol Exp Neurol 1994;53:429–437.
9 Strittmatter WJ, Saunders AM, Schmechel DE, Pericak-Vance MA, Enghild J, Salvesen GS, Roses AD: Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 1993;90:1977–1981.
10 Tang MX, Stern Y, Marder K, Bell K, Gurland B, Lantigua R, Andrews H, Feng L, Tycko B, Mayeux R: The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. JAMA 1998;279:751–755.
11 Evans DA, Bennett DA, Wilson RS, Bienias JL, Morris MC, Scherr PA, Hebert LE, Aggarwal N, Beckett LA, Joglekar R, Berry-Kravis E, Schneider J: Incidence of Alzheimer disease in a biracial urban community: relation to apolipoprotein E allele status. Arch Neurol 2003;60:185–189.
12 Tycko B, Lee JH, Ciappa A, Saxena A, Li CM, Feng L, Arriaga A, Stern Y, Lantigua R, Shachter N, Mayeux R: APOE and APOC1 promoter polymorphisms and the risk of Alzheimer disease in African American and Caribbean Hispanic individuals. Arch Neurol 2004;61:1434–1439.
13 Green RC, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, Williams M, Hipps Y, Graff-Radford N, Bachman D, Farrer LA; MIRAGE Study Group: Risk of dementia among white and African American relatives of patients with Alzheimer disease. JAMA 2002;287:329–336.
14 Ioannidis JP, Trikalinos TA, Khoury MJ: Implications of small effect sizes of individual genetic variants on the design and interpretation of genetic association studies of complex diseases. Am J Epidemiol 2006;164:609–614.
15 Teresi JA, Kleinman M, Ocepek-Welikson K: Modern psychometric methods for detection of differential item functioning: application to cognitive assessment measures. Stat Med 2000;19:1651–1683.
16 Lee S, Kawachi I, Berkman LF, Grodstein F: Education, other socioeconomic indicators, and cognitive function. Am J Epidemiol 2003;157:712–720.
17 Fillenbaum G, Heyman A, Williams K, Prosnitz B, Burchett B: Sensitivity and specificity of standardized screens of cognitive impairment and dementia among elderly black and white community residents. J Clin Epidemiol 1990;43:651–660.
18 Gurland BJ, Wilder DE, Cross PE, Teresi JA, Barrett VW: Screening scales for dementia: toward reconciliation of conflicting cross-cultural findings. Int J Geriatr Psychiatry 1992;7:105–113.
19 Lyketsos CG, Chen LS, Anthony JC: Cognitive decline in adulthood: an 11.5-year follow-up of the Baltimore Epidemiologic Catchment Area Study. Am J Psychiatry 1999;156:58–65.
20 Miles TP, Froehlich TE, Bogardus ST, Inouye SK: Dementia and race: are there differences between African Americans and Caucasians? J Am Geriatr Soc 2001;49:477–484.
21 Demirovic J, Prineas R, Loewenstein D, Bean J, Duara R, Sevush S, Szapocznik J: Prevalence of dementia in three ethnic groups: the South Florida program on aging and health. Ann Epidemiol 2003;13:472–478.
22 Sachs-Ericsson N, Blazer DG: Racial differences in cognitive decline in a sample of community-dwelling older adults: the mediating role of education and literacy. Am J Geriatr Psychiatry 2005;13:968–975.
23 Blazer DG, Landerman LR, Hays JC, Grady TA, Havlik R, Corti M: Blood pressure and mortality risk in older people: comparison between African Americans and whites. J Am Geriatr Soc 2001;49:375–381.
24 Murrell JR, Price B, Lane KA, Baiyewu O, Gureje O, Ogunniyi A, Unverzagt FW, Smith-Gamble V, Gao S, Hendrie HC, Hall KS: Association of apolipoprotein E genotype and Alzheimer disease in African Americans. Arch Neurol 2006;63:431–434.
25 Graff-Radford NR, Green RC, Go RC, Hutton ML, Edeki T, Bachman D, Adamson JL, Griffith P, Willis FB, Williams M, Hipps Y, Haines JL, Cupples LA, Farrer LA: Association between apolipoprotein E genotype and Alzheimer disease in African American subjects. Arch Neurol 2002;59:594–600.
26 Perry RT, Collins JS, Harrell LE, Acton RT, Go RC: Investigation of association of 13 polymorphisms in eight genes in southeastern African American Alzheimer disease patients as compared to age-matched controls. Am J Med Genet 2001;105:332–342.
27 Cornoni-Huntley J, Blazer D, Lafferty M, Everett D, Brock D, Farmer M (eds): Established Populations for Epidemiologic Studies of the Elderly: Resource Data Book. Bethesda, National Institute on Aging, 1990.
28 Pfeiffer E: A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. J Am Geriatr Soc 1975;23:433–441.
29 Rosow I, Breslau N: A Guttman health scale for the aged. J Gerontol 1966;21:556–559.
30 Douglas CE: Mortality differences by APOE genotype estimated from demographic synthesis. Genet Epidemiol 2002;22:146–155.
31 Rasbash J, Steele F, Browne W, Prosser B: A User's Guide to MLwiN Version 2.0. Bristol, University of Bristol, 2005.
32 Singer JD, Willett JB: Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. New York, Oxford University Press, 2003.
33 DeKosky ST, Marek K: Looking backward to move forward: early detection of neurodegenerative disorders. Science 2003;302:830–834.
34 Stewart R, Russ C, Richards M, Brayne C, Lovestone S, Mann A: Depression, APOE genotype and subjective memory impairment: a cross-sectional study in an African-Caribbean population. Psychol Med 2001;31:431–440.
35 Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W: Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144:73–81.
36 Spangler JG, Konen JC: Predicting exercise and smoking behaviors in diabetic and hypertensive patients. Age, race, sex, and psychological factors. Arch Fam Med 1993;2:149–155.
37 Lewis TT, Everson-Rose SA, Sternfeld B, Karavolos K, Wesley D, Powell LH: Race, education, and weight change in a biracial sample of women at midlife. Arch Intern Med 2005;165:545–551.
38 Gary TL, Baptiste-Roberts K, Gregg EW, Williams DE, Beckles GL, Miller EJ 3rd, Engelgau MM: Fruit, vegetable and fat intake in a population-based sample of African Americans. J Natl Med Assoc 2004;96:1599–1605.
39 Reusser ME, McCarron DA: Reducing hypertensive cardiovascular disease risk of African Americans with diet: focus on the facts. J Nutr 2006;136:1099–1102.
40 Markides KS, Martin HW: Predicting self-related health among the aged. Res Aging 1979;1:97–112.
41 Pettit JW, Kline JP, Gencoz T, Gencoz F, Joiner TE: Are happy people healthier? The specific role of positive affect in predicting self-reported health symptoms. J Res Pers 2001;35:521–536.
42 Pettit T, Livingston G, Manela M, Kitchen G, Katona C, Bowling A: Validation and normative data of health status measures in older people: the Islington Study. Int J Geriatr Psychiatry 2001;16:1061–1070.
43 Mossey JM, Shapiro E: Self-rated health: a predictor of mortality among the elderly. Am J Public Health 1982;71:800–808.
44 Fillenbaum GG, Blazer DG, Burchett BM, Saunders AM, Taylor DH Jr: Apolipoprotein E ε4 and risk of mortality in African American and white older community residents. Gerontologist 2002;42:381–386.