

# Apolipoprotein E Genotype and Age-Related Myelin Breakdown in Healthy Individuals

## Implications for Cognitive Decline and Dementia

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**Context:** Apolipoprotein E (APOE) genotype is the most influential Alzheimer disease (AD) risk factor after advanced age. The APOE4 alleles decrease and the APOE2 alleles increase age at onset of AD. Human and nonhuman primate data suggest that in midlife, the structural integrity of myelin sheaths begins breaking down, with an accelerating age-related trajectory most evident in the brain's later-myelinating association regions. This may result in a progressive "disconnection" of widely distributed neural networks that may underlie the age risk factor for AD.

**Objective:** To assess, using magnetic resonance imaging, whether the shift in age at onset of AD observed with the APOE genotype is associated with the trajectory of age-related myelin breakdown.

**Design:** Cross-sectional.

**Setting:** Metropolitan university medical center.

**Participants:** Healthy individuals (N=104) aged 55 to 75 years who underwent genotyping for APOE.

**Main Outcome Measures:** Calculated transverse relaxation rates, an indirect measure of white matter struc-

tural integrity, for late-myelinating frontal lobe white matter (Fwm) and early- and later-myelinating regions of the corpus callosum, the splenium (Swm) and the genu (Gwm).

**Results:** The presence of the protective APOE2 allele was associated with significantly higher relaxation rates in Fwm and Gwm but not in Swm. Furthermore, APOE status impacted the trajectory of age-related myelin breakdown in late-myelinating regions (Fwm and Gwm) but not in Swm. In Fwm and Gwm, APOE4+ individuals had a steeper slope of decline in relaxation rates with age than APOE2+ individuals; those with APOE3/3 alleles had an intermediate slope.

**Conclusions:** In later-myelinating regions, the severity and rate of myelin breakdown in healthy older individuals are associated with APOE status and support the hypothesis that this process may contribute to age at onset of AD. Combining APOE status with noninvasive measures of myelin breakdown may be useful in assessing treatment strategies for the primary prevention of AD.

*Arch Gen Psychiatry.* 2006;63:63-72

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**T**HE PROTRACTED MYELINATION of the human brain results in a generally quadratic (inverted U) trajectory of myelin content, reaching a maximum in midlife and then declining in older age.<sup>1,2</sup> The extensive scope of myelination is arguably the most uniquely human aspect of the brain<sup>3,4</sup>; it results in the high processing speeds that underlie our cognitive functions, and it is extremely vulnerable during brain development and degeneration.<sup>5</sup> The relationships among myelin breakdown, subsequent "disconnection," and various risk factors for age-related neurodegenerative diseases have not been well explored.

Oligodendrocytes (the cells that produce myelin) and their precursors are ex-

ceptionally vulnerable to a variety of developmental abnormalities and toxic insults, including those caused by  $\beta$ -amyloid fibrils.<sup>6</sup> The developmental process of myelination continues until midlife and produces a continuum of increasingly vulnerable oligodendrocytes in the later-myelinating association regions, such as the frontal lobes.<sup>3,7-9</sup> In primates, these later-differentiating oligodendrocytes ensheath increasing numbers of axons with smaller axon diameters,<sup>10,11</sup> and these myelin sheaths are differentially lost with age (27%-45% reductions).<sup>1,12,13</sup> Thus, during development, the myelination process produces a more or less bilaterally symmetrical continuum of oligodendrocyte vulnerability that in older age, under the influence of multiple risk factors, manifests as a progres-

**Table 1. Demographic, Health, and Cognitive Variables by APOE Group\***

	APOE2/3 (n = 12)	APOE3/3 (n = 70)	APOE3/4 or 4/4 (n = 20)	F	P Value
Demographic variables					
Age, mean (SD), y	67.3 (5.2)	66.1 (5.2)	65.6 (5.0)	0.43	.65
Education, mean (SD), y	14.7 (2.5)	15.5 (2.4)	15.7 (2.5)	0.69	.51
Sex, M/F, No.	6/6	24/46	9/11	1.55†	.46
Health variables, No.‡					
Hypertension	0	2	0	NA	NA
Elevated cholesterol	0	2	0	NA	NA
Diabetes mellitus	0	0	0	NA	NA
Cardiovascular disease	0	0	0	NA	NA
Cerebrovascular disease	0	0	0	NA	NA
Peripheral vascular disease	0	1	0	NA	NA
Cognitive variables					
MMSE score, mean (SD)§	28.3 (1.0)	28.7 (1.0)	28.7 (1.1)	0.41	.67
CVLT long delay score, mean (SD)	12.0 (1.2)	11.5 (2.6)	11.0 (2.6)	0.26	.77

Abbreviations: APOE, apolipoprotein E; CVLT, California Verbal Learning Test; MMSE, Mini-Mental State Examination; NA, not applicable.

\*There were no participants with the APOE2/2 genotype. Two participants with the APOE2/4 genotype are not included because the sample size was too small for meaningful analyses, they had no positive health variables, and their inclusion in either the APOE2+ or the APOE4+ subgroup does not meaningfully alter the remaining results in the table.

† $\chi^2$  Test.

‡For meaningful interpretation of  $\chi^2$  analyses, each cell should have at least 5 participants as opposed to most having zero in this healthy population.

§Participants with elevated cholesterol levels and hypertension were well controlled with treatment.

¶For the MMSE, 7 participants with APOE2/3, 46 with APOE3/3, and 12 with APOE3/4 or 4/4 were included.

||For the CVLT, 5 participants with APOE2/3, 24 with APOE3/3, and 8 with APOE3/4 or 4/4 were included.

sive pattern of myelin breakdown that recapitulates the developmental process of myelination in reverse.<sup>5,14</sup>

Bartzokis<sup>5,9</sup> hypothesized that many of the risk factors associated with Alzheimer disease (AD), such as elevated brain cholesterol and iron levels, head trauma, and apolipoprotein E (APOE) alleles, may impact age-related myelin breakdown and thus contribute to the ultimate manifestations of degenerative disorders in older age. Postmortem and in vivo data<sup>15-20</sup> indicate that individuals with AD have more severe myelin breakdown than matched controls in the absence of gross axonal damage.

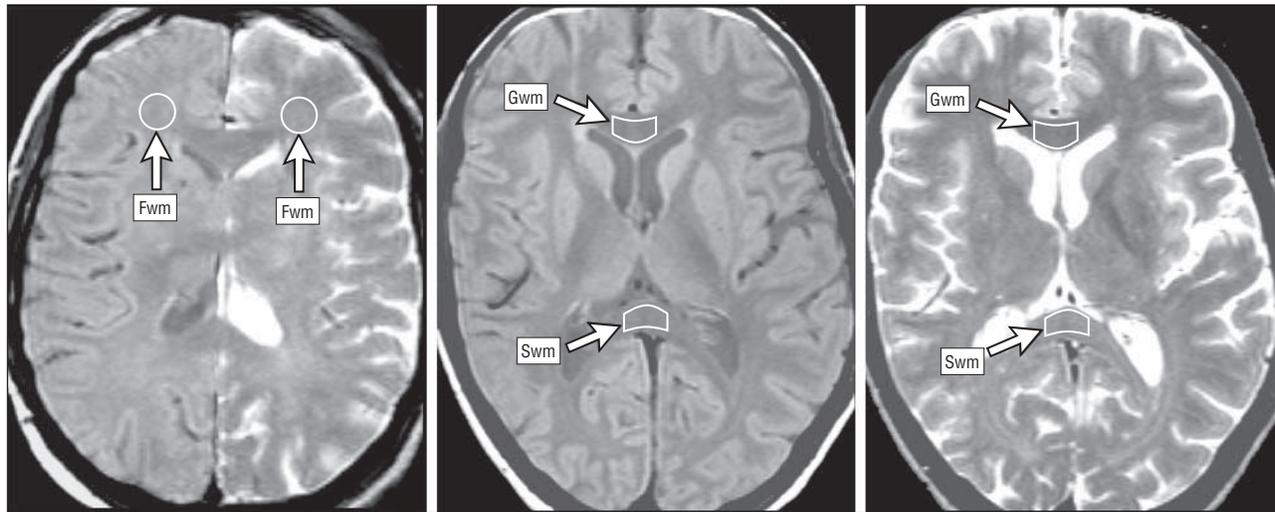
The breakdown in the structural integrity of myelin sheaths can be indirectly measured in vivo using magnetic resonance imaging (MRI) and transverse relaxation rate ( $R_2$ ) measures that are markedly sensitive to small changes in the amount of tissue water.<sup>21</sup> Results of ultrastructural electron microscopy studies<sup>19,22</sup> demonstrate that age-related myelin breakdown results in microvacuolations consisting of splits of myelin sheath layers that create microscopic fluid-filled spaces that increase MRI "visible" water and thus decrease  $R_2$ . These microvacuolations are ultrastructurally similar to reversible myelinopathies produced by certain toxins.<sup>22-25</sup> Animal studies<sup>23-27</sup> have confirmed that this type of myelin breakdown can be detected using MRI in circumscribed susceptible regions and that the histopathologic changes produced by toxins and the recovery process can be tracked by means of MRI. Although  $R_2$  has not been directly correlated with myelin breakdown due to normal aging (as opposed to the reversible toxin-induced myelin breakdown described above), in humans and primates, healthy aging is not associated with neuronal loss,<sup>28-30</sup> whereas the process of myelin breakdown and loss has been thoroughly demonstrated,<sup>1,12,13,22,31-34</sup> and herein the term *myelin breakdown* will be used to refer to the  $R_2$  findings.

After advanced age itself, APOE status is the strongest risk factor for AD.<sup>35</sup> Apolipoprotein E 4 increases and APOE2 decreases the risk of AD primarily by affecting age at onset of disease.<sup>35,36</sup> We tested the hypothesis that APOE status may impact age at onset of AD and assessed whether these alleles affect the process of age-related myelin breakdown. Specifically, we assessed whether in healthy older individuals the APOE4 allele increases and the APOE2 allele decreases age-related myelin breakdown.

## METHODS

### PARTICIPANTS

The healthy volunteers participating in the study were older than 55 years, were recruited from the community and hospital staff for a study of healthy aging, and were first evaluated using MRI and later underwent APOE genotyping. Potential participants were excluded if they had a history of neurologic disorder or a family history of AD or other neurodegenerative disorders, psychiatric illness (including drug or alcohol abuse), or head injury resulting in loss of consciousness for longer than 10 minutes. Individuals were excluded if they were obese or if they had a current or previous serious illness or a medical history of diabetes mellitus, cardiovascular disease, or difficult-to-control hypertension. Medication use was ascertained, and only 2 participants were taking medications for any of the previously mentioned conditions (**Table 1**). They were independently functioning and had no evidence of neurocognitive impairment or gross neurologic abnormalities on clinical interview and brief neurologic examination performed by the first author (G.B.). The final population of 111 individuals included none older than 75 years with an APOE4 allele. Analyses were thus based on 104 individuals younger than 76 years. There were 63 women and 41 men in the sample; 78 (75%) were white, 18 (17%) were Asian, 6 (6%) were black, and 2 (2%) were Hispanic.



**Figure 1.** White matter regions of interest (ROIs). Used together, the early-echo (echo time [TE], 20 milliseconds) (left side of left panel and middle panel) and late-echo (echo time, 90 milliseconds) (right side of left panel and right panel) axial images maximize contrast needed for optimal ROI definition. Frontal lobe white matter (Fwm): The ROI is manually edited to exclude any hyperintensities or gray matter. For the genu and splenium corpus callosum regions (Gwm and Swm, respectively), a standard rectangular ROI template is positioned on the midline followed by manual editing of the anterior and posterior borders to exclude non-corpus callosum tissue. Lateral borders are defined by the dimensions of the rectangular template. Gwm and Swm ROIs are usually on different slices. Gwm: Slice choice (see text) results in a sample consistently in the middle of the structure. Swm: Slice choice (see text) results in a sample in the lower half of the splenium, which contains predominantly primary sensory (visual) fibers.

Of these 104 participants, 67 were administered the Mini-Mental State Examination (MMSE). Their scores ranged from 27 to 30 (mean  $\pm$  SD score,  $28.6 \pm 1.0$ ). The 37 participants without MMSE scores were administered a relatively brief battery of neuropsychologic tests, assessing a variety of independent cognitive abilities, including memory for verbal and visual material (the California Verbal Learning Test and the Benton Visual Retention Test), which is likely to be sensitive to the effects of dementia, and the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised, often considered a global measure of brain integrity. None of the scores were in the impaired range based on published normative scores.<sup>37-39</sup>

### MRI PROTOCOL

All the participants underwent imaging using the same 1.5-T MRI instrument and the same imaging protocol, and image timing was irrespective of demographic (eg, age and sex) and genotypic variables. Details of the protocol have been published previously<sup>18,19</sup> and will only be summarized herein. Two pilot sequences were obtained to specify the location and spatial orientation of the head and the position of the axial image acquisition grid. A coronal pilot spin-echo image (repetition time, 100 milliseconds; echo time [TE], 30 milliseconds; number of excitations, 1; and thickness, 10 mm) was used to align the subsequent sagittal pilot images. The middle slice of the sagittal pilot images was aligned on the coronal pilot image to obtain a true midsagittal image of the brain. After the sagittal pilot spin-echo images (repetition time, 550 milliseconds; TE, 26 milliseconds; number of excitations, 2; and thickness, 5 mm) were acquired, the midsagittal image was used to position the axial image acquisition grid. The axial image acquisition sequence acquired interleaved contiguous slices using a Carr-Purcell-Meiboom-Gill dual spin-echo sequence (repetition time, 2500 milliseconds; echo time, 20 and 90 milliseconds; number of excitations, 2; slice thickness, 3 mm; view matrix,  $256 \times 192$ ; and field of view, 25 cm).

### IMAGE ANALYSIS

Transverse relaxation time ( $T_2$ ) was calculated for each voxel using an automated algorithm from the 2 signal intensities (TE, 20 and 90 milliseconds) of the robust dual spin-echo sequence that used  $90^\circ$  refocusing pulses to produce grayscale-encoded  $T_2$  maps of the brain<sup>40</sup> that were not normalized. The  $T_2$  measures were extracted using a configured image analysis workstation (Macintosh; Apple Computer Inc, Cupertino, Calif). A single rater, who was masked to clinical information, performed all the measurements. The image analysis software permitted the rater to delineate the region of interest (ROI) using a computer mouse.

For all 3 regions, 2 contiguous slices were chosen for analysis. For analysis of the frontal lobe white matter (Fwm), a circular ROI sample of supraorbital white matter was placed manually by the rater in the Fwm on the second and third contiguous slices above the last image containing the orbitofrontal cortex.<sup>18</sup> For analysis of the genu of the corpus callosum (Gwm), the 2 slices on which the angle formed by the left and right sides of the genu appeared the most linear were chosen to obtain a sample that would be consistently in the middle of the structure, which contains primarily fibers connecting the prefrontal cortices.<sup>19</sup> For the splenium of the corpus callosum (Swm), the second and third lowest slices on which the fibers of the splenium connected in the midline were chosen to sample primarily the lower half of the splenium, which contains predominantly primary sensory (visual) fibers.<sup>10,11</sup> For both structures, a rectangular ROI template centered along the midline of each region was positioned manually by the rater (**Figure 1**).

Once the choice of slices and position of the ROI were completed, the rater used the gray matter/white matter contrast of the early-echo (TE, 20 milliseconds) and late-echo (TE, 90 milliseconds) images to ensure that the ROI did not include gray matter regions of the central sulcus,  $T_2$  hyperintensities, or other hyperintense structures, such as periventricular halos.<sup>18,19</sup> The ROIs thus contained normal-appearing white matter free of  $T_2$  hyperintensities (Figure 1). The ROIs were then transferred onto the corresponding  $T_2$  maps. All voxels that had a  $T_2$  value above

the right side inflection point of the histogram of the ROI were removed to ensure that partial volume with cerebrospinal fluid structures was eliminated.<sup>40</sup>

The  $T_2$  data for each ROI were obtained from contiguous pairs of slices. The  $R_2$  was calculated as the reciprocal of  $T_2 \times 1000$ . The average  $R_2$  of the 2 slices from both hemispheres were the final measures used in the subsequent analyses. Reliability using the intraclass correlation coefficient ( $R_{xx}$ ) was very good (Fwm:  $R_{xx}=0.91$ ,  $F_{1,12}=21.3$ ; Gwm:  $R_{xx}=0.99$ ,  $F_{1,11}=138.0$ ; and Swm:  $R_{xx}=0.95$ ,  $F_{1,11}=20.5$ ;  $P<.001$  for all).<sup>18,19</sup>

## STATISTICAL ANALYSIS

Demographic and cognitive variables were compared among *APOE* subgroups using 1-way analysis of variance. For dichotomous variables, such as sex and MMSE score (participants were divided into those who scored  $\leq 28$  on the MMSE and those who scored  $> 28$ ),  $\chi^2$  analyses were performed to detect any significant differences in frequency distribution of the dependent variables among the 3 *APOE* subgroups. The relationship between the  $R_2$  of the 3 white matter regions and frontal gray matter volume was explored using the Pearson product-moment correlation.

The data analyses focused on 2 issues: the age-adjusted effects of *APOE2* and *APOE4* on  $R_2$  in the Fwm, Gwm, and Swm regions and the effects of these 2 alleles on the aging trajectories themselves in each of the 3 regions. Data on *APOE3* were not analyzed because only 4 participants were without any *APOE3* allele. Seven individuals 76 years and older were excluded from the analyses because inspection of the age distributions stratified by *APOE4* revealed no individuals older than that age. Analyses were thus based on 104 participants aged 55 to 75 years consisting of 63 women and 41 men. Preliminary analyses were performed including sex as a predictor, but  $P>.10$  for all involving effects of sex, so it was dropped from the models to simplify the interpretation and presentation of the results.

To evaluate the overall age-adjusted effects of the alleles on  $R_2$ , analyses of covariance controlling for age were performed using the presence of *APOE2* and *APOE4* as the grouping variable and  $R_2$  values in the 3 regions as the dependent variables. Age was highly associated with  $R_2$ , so including it in the covariance analyses markedly increased statistical power. However, in this healthy sample, age was not associated with the presence of either *APOE2* ( $r_{102}=-0.02$ ;  $P=.86$ ) or *APOE4* ( $r_{102}=-0.12$ ;  $P=.21$ ), so the adjusted means were very close to the unadjusted means, and only the unadjusted means (and SDs) are reported herein. Standardized mean differences (effect sizes or Cohen  $d$ ) were calculated using the square root of the analysis of covariance error term and are interpreted with reference to Cohen's (1988) conventional values. For these analyses of slope differences, effect sizes were estimated by translating the  $t$  tests for the interaction parameter into equivalent values of  $d$  when  $P<.50$ . To evaluate possible effects of the 2 alleles on aging trends, separate multiple regression analyses were performed for each allele on  $R_2$  values in each region, including linear effect of age, allele presence (present vs absent), and the interaction term. The  $t$  tests for within-group age slopes of  $R_2$  (ie, change per year) in each region were performed using pooled error degrees of freedom from the regression model. Comparisons of the aging slopes for *APOE2+* vs *APOE4+* participants were performed using multiple regression analyses in each of the 3 regions. The tests reported herein are for interaction terms that tested the change in aging slope associated with *APOE4+* relative to *APOE2+* (effects on the intercepts are not reported). Only 2 participants had both *APOE2* and *APOE4* alleles. These 2 individuals were excluded from the analyses, so

the *APOE2+* vs *APOE4+* comparison groups were mutually exclusive. The average of the left and right frontal lobe  $R_2$  measures is shown for simplicity of presentation because the lateralized findings were not meaningfully different than the averaged results. Significance tests are unadjusted for multiple comparisons and are reported to be statistically significant at  $P=.05$  (2-tailed).

## RESULTS

As summarized in Table 1, the *APOE* subgroups (*APOE2/3*, *APOE3/3*, and *APOE3/4* or *APOE4/4*) did not differ in age, education, or sex and were very healthy, with minimal vascular risk factors. Pearson correlation analysis did not reveal any significant relationship between age and education for the entire study sample ( $P=.55$ ) or any of the *APOE* subgroups ( $r<0.30$ ;  $P=.35$  for *APOE 2/3*,  $P=.96$  for *APOE 3/3*, and  $P=.84$  for *APOE3/4* or *APOE4/4*).

In these healthy individuals, MMSE scores did not differ meaningfully among the *APOE* groups. A  $\chi^2$  analysis examining the distribution of genotypes across the MMSE scores of those who scored 28 and less did not reveal any significant genotype differences ( $\chi^2=1.69$ ;  $P=.43$ ). For the 37 participants without MMSE data, the California Verbal Learning Test delayed free recall score was examined, and although the performances were generally in the expected direction (ie, best scores in the *APOE2/3* group and worst scores in the *APOE3/4* and *APOE4/4* group), the relationship was not statistically significant (Table 1).

Fourteen individuals in the present sample were also part of a contemporaneous study<sup>2</sup> that examined frontal lobe volumes, and we assessed whether gray matter atrophy may be associated with the 3 white matter  $R_2$  measures. Pearson correlation analyses showed no significant relationships between  $R_2$  and gray matter volumes ( $r_{12}=-0.10$ ;  $P=.73$ ).

Analyses of the age-adjusted effects of *APOE2+* and *APOE4+* are summarized in **Table 2** and graphically presented in **Figure 2**. Presence of the *APOE2* allele was associated with significantly higher  $R_2$  values in Fwm and Gwm but not in Swm. The *APOE2+* standardized mean differences (effect sizes) were relatively large. The presence of the *APOE4* allele was not associated with  $R_2$  in any region, and the effect sizes were small.

Analyses of age-related change are summarized in **Table 3**. The presence of *APOE2* was associated with significantly less decline per year in  $R_2$  in Fwm. Participants without the *APOE2* allele showed significant declines in Fwm and Gwm, whereas *APOE2+* participants did not. None of the analyses indicated significant differences in rates of change as a function of *APOE4*, although as Table 3, **Figure 3**, and **Figure 4** document, there was a general age-related decline in  $R_2$  in Fwm and Gwm regardless of *APOE4* allele status (as noted previously herein, this was markedly and significantly less true for the *APOE2+* group).

Figure 4 depicts the linear aging slopes between *APOE2+* and *APOE4+* individuals (these were mutually exclusive groups because of the exclusion of 2 participants with both alleles). Tests comparing the linear aging slopes depicted in Figure 4 revealed a significant difference only in Fwm  $R_2$  (slope for *APOE2+*/*APOE4+*

**Table 2. Age-Adjusted Mean (SD) Relaxation Rates by the Presence of *APOE2* and *APOE4* Alleles in 3 White Matter Regions**

Region	<i>APOE</i> Status*		Difference Between Groups		
	Absent	Present	ANCOVA $F_{101}$	<i>P</i> Value	Effect Size†
<b><i>APOE2</i> Allele</b>					
Fwm	15.65 (0.55)	15.97 (0.39)	5.39	.02	0.69
Gwm	15.87 (0.53)	16.24 (0.35)	7.59	.007	0.81
Swm	14.24 (0.55)	14.34 (0.43)	0.44	.51	0.19
<b><i>APOE4</i> Allele</b>					
Fwm	15.68 (0.50)	15.76 (0.68)	0.0	>.99	0.17
Gwm	15.92 (0.49)	15.91 (0.63)	0.55	.46	-0.02
Swm	14.24 (0.54)	14.28 (0.47)	0.0	.98	0.08

Abbreviations: ANCOVA, analysis of covariance; *APOE*, apolipoprotein E; Fwm, frontal lobe white matter; Gwm, genu of corpus callosum white matter; Swm, splenium of corpus callosum white matter.

\*The *APOE2* allele was absent in 90 participants and present in 14; the *APOE4* allele was absent in 82 participants and present in 22.

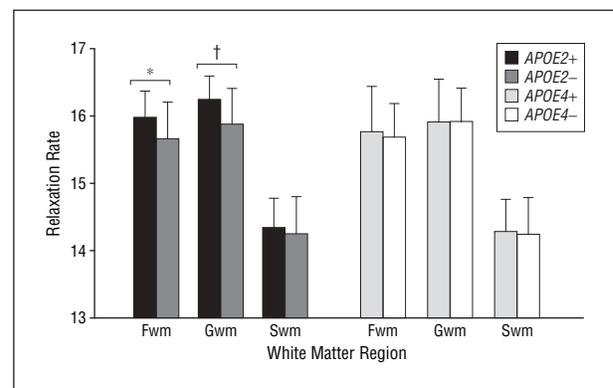
†Effect size conventions: 0.20 indicates small; 0.50, medium; and 0.80, large.

$= -0.002 \pm 0.023$ ,  $t_{10} = -0.09$ ;  $P = .93$ ; slope for *APOE4*+/+ *APOE2*- =  $-0.086 \pm 0.024$ ,  $t_{18} = -3.47$ ;  $P = .003$ ; difference in slopes =  $0.084 \pm 0.037$ ,  $t_{28} = -2.30$ ;  $P = .03$ ). This difference did not reach statistical significance in Gwm ( $t_{28} = -1.53$ ;  $P = .14$ ) and was absent in Swm ( $t_{28} = 0.71$ ;  $P = .48$ ). In the Fwm and Gwm regions, the linear aging slopes for individuals with the *APOE3/3* genotype were intermediate between the *APOE2*+ and *APOE4*+ genotypes but not significantly different from them.

### COMMENT

This is the first study to demonstrate that the *APOE* genotype can impact the trajectory of age-related myelin breakdown in healthy older individuals. In late-myelinating regions, individuals with the *APOE4* genotype had a steeper slope of decline in  $R_2$  with age than participants with the *APOE2* genotype, whereas the *APOE3/3* homozygotes had an intermediate slope. These observations are consistent with the hypothesis that later-myelinating regions are more susceptible to myelin breakdown and that this process causes a progressive disconnection of widely distributed neural networks that results in cognitive decline and contributes to the age risk factor for AD.<sup>5,9</sup> The data further show that the *APOE* genotype is significantly associated with vulnerability to age-related myelin breakdown, raising the possibility that *APOE* shifts the age at onset of AD by affecting this process.

Published studies examining the effect of the *APOE* genotype on age-related cognitive decline in groups of asymptomatic healthy older individuals are consistent with this interpretation of our imaging data. The presence of an *APOE2* allele seems to mitigate against cognitive decline,<sup>41-43</sup> whereas an *APOE4* allele is associated with more rapid age-related cognitive decline.<sup>42,44-49</sup> Consistent with the existence of differential vulnerability of late-myelinating regions and functions (Figure 3, Figure 4, Table 2, and Table 3)<sup>5</sup> the *APOE4* genotype-related declines in cognitive function are not global. Rather, they are detected primarily using instruments that measure new learning.<sup>42,44,47,50</sup> Our own data on cognition and myelin breakdown are also consistent with this interpreta-



**Figure 2.** Mean transverse relaxation rates as a function of the presence or absence of apolipoprotein E 2 (*APOE2*) and *APOE4* in 3 white matter regions: frontal lobe (Fwm), genu of corpus callosum (Gwm), and splenium of corpus callosum (Swm). Asterisk indicates  $P < .05$ ; dagger,  $P < .01$ . Error bars represent SD.

tion and show the performance of time-sensitive tasks to be significantly associated with  $R_2$  measures in the expected direction (G.B. et al, unpublished data, 2005).

The literature on the impact of the *APOE* genotype on brain metabolism (measured using positron emission tomography) of asymptomatic older individuals is also consistent with our findings on myelin breakdown. Cross-sectional and prospective studies have demonstrated that the metabolism of healthy *APOE4* carriers has a faster age-related decline trajectory than that of noncarriers in approximately the same parietal cortex regions in which patients with AD show reduced metabolism.<sup>51-55</sup> We hypothesize that myelin breakdown may contribute to disconnecting vulnerable myelinated circuits that provide input to parietal regions, causing the loss of synapses and their considerable contribution to cortical glucose consumption<sup>56,57</sup> and resulting in the declines in metabolic activity observed by using positron emission tomography.<sup>9,19</sup> This assertion is supported by primate studies<sup>58,59</sup> demonstrating that reductions in cortical metabolism can be caused by distant lesions that disconnect the cortex from its afferent input. Thus, damage of late-myelinating medial temporal lobe structures (where the lesions associ-

**Table 3. Relaxation Rate Slope (SE) by Age as a Function of the Presence of *APOE2* and *APOE4* Alleles in 3 White Matter Regions**

Region	<i>APOE</i> Status*		Difference Between Slopes		
	Absent	Present	$t_{100}$	<i>P</i> Value	Effect Size
<b><i>APOE2</i> Allele</b>					
Fwm	-0.059 (.01)†	-0.011 (.02)	2.16	.03	0.62
Gwm	-0.049 (.01)‡	-0.013 (.02)	1.64	.10	0.45
Swm	-0.015 (.01)	-0.032 (.02)	-0.66	.51	NA
<b><i>APOE4</i> Allele</b>					
Fwm	-0.043 (.01)§	-0.077 (.02)	-1.62	.11	0.39
Gwm	-0.037 (.01)	-0.067 (.02)#	-1.42	.16	0.34
Swm	-0.015 (.01)	-0.028 (.02)	-0.55	.58	NA

Abbreviations: *APOE*, apolipoprotein E; Fwm, frontal lobe white matter; Gwm, genu of corpus callosum white matter; NA, not applicable; Swm, splenium of corpus callosum white matter.

\*The *APOE2* allele was absent in 90 participants and present in 14; the *APOE4* allele was absent in 82 participants and present in 22.

†Within-group  $t_{100} = 6.31$ ;  $P < .001$ .

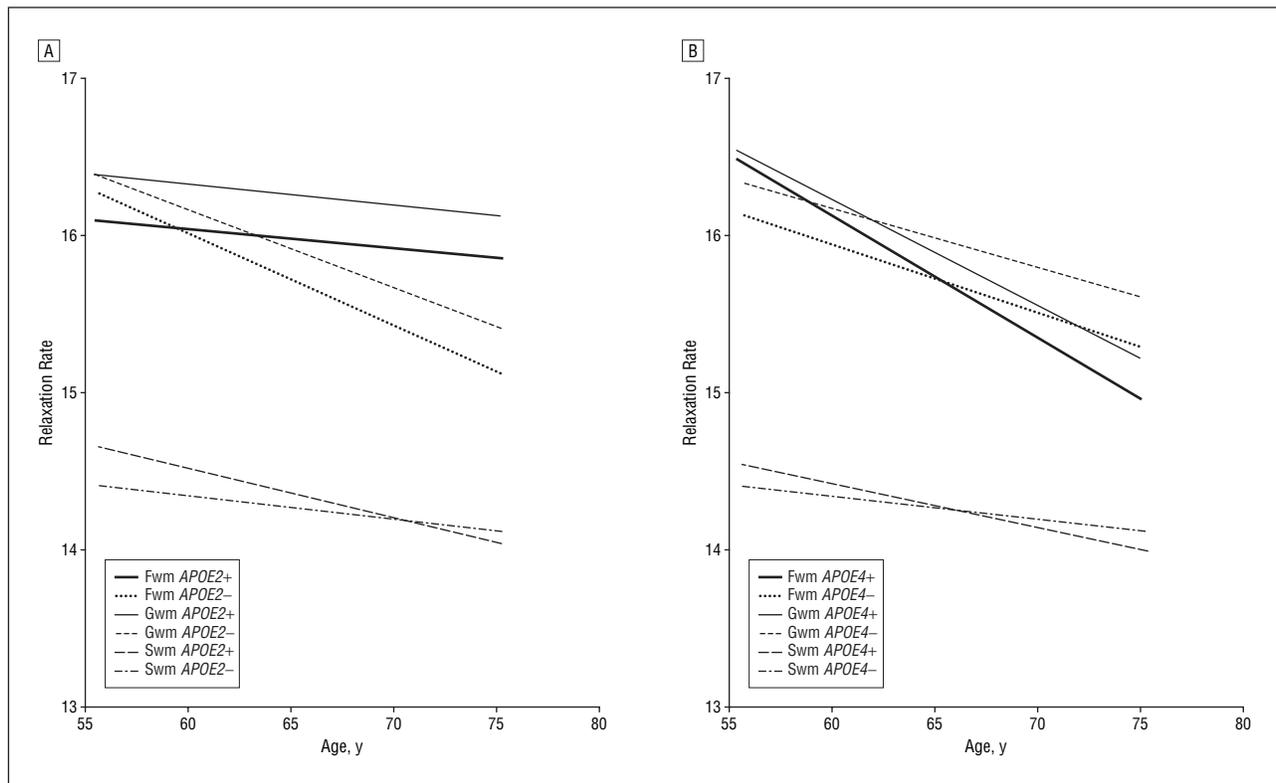
‡Within-group  $t_{100} = 5.29$ ;  $P < .001$ .

§Within-group  $t_{100} = 4.16$ ;  $P < .001$ .

||Within-group  $t_{100} = 4.28$ ;  $P < .001$ .

¶Within-group  $t_{100} = 3.71$ ;  $P < .001$ .

#Within-group  $t_{100} = 3.63$ ;  $P < .001$ .

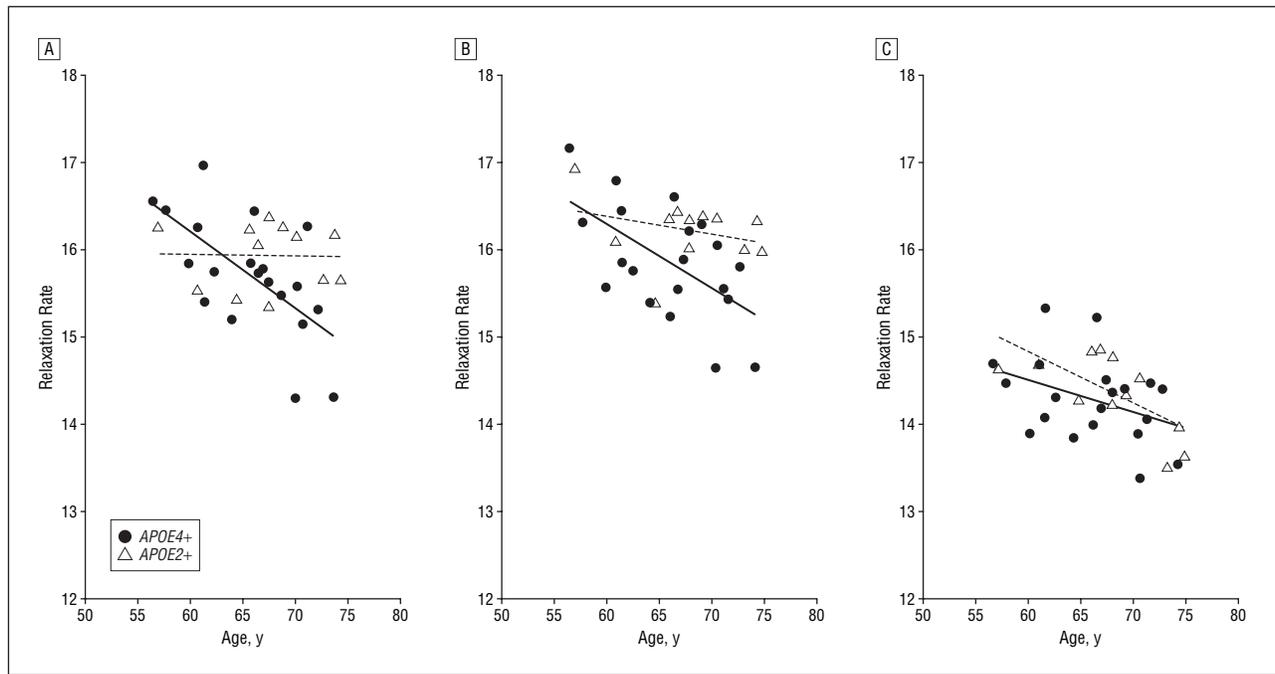


**Figure 3.** Regression lines of transverse relaxation rates by age as a function of the presence or absence of apolipoprotein E 2 (*APOE2*) (A) and *APOE4* (B) alleles in 3 white matter regions: frontal lobe (Fwm), genu of corpus callosum (Gwm), and splenium of corpus callosum (Swm). The related statistics are given in Table 3.

ated with AD first appear) produces metabolic reductions in distant cortical regions, such as the parietal lobes, in a pattern consistent with that observed in AD.<sup>58,59</sup>

Our findings and the neurocognitive and functional imaging literature are consistent with the epidemiologic characteristics of *APOE* genotypes and their impact on age at onset of AD. The *APOE4+* genotype is associated with a considerably younger age at onset in

carriers, and, conversely, the onset is delayed in those with the *APOE2* allele.<sup>35,36,60-63</sup> It is estimated that the *APOE* genotype shifts age at onset by more than a decade and thus accounts for most of the observed cases of AD, especially when they manifest before age 80 years.<sup>35,63-65</sup> Bartzokis<sup>5,9</sup> previously argued that the developmental process of myelination and subsequent age-related myelin breakdown underlies the age risk factor for AD. We now



**Figure 4.** Transverse relaxation rates of the frontal lobe (A), genu of corpus callosum (B), and splenium of corpus callosum (C) white matter regions vs age in healthy individuals stratified by apolipoprotein E 2 (*APOE2*) and *APOE4* alleles. The *APOE2* and *APOE4* individuals are mutually exclusive. For better visualization, individuals with the *APOE3/3* genotype, whose regression line is intermediate between those of the 2 depicted genotypes but not significantly different from them, are not shown.

suggest that the *APOE* genotype may also act at least in part through the same myelin breakdown process as age and that by altering the rate of myelin breakdown, the *APOE* genotype affects the rate of age-related cognitive decline and, ultimately, the age at onset of AD.

Several limitations need to be considered before further interpretation of these data. First, the selection of healthy older individuals may underestimate age-related  $R_2$  declines if such declines are associated with cognitive symptoms, debility, or mortality that caused potential participants to be excluded. The rate of age-related  $R_2$  decline in *APOE4+* individuals may be especially underestimated because such individuals may have been differentially excluded from our sample based on a family history of dementia or the presence of cognitive symptoms. This possibility is supported by the faster rate of  $R_2$  decline in *APOE4+* individuals and the absence from our sample of such individuals older than 75 years. Second, a variety of tissue changes, such as subtle edema, alteration in regional vasculature, or alterations of axons that are unrelated to myelin breakdown, could result in small changes in regional water content, thus affecting  $R_2$ . This possibility is unlikely, however, because all the participants were 75 years or younger, were thoroughly assessed and found to be in excellent health, and had almost no risk factors for vascular disease and no history of meaningful head trauma. Finally, in a cross-sectional study, interpretation of differences between age group means as “changes” or “increases/decreases” and “cause-and-effect” interpretations must be made with caution,<sup>66</sup> and whether the process of myelin breakdown begins earlier in *APOE4* carriers, whether *APOE4* accelerates the myelin breakdown process, or both can be unambiguously answered only through prospective studies.

Within the context of these limitations, the mechanism through which *APOE* impacts brain aging and age-related disease states can be considered from the perspective of myelin and its metabolism. The known physiologic roles of *APOE* support its involvement in brain lipid and myelin membrane metabolism. Apolipoprotein E is the major brain apolipoprotein, and it functions as the primary transporter of endogenously produced lipids.<sup>67-70</sup> In the brain, cholesterol and certain lipids, such as sulfatides, are essentially produced *de novo* by oligodendrocytes.<sup>71,72</sup> Apolipoprotein E coordinates the mobilization and transport of such lipids for uptake and use in the repair, growth, and maintenance of myelin and all other membranes, including synapses and dendrites essential for brain plasticity and learning.<sup>67</sup>

The uniquely extensive myelination of the human brain makes myelin maintenance and repair especially critical for sustaining the high processing speeds that underlie cognitive functions.<sup>9,73</sup> A process of brain myelin breakdown and remyelination that continues into very old age has been demonstrated in the primate model.<sup>31-34</sup> Boyles et al<sup>74</sup> demonstrated that *APOE* is essential to the process of “recycling” lipids by degrading damaged myelin and supplying the lipids required for rapid membrane biogenesis during remyelination.

In older age, myelin repair efficiency likely increasingly depends on the recycling of endogenously produced lipids, such as cholesterol, that are metabolically expensive to synthesize *de novo*.<sup>9</sup> The number of *APOE* molecules available for such recycling processes is highest in individuals with *APOE2/3* and especially *APOE2/2* alleles (approximately 17% and 35% higher than *APOE3/3* carriers), whereas *APOE4/3* and *APOE4/4* carriers have the lowest number of *APOE* molecules (12% and 20%

fewer than *APOE3/3* carriers).<sup>75</sup> Thus, consistent with the cognitive and genetic literature reviewed herein and the  $R_2$  data presented herein, the *APOE2* genotype may protect from AD more than *APOE4* predisposes to AD because higher levels of *APOE* molecules could promote cholesterol recycling and membrane repair.<sup>9</sup> Thus, increasing *APOE* levels may be a viable intervention for preventing AD<sup>75</sup> and is especially pertinent to myelin repair because myelin contains the highest cholesterol levels of any membrane and thus may be most vulnerable to differences in repair abilities.<sup>9,76</sup>

Decrements or failure of this remyelination process could thus contribute to many age-related neuropsychiatric diseases that, unlike AD, do not necessarily involve  $\beta$ -amyloid fibril toxicity.<sup>5,77</sup> For example, the *APOE* genotype may impact the age at onset of Parkinson disease<sup>78,79</sup> and schizophrenia.<sup>80</sup> Furthermore, the *APOE4* genotype is associated with more severe myelin breakdown in multiple sclerosis<sup>81,82</sup> and poor recovery from brain insults such as traumatic brain injury,<sup>83-88</sup> human immunodeficiency virus infection,<sup>89-91</sup> and cerebrovascular accidents (ischemic and hemorrhagic).<sup>92-94</sup> These insults challenge the brain's ability to repair itself and can result in dementia syndromes.<sup>5</sup> We, therefore, propose that the observed impact of *APOE* on age-related myelin breakdown occurs at least in part through its effect on crucial ongoing processes of myelin repair and remyelination and that this effect also contributes to the association between *APOE* alleles with AD and other disorders.

This hypothesis has important implications for the development of treatment interventions for AD and other neuropsychiatric disorders.<sup>5,9,73,77</sup> Because myelin breakdown in healthy individuals begins in midlife, there is a decades-long period during which therapeutic interventions could alter the course of brain aging and possibly of age-related neurodegenerative disorders, such as AD, even before clinical evidence of neurocognitive decrements appear.<sup>2,5,9,19</sup> This myelin-centered perspective and the ability to measure the development and breakdown of myelin *in vivo* provides the framework for efforts to develop novel treatment targets that should include *APOE*.<sup>95-98</sup> Noninvasive, serial evaluations of brain  $R_2$  could be used to monitor the effects of new treatments and currently available treatments that may impact the process of myelin breakdown as early as midlife. Such treatments may have a wide spectrum of efficacy and could potentially be useful in delaying brain aging and neurodegenerative disorders, such as AD.<sup>5,76,77</sup>

**Submitted for Publication:** April 19, 2005; final revision received July 5, 2005; accepted September 23, 2005.

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**Funding/Support:** This study was supported in part by grants MH51928, MH6357-01A1, and MH066029-01A2 from the National Institute of Mental Health, Bethesda, Md; grant P50 AG 16570 from the National Institute on Aging Alzheimer's Disease Center, Bethesda; contract 013608-001 from the California Department of Health Services, Sacramento; the Sidell-Kagan Foundation, Los Angeles; and a merit review grant from the Department of Veterans Affairs, Washington, DC.

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#### Announcement

Online Submission and Peer Review System Now Available. The Archives of General Psychiatry editorial office has introduced an online manuscript submission and peer review system developed by eJournalPress that will serve the needs of authors, reviewers, and editors. The new system went live on January 3. See <http://archpsyc.ama-assn.org> for more detailed information.