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The Joint Effect of Apolipoprotein E ε4 and MRI Findings on Lower-Extremity Function and Decline in Cognitive Function

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Background. Cognitive decline and poor physical function are risk factors for disability in old age and may occur more often in subjects with the apolipoprotein E ε4 (ApoE-ε4) allele. The objective of this study was to investigate the joint effect of ApoE-ε4 and structural changes detected on MRI brain scans on cognitive decline and lower-extremity function.

Methods. Brain MRI (1.5 T), neuropsychological tests, and lower-extremity physical function tests were administered to World War II male veteran twins ages 69 to 80. Quantification of MRI scans used a previously published algorithm to segment brain images into total cerebral brain (TCB), cerebrospinal fluid (CSF), and white-matter hyperintensity (WMH) volumes. A short battery of physical performance tests was used to assess lower-extremity function. Ten-year changes in performance on the Mini-Mental State Exam (MMSE), the Benton Visual Retention Test (BVRT), and the Digit Symbol Substitution (DSS) test were used to assess cognitive decline.

Results. For the sample as a whole, the comparison of subjects by median split of total cerebral brain volume found that those with brain volumes below the median performed worse on tests of gait and balance ($p < .01$) and experienced greater cognitive decline on the MMSE and BVRT cognitive test batteries (both $p < .01$). In addition, subjects with WMH volumes above the median had poor performance on the standing balance tasks and experienced greater decline on the DSS test ($p < .01$). Stratified analyses revealed that the joint effect of radiological findings and the ApoE-ε4 allele on cognitive decline and lower-extremity function was often greater than that expected from the separate effects combined.

Conclusions. We conclude that radiological findings in conjunction with ApoE-ε4 may single out a group at higher risk for dementia. We speculate that the observed interaction effect may be due to increased susceptibility to brain injury or impaired repair mechanisms in subjects with ApoE-ε4.

STUDIES of community-living elders have indicated that poor performance on neuropsychological and physical function tests is an important predictor of future adverse health outcomes, including disability, institutionalization, and all-cause mortality (1,2). Previous epidemiological studies have identified sociodemographic variables (e.g., age, gender, education) and chronic diseases (e.g., cardiovascular disease and neurological disorders) as major risk factors of physical disability and cognitive decline in the elderly population (3–5). Recently, an intensive search has begun for gene markers that may differentially influence brain aging. From a population perspective, however, brain aging can be viewed as the end result of cumulative effects of environmental insults acting on a broad population genetic potential for frailty at the end of the life cycle (6). The identification, therefore, of those individuals at high genetic risk for developing early disability and cognitive deficits has both clinical and public health importance, because these individuals could be offered preventive interventions and singled out for newly developed treatments (7).

A major genetic risk factor that has emerged as a potential marker of cognitive loss and Alzheimer's disease (AD) is the ε4 variant of the apolipoprotein E gene (8,9). Although the biological basis for the relationship of ApoE-ε4 with AD and cognitive decline is unknown, there is general agreement that presence of this allele increases the risk of developing dementia and lowers the mean age of onset of AD (10,11).

More recently, interest has also focused on the association of early observed changes in brain morphology as detected on MRI brain scans of normal geriatric patients and poor cognitive and physical function (12,13). Few studies, however, have examined the extent to which presence of the ApoE-ε4 allele influences these relationships (14). Given the association of ApoE-ε4 with AD, it is reasonable to expect that individuals with both the ApoE-ε4 allele and early signs of brain atrophy are at greater risk for physical and cognitive impairment.

We were able to test this hypothesis by using magnetic resonance imaging (MRI) volumetric data collected on a large sample of men who were genotyped for the apolipoprotein E gene and for whom longitudinal cognitive data and performance-based measures of lower-extremity function were available.

Subjects in the present study are male World War II veteran twins participating in the fourth examination cycle of the National Heart, Lung, and Blood Institute (NHLBI) Twin Study (15). The main objective of the present study was to determine the joint effect of MRI findings and the ApoE-ε4 allele on lower-extremity function and 10-year decline in cognitive function.

Methods

Study population.—The NHLBI Twin Study is a longitudinal study of cardiovascular disease (CVD) and associated CVD risk factors in 514 pairs of male twins, 254 monozygotic (MZ) and 260 dizygotic (DZ), born between 1917 and 1927 and 42 to 56 years old when first examined in 1969–72 (15). Three follow-up examinations, after 10, 16, and 25 years, assessed CVD status and collected repeat measurements of physiological, biochemical, and psychosocial risk factors (16). In the most recent follow-up (1995–97) of the NHLBI Twin Study, brain MRI and performance-based measures of lower-extremity function were added to the sequence of tests previously given to these subjects (17,18). Cognitive function was first assessed at the third cardiovascular exam of this cohort and repeated during the last exam. Analyses in the present study are limited to 414 individual twin subjects who participated in the fourth exam of this cohort and for whom MRI data were available.

Cerebral MRI scans and image analysis.—MRI (1.5 T) scanning on GE scanners was performed at four study sites using a conventional spin-echo, double-echo sequence in the axial orientation with TR = 2000, TE = 20/100, 24 cm field of view, and 5 mm contiguous slices from the vertex to the foramen magnum imaged in a 256×192 matrix and interpolated to 256×256 with one excitation. Axial images were angled to be parallel to the anterior commissure-posterior commissure line. After acquisition of the MRI scans, the digital information was transferred to a central location for processing and analysis by one of the authors (CD), who was blind to zygosity and medical history of subjects. Quantitative analysis of the MRI scans was performed with a custom-written program operating on a Sun Microsystems Ultra 1 workstation. Image evaluation was based on a semiautomated segmentation analysis that involves operator-guided removal of nonbrain elements, as previously described (19). For segmentation of brain parenchyma from cerebrospinal fluid (CSF), a difference image was created by the subtraction of the second-echo image from the first-echo image. Image intensity nonuniformities were then removed from the difference image, and the resulting corrected image was modeled as a mixture of two Gaussian probability functions (19,20). The segmentation threshold was determined at the minimum probability between the modeled CSF and brain matter intensity distribution (21). For segmentation of white-matter hyperintensity (WMH) from brain matter, the first- and second-echo images were summed, and, after removal of CSF and correction of image intensity nonuniformities, a lognormal distribution was fitted to the summed image data. A segmentation threshold for WMH was determined a priori as 3.5 standard deviations in pixel intensity above the mean of the fitted distribution of brain parenchyma. Intra- and interrater reliabilities of this method have been published (19).

Physical performance measures.—Performance measures were adapted from previously used measures (22) of lower-extremity function and were administered by a single interviewer at each of the four exam sites. To ensure uniformity of administration, interviewers were trained at SRI International by using a videotape that included detailed instructions for administering and scoring each of the tests.

Tests of standing balance included tandem, semi-tandem, and side-by-side stands. Participants began with the semi-tandem stand, in which the heel of one foot was placed to the side of the first toe of the other foot, with participants choosing which foot to place forward. Those unable to hold the semi-tandem position for 10 seconds were evaluated with the feet in the side-by-side position. Those able to maintain the semi-tandem position for 10 seconds were further evaluated with the feet in full tandem position, with the heel of one foot directly in front of the toes of the other foot.

To test walking speed, an 8-foot walking course, with no obstruction for an additional 2 feet at either end, was denoted. Participants were instructed to "walk to the other end of the course at usual speed, just as if you were walking down the street to go to your store." Each participant was timed for two walks, and the faster of the two was used in the present analyses.

To test the ability to rise from a chair (termed the chair stand), a straight-backed chair was placed next to a wall; participants were asked to fold their arms across their chest and to stand up from the chair one time. If successful, participants were asked to stand up and sit down five times as quickly as possible, and were timed from the initial sitting position to the final standing position at the end of the fifth stand.

Categories of performance were created for each set of performance measures to permit analyses that included those unable to perform a task. For the 8-foot walk and repeated chair stands, those who could not complete the task were assigned a score of 0. Those completing the task were assigned scores of 1 to 4, corresponding to the quartiles of time needed to complete the task in a large representative sample of older adults, and with the fastest times scored as 4. Similarly, the three tests of standing balance were considered as hierarchical in difficulty and were assigned a single score of 0 to 4. A summary performance scale was then created by summing the single-category scores for the 8-foot walk, chair stand, and standing balance tasks (22).

Neuropsychological measures.—Analyses in the present study are limited to three cognitive tests administered first in 1985–86 and again in 1995–97: (a) the 30-point Mini-Mental State Exam [MMSE; (23)], (b) the Digit Symbol Substitution (DSS) test from the Wechsler Adult Intelligence Scale-Revised (24), and (c) the Benton Visual Retention Test (BVRT), Administration A, Form C (25). The MMSE includes questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction. Although originally designed as a clinical screening test, the MMSE has been used extensively in epidemiological studies of elderly people. The DSS test is considered a measure of psychomotor speed that combines several cognitive and perceptual-motor functions, including sustained attention, visual perception, and short-term memory. In the BVRT, subjects are asked to reproduce a series of geometric designs after brief exposure to each.

The BVRT places emphasis on attention and short-term visual memory.

ApoE genotyping.—For apolipoprotein E structural locus genotyping, the polymerase chain reaction (PCR) was used to amplify 244-base-pair fragments that contain variant amino-acid residues 112 (cystine → arginine = ε4 allele) and 158 (arginine → cystine = ε2 allele). PCR products were then digested with the restriction enzyme Hhal and electrophoresed on an 8% polyacrylamide nondenaturing gel (26). With this technique, genotyping was available for 589 exam 4 participants, resulting in allele frequencies of ε2 = .09, ε3 = .76, and ε4 = .15, consistent with expected frequencies in other Caucasian populations (27).

Statistical analysis.—Prior to analyses, MRI brain volumes were adjusted for age and total cranial volume. ApoE-ε4 carriers were defined as homozygote or heterozygote for the ApoE-ε4 allele after exclusion of ε4ε2 heterozygotes. The relationship between MRI volumes and clinical outcomes was examined separately for lower-extremity physical function and cognitive decline. To investigate the joint effect of MRI volumes (total cerebral brain volume or WMH volume) and ApoE-ε4 on physical function and cognitive decline, we divided subjects into four subgroups: subjects without the ApoE-ε4 allele and brain volumes above the median (reference group); subjects without ApoE-ε4 and brain volumes below the median; subjects with ApoE-ε4 and brain volumes above the median; and subjects with ApoE-ε4 and brain volumes below the median. The significance of main effects and interactions was tested with a general linear model that adjusted for age, education, presence of cardiovascular disease, and baseline cognitive test scores.

For this report, subjects were treated as genetically unrelated individuals (i.e., all the available data from intact twin pairs and singletons were included in these analyses). Because a potential bias may exist in estimating the standard error of a regression coefficient calculated from a sample of nonindependent observations (i.e., twin pairs), we used bootstrap methods (28) to calculate an empirical estimate of the standard error. In critical cases, where the significance levels were marginal, we created 1,000 bootstrap data sets by resampling the data with replacement and using twin pairs as the unit of sampling. All analyses were conducted with the SAS statistical package (version 6.09).

Results

Mean age of twins was 72.3 (SD = 2.9) years when MRI scanned. Table 1 shows demographics, health histories, MRI volumes, cognitive change scores, and physical performance scores in individuals with and without the ApoE-ε4 allele. The exclusion of ε2ε4 subjects resulted in 82 (21%) men with ApoE-ε4 and 308 (79%) without this allele. MRI volumes were adjusted for age and head size, and 10-year change scores in cognitive performance were adjusted for age, education, and baseline scores. There was no significant difference between subgroups on age, education level, and lower-extremity function. Overall, the incidence of cardiovascular disease was higher among ApoE-ε4 carriers, reaching statistical significance for coronary heart disease (46.3% vs 32.8%, p = .02) and marginal significance for peripheral arterial disease (14.6% vs 7.8%, p = .06). On average, total cranial brain (TCB) volume was significantly smaller, and CSF volume was significantly larger in subjects with the ApoE-ε4 allele; no significant relationship, however, was observed between ApoE-ε4 and WMH volumes. Similarly, on average, ApoE-ε4 carriers showed greater declines in performance on DSS and MMSE tests but not on the BVRT battery (Table 1).

Table 2 shows the separate and joint relationship of MRI findings and ApoE-ε4 with performance on the 8-foot walk, the repeated chair stands, the standing balance tests, and the overall lower-extremity summary score. In the sample as a whole, subjects with brain volume below the median had significantly lower performance scores on the 8-foot walk, the standing balance tests, and the summary scale (all $p < .01$). Independently, those with WMH volumes above the median also scored significantly lower on the standing balance tests.

Stratified by ApoE-ε4, the data in Table 2 show that the relationship of TCB volume with performance on the 8-foot walk, the standing balance tests, and summary scale was significant regardless of ApoE genotype. However, subjects with both ApoE-ε4 and low brain volume scored the lowest on the summary scale, and the joint effect of ApoE-ε4 and low TCB was 1.6 times the sum of the separate effects combined (see Figure 1). Similarly, regardless of ApoE genotype, subjects with WMH volume above the median performed poorer on the standing balance task, with the joint effect of high WMH volume and ApoE-ε4 being 1.3 times the sum of the separate effects combined.

Table 3 summarizes the joint association of MRI findings and ApoE-ε4 with 10-year decline in performance on the DSS,

Table 1. Subject Characteristics by Presence or Absence of the ApoE-ε4 Allele, After Exclusion of ε2ε4 Genotypes

Characteristic	ApoE-ε4 Absent n = 308	ApoE-ε4 Present n = 82	p-value
Age, yr	72.5 (3.0)	71.9 (2.8)	.08
Education, yr	13.5 (3.0)	13.5 (3.7)	NS
Medical history (yes, no)			
Coronary heart disease	32.8%	46.3%	.02
Cerebrovascular disease	11.4%	13.4%	NS
Peripheral arterial disease	7.8%	14.6%	.06
MR volumes, cc			
Total cranial brain	953.2 (34.3)	942.0 (34.2)	.01
Cerebrospinal fluid	312.3 (34.0)	323.3 (34.0)	.01
White-matter hyperintensity	3.9 (5.7)	4.0 (5.6)	NS
Cognitive decline			
Digit Symbol Substitution	−3.1 (6.6)	−5.0 (6.7)	.02
Mini-Mental State Exam	−0.3 (2.4)	−0.9 (2.5)	.04
Benton Visual Retention	−0.5 (1.6)	−0.6 (1.6)	NS
Lower-extremity function			
8 foot walk, sec	2.6 (1.1)	2.4 (1.1)	NS
Standing balance, score	3.8 (0.5)	3.7 (0.5)	NS
Repeated chair stands, sec	2.5 (1.2)	2.6 (1.2)	NS
Summary performance score	8.8 (1.9)	8.6 (1.9)	NS

Notes: Standard deviation in parentheses; ns = not significant. MR volumes adjusted for age, education, and head size; cognitive decline adjusted for age, education, and baseline scores.

Table 2. Lower-Extremity Function Scores by Median Split of Brain Volumes and Presence of the ApoE-ε4 Allele, Adjusted for Age, Education, and Evidence of Clinical Stroke

	Total Sample			ApoE-ε4 Absent		ApoE-ε4 Present	
Measure	Low	High	Difference	Low	High	Low	High
TCB volume							
8-foot walk, sec	2.28	2.67	0.38**	2.47	2.71	2.11	2.63
Standing balance, score	3.66	3.86	0.20**	3.71	3.86	3.62	3.85
Repeated chair stands, sec	2.47	2.64	0.17	2.43	2.51	2.50	2.78
Summary performance, score	8.39	9.04	0.65**	8.54	9.05	8.22	9.04
WMH volume							
8-foot walk, sec	2.42	2.53	0.11	2.64	2.52	2.20	2.54
Standing balance, score	3.85	3.68	0.17**	3.86	3.71	3.84	3.64
Repeated chair stands, sec	2.68	2.43	0.25	2.47	2.45	2.89	2.40
Summary performance , score	8.87	8.55	0.32	8.91	8.65	8.82	8.45

**$p < .01$, *$p < .05$, for difference in adjusted mean scores comparing subjects below and above the median of MRI brain volume.

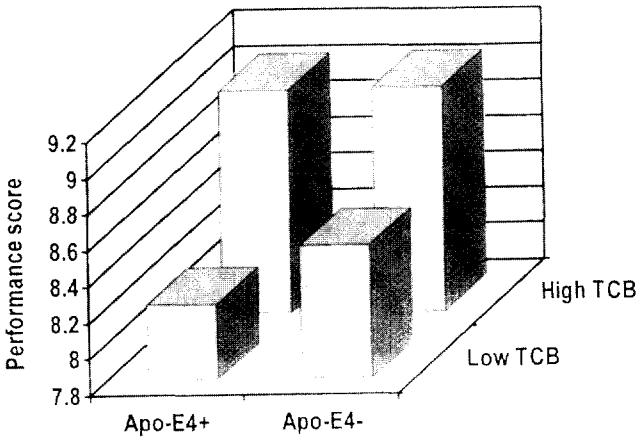

Figure 1. Overall mean lower-extremity summary score, by ApoE-ε4 and low (below median) and high (above median) total cranial brain volume (TCB). Results obtained after adjustment of performance ratings for age, education, and history of cerebrovascular disease. Adjusted mean of subjects with the ApoE-ε4 allele and low brain volume was significantly lower than values obtained in all other subgroups.

MMSE, and BVRT cognitive function tests. After adjustment for age, education, baseline performance scores, and clinical evidence of stroke, there was a significant relationship between low brain volume and decline on the MMSE and BVRT tests (column 3, Table 3). Stratified by ApoE-ε4, the data in Table 3 show that this relationship was significantly affected by the presence of the ApoE-ε4 allele. For example, in ApoE-ε4 carriers, the difference in change scores on the MMSE between those with low and high brain volumes was −1.67 and significant, whereas in noncarriers the difference was 0.14 and not significant (Figure 2). Because the joint effect of low TCB and ApoE-ε4 was sixfold that of the sum of the separate effects combined, we have evidence of a significant interaction effect ($F = 6.2, p < .02$). The presence of an interaction effect was also found for 10-year decline on BVRT ($F = 12.2, p < .001$), where the joint effect of ApoE-ε4 and low TCB was fivefold the sum of the separate effects combined.

Finally, subjects with WMH volume above the median experienced a significantly greater decline on the DSS test, which was also magnified in those with the ApoE-ε4 allele. In ApoE-ε4 carriers, the difference between those with high and low WMH volume is −3.96 and significant, whereas in noncarriers the difference is −1.38 and not significant (see Table 3, Figure 3). Jointly, the effect of high WMH volume and ApoE-ε4 is also 3.3 times that of the sum of the separate effects combined.

Discussion

Subjects in this study are male World War II veteran twins, tested repeatedly for cognitive function over 10 years of adult life and aged 69 to 80 years when MRI brain-scanned and assessed for lower-extremity physical function. We found for this sample of community-living elderly men that structural changes on MRI in conjunction with presence of the ApoE-ε4 allele may single out a group at higher risk for cognitive and physical impairment in old age.

Specifically, longitudinal analyses of the cognitive data revealed that subjects with brain volumes below the median and the ApoE-ε4 allele experienced the greatest decline on the MMSE and BVRT, whereas those with WMH volumes above the median and who were ApoE-ε4 carriers experienced the greatest decline on the DSS test. Similarly, from cross-sectional analyses of the physical function data we found that subjects with radiological findings and ApoE-ε4 had the poorest lower-extremity function. These results were independent of other risk factors including age, education level, and history of cardiovascular disease.

Measures of cerebral atrophy similar to those used in the present study are widely accepted as sensitive indicators of brain aging and have been previously linked with physical dysfunction and cognitive decline in elderly subjects (12,29,30). The extent, however, to which presence of the ApoE-ε4 allele modifies the association between MRI findings and physical and cognitive function has not been studied extensively. We know of three community-based studies of older adults in which the relationship of ApoE-ε4 to MRI findings and cognitive performance has been investigated (14,31,32). In two of these studies (31,32), no significant relationship was found between ApoE-ε4 and MRI measures of brain atrophy. The third and largest population-based MRI study found independent relationships of ApoE-ε4 and MRI findings to poor cognitive performance (14), but did not attempt to study the presence of interaction effects.

Table 3. 10-Year Decline in Cognitive Function by Median Split of Brain Volumes and by Presence of the ApoE-ε4 Allele, Adjusted for Age, Education, Baseline Test Scores, and Evidence of Clinical Stroke

	Total Sample			ApoE-ε4 Absent		ApoE-ε4 Present	
Measure	Low	High	Difference	Low	High	Low	High
TCB volume							
Digit Symbol Substitution	–4.39	–3.79	–0.60	–3.67	–2.51	–5.09	–4.99
Mini-Mental State Exam	–1.07	–0.16	–0.90**	–0.38	–0.25	–1.75	–0.08
Benton Visual Retention	–0.71	–0.40	–0.31*	–0.68	–0.29	–1.14	–0.12
WMH volume							
Digit Symbol Substitution	–2.73	–5.40	–2.67**	–2.40	–3.78	–3.06	–7.02
Mini-Mental State Exam	–0.40	–0.83	–0.43	–0.10	–0.53	–0.70	–1.13
Benton Visual Retention	–0.55	–0.57	–0.02	–0.35	–0.62	–0.75	–0.51

**$p < .01$, *$p < .05$, for difference in adjusted change scores comparing subjects above and below the median total cranial volume.

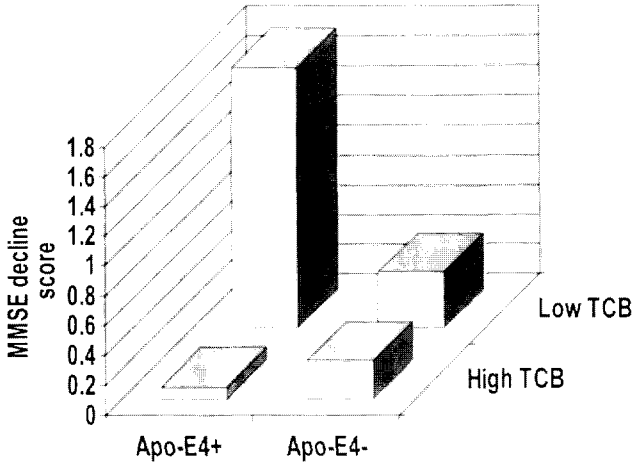

Figure 2. Mean decline on the Mini-Mental State Exam, by ApoE-ε4 and low (below median) and high (above median) total cranial brain volume (TCB). Results obtained after adjustment of change scores for age, education, history of cerebrovascular disease, and baseline score. Mean decline on MMSE for subjects with low brain volume and the ApoE-ε4 allele was significantly larger than those observed in all the other subgroups.

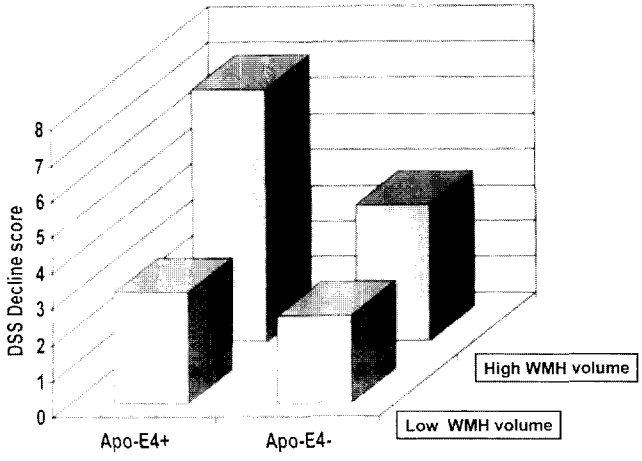

Figure 3. Mean decline on the Digit Symbol Substitution test, by ApoE-ε4 and low (below median) and high (above median) white-matter hyperintensity (WMH) volume. Results obtained after adjustment of change scores for age, education, history of cerebrovascular disease, and baseline score. Mean decline on DSS for subjects with high WMH volume and the ApoE-ε4 allele was significantly greater than those observed in all the other subgroups.

Likewise, a handful of studies have investigated the relationship of abnormalities detected on MRI to lower-extremity function. Sudarsky and Ronthal (33) found computed tomography (CT) measurements of ventricular enlargement to be significantly greater in 30 patients with gait disorders than in 28 age-matched controls with normal gait. Hendrie and colleagues (34) found no statistically significant association between the presence of white-matter lesions and poor gait, balance, and neuromuscular function; however, Baloh and associates (35) found that patients with abnormalities of gait and balance had significantly more subcortical white-matter hyperintensities on MR imaging than did a matched normal control group. More recently, using MRI data collected in the Cardiovascular Health Study, Tell and colleagues (13) reported a significant association between white-matter disease and poor performance on tests of balance. Unfortunately, the role of ApoE-ε4 in the above associations was not examined.

A potentially confounding variable in this type of study is the role of cardiovascular disease. ApoE-ε4 is a known risk factor for arteriosclerosis, and evidence for the presence of synergistic effects between ApoE-ε4 and CVD on decline in cognitive function and increased risk for developing Alzheimer's disease has been reported (36,37). In separate analyses of these data we focused on the joint relationship of ApoE-ε4 and CVD on brain atrophy and WMH volume (38). We found that ApoE-ε4 carriers with clinical manifest CVD had the largest reduction in brain volume and greatest increase in WMH volume. The enhanced effect, however, of ApoE-ε4 was observed in subjects with CVD but not in those without disease.

To speculate on the possible mechanisms involved in the negative effects of ApoE-ε4 on brain structure and function, a number of known functions of the ApoE gene may be contributing factors. ApoE is the primary apolipoprotein in the brain, produced by astrocytes and oligodendrocytes, and can affect brain function through different pathways: (a) ApoE helps to maintain the dendritic cytoskeleton, as shown by homozygous ApoE deficient mice that display significant loss of synapses and marked dendritic disruption with age (39); (b) it

has an antioxidant effect (ε3 being more efficient than ε4), which may protect neurons (40); (c) presence of the ApoE-ε4 allele encourages the deposition of amyloid-β protein, which is known to damage endothelial cells by producing superoxide radicals (41); (d) ApoE-ε4 has been associated with decreased choline acetyltransferase (ChAT) activity in the cortex (42) or diminished neuronal activity in the nucleus basalis of Meynert seen in patients with Alzheimer's disease (43). Thus, compared to non–ApoE-ε4 carriers who are able to compensate for neuronal injury with an efficient reinnervation process, those with the ApoE-ε4 allele seem to lack important constituents necessary for this process.

The present data also suggest that WMH-related ApoE-ε4 impairment of brain function may be different from impairment resulting from brain atrophy. We found that ApoE-ε4 carriers with WMH volumes above the median had poorer postural control and the largest 10-year decline on a test of psychomotor speed (DSS), whereas ApoE-ε4 carriers with low brain volumes had overall poorer lower-extremity function and the largest decline in global cognitive function as assessed by the MMSE. This dichotomy may reflect differences in pathophysiologic processes mediated by the presence of ApoE-ε4. Whereas the reduction in brain volume and decline in global physical and cognitive functioning in ApoE-ε4 carriers may single out a group at higher risk for Alzheimer's disease, poor postural control and decline in psychomotor speed may be indicators of disrupted frontal-subcortical circuits caused by white matter changes (44).

Finally, given the fact that inheritance of ApoE-ε4 and brain atrophy are both associated with Alzheimer's disease, we repeated our analyses excluding subjects with MMSE scores less than 23. We found that qualitatively the results were the same in support of our previous conclusion that structural brain changes on MRI in ApoE-ε4 presymptomatic individuals may single out the subgroup at highest risk for AD. We are currently conducting repeat MRI testing in subjects of this cohort that will allow for further examination of how early changes on MRI progress over time in subjects with and without ApoE-ε4.

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