Apolipoprotein E Affects Both Myelin Breakdown and Cognition: Implications for Age-Related Trajectories of Decline Into Dementia

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Background: Age-related myelin breakdown is most evident in later-myelinating white matter (LMwm) brain regions. This process might degrade cognitive processing speed (CPS) underlying age-related cognitive decline and the predominance of age as a risk factor for Alzheimer's disease (AD). Apolipoprotein E (ApoE) 4 allele is the second most important AD risk factor. We tested the hypothesis that ApoE4 accelerates age-related slowing in CPS through the process of myelin breakdown.

Methods: Calculated transverse relaxation rates (R_2), an indirect magnetic resonance imaging measure of myelin breakdown in LMwm, and measures of CPS were obtained in 22 ApoE4+ and 80 ApoE4−, healthy "younger-old" individuals. To assess specificity, contrasting early-myelinating white matter region and memory task were also examined.

Results: The CPS versus LMwm R_2 remained significant in the ApoE4+ group even after age was statistically adjusted ($r = .65$, $p = .001$) and differed from the correlation observed in the ApoE4− group (Fisher's z test = 3.22, $p < .002$). No significant associations were observed with the contrast region and memory task in either ApoE subgroup.

Conclusions: A specific association between CPS and myelin breakdown in LMwm exists in asymptomatic "younger-old" individuals at increased genetic risk for AD. Although inferences of change over time and causality are limited by the cross-sectional study design, this finding lends support to the hypotheses that myelin breakdown underlies age-related slowing in CPS and that by altering the trajectory of myelin breakdown, ApoE alleles shift the age at onset of cognitive decline. Combined use of biomarkers and CPS measures might be useful in developing and targeting primary prevention treatments for AD.

Key Words: Age, Alzheimer, ApoE, apolipoprotein, brain, breakdown, cognition, dementia, MRI, myelin, onset, prevention, processing, R_2, risk, speed, T_2, treatment, white matter

The protracted myelination of the human brain results in roughly quadratic (inverted U) trajectories of myelin content and integrity reaching a maximum in mid-life and then declining in older age (1–3). The extensive scope of myelination is arguably the most uniquely human aspect of our brain (4,5) and results in the high processing speeds underlying our cognitive and behavioral functions (reviewed in 6,7).

By middle age, the developmental process of myelination produces a continuum of increasing vulnerability of oligodendrocytes from early-myelinating regions such as the visual pathways to later-myelinating association brain regions such as the frontal lobes (8–10). Later-differentiating oligodendrocytes ensheath increasing numbers of axons with smaller axon diameters (11,12) and, as a result of the increased complexity and metabolic demands, these more vulnerable later-myelinating myelin sheaths are differentially lost with age (27%–45% reductions) (1,10,13,14). Under the influence of multiple risk factors such as Apolipoprotein E (ApoE) genotype, for example (15), a progressive pattern of myelin breakdown occurs in older age that recapitulates the developmental process of myelination in reverse and might contribute to the increasing prevalence of dementing disorders such as Alzheimer's disease (AD) with age (6,16). Individuals with AD evidence more severe myelin breakdown than matched control subjects in the absence of gross axonal damage (3,10,17–23). Age-related myelin breakdown has been demonstrated to underlie cognitive decline in primates (24,25) but this has yet to be demonstrated in humans.

An age-related slowing in cognitive processing speed (CPS) likely underlies the age-related decline in most if not all human cognitive functions (26–29). Salthouse and others (27–29) have demonstrated that age-related differences in a wide variety of cognitive variables are not independent and that age-related differences in CPS variables seem to underlie this lack of independence. The uniquely extensive myelination of the human brain makes myelin maintenance and repair especially critical for sustaining our high CPS (7,30).

In non-human primates, myelin repair and remyelination is a process that continues into old age (31–33). In humans, ApoE genotype, the second most important risk factor for AD after age itself, might significantly impact myelin repair (15). ApoE is the primary transporter of endogenously produced lipids such as cholesterol and sulfatide (34–39) that are essential for myelin production and function (38–41). ApoE coordinates mobilization and transport of such lipids for uptake and use in repair, growth, and maintenance of myelin (15,34). Individuals with the apolipoprotein E4 allele (ApoE+) have fewer ApoE molecules compared with non-carriers (ApoE4−) (42), and we hypothesized that the reduced capacity of ApoE4+ individuals to mobilize essential lipids impairs their myelin repair mechanisms and

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results in an acceleration of their age-related decline of myelin integrity (15).

The influence of ApoE genotype on the relationships between age-related decline in CPS and myelin breakdown has not been previously examined. The breakdown in the structural integrity of myelin sheaths can be indirectly measured in vivo with magnetic resonance imaging (MRI) with transverse relaxation rate (R_2) measures that are markedly sensitive to small changes in the amount of tissue water (43). Ultrastructural electron microscopy studies 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 (10,44). These microvacuolations are ultrastructurally very similar to reversible myelinopathies produced by certain toxins (44–47). Animal studies have confirmed that this type of myelin breakdown can be detected with MRI in circumscribed susceptible regions and that the histopathologic changes produced by toxins as well as the recovery process can be tracked by MRI (45–48; reviewed in 49). The R_2 has yet to be directly correlated with myelin breakdown due to normal aging (as opposed to the reversible toxin-induced myelin breakdown described in the preceding text) and thus cannot be considered fully validated. Nevertheless, in humans and primates, healthy aging is not associated with neuronal loss (50; reviewed in 51,52) whereas the process of myelin breakdown and loss has been thoroughly demonstrated (1,13,14,31–33,44,53). Herein the term "myelin breakdown" will be used to refer to the R_2 findings (15).

We tested the hypothesis that in healthy older individuals myelin breakdown in late-myelinating white matter regions (LMwm) underlies age-related CPS slowing (6). In ApoE4 carriers the association of myelin breakdown with CPS should not be "masked" by effective myelin repair mechanisms (15). We therefore specifically assessed whether, in a subgroup of very healthy "younger-old" ApoE4+ individuals that are at increased risk for developing AD earlier (54,55), the association of myelin breakdown and CPS is present and is independent of aging effects.

Methods and Materials

The subjects, imaging, and genetic methods were described in detail in prior publications and will only be summarized here (10,15).

Subjects

Normal adult volunteers participating in the study were over the age of 55 years, recruited from the community and hospital staff for a study of healthy aging. To focus on healthy aging and avoid any conditions that would affect the central nervous system and myelin integrity potential, subjects were excluded if they had a history of neurological disorder or a family history of AD or other neurodegenerative disorder, psychiatric illness (including drug or alcohol abuse), or head injury resulting in loss of consciousness for more than 10 min. The subjects were physically very healthy and were excluded if they were obese (defined as body mass index of > 30 Kg/m^2); had a current or prior serious illness or history of diabetes, hypertension, or cardiovascular disease; and/or were taking medication for any of the aforementioned conditions.

The participants were independently functioning and had no complaints of or evidence of neurocognitive impairment or gross neurological abnormalities on clinical interview and brief neurological examination with the study primary investigator. The subjects were on an ad libitum diet (were not instructed to fast). Time of day that the MRI was conducted varied (between 9:00 AM and 5:00 PM) among subjects depending on their availability but was not dependent on their genetic status or cognitive performance. The final population contained no individuals over the age of 75 with an ApoE4 allele. Analyses were thus based on a total of 102 individuals under age 76. There were 62 women and 40 men in the sample. All of the female subjects were either post-menopausal or post-hysterectomy. Of the 102 subjects, 76 (74%) were Caucasian, 18 (18%) were Asian, 6 (6%) were African American, and 2 (2%) were Hispanic.

Neurocognitive Measures

Trailmaking Test—Part A. Part A of the Trailmaking Test (Trails A) (56) assesses psychomotor speed and visualspatial tracking. Subjects are required to rapidly connect 25 consecutively numbered circles. Time to complete the task serves as the variable of interest.

Digit Symbol Subtest From the Wechsler Adult Intelligence Scale–Revised. This test involves rapid copying of symbols and integrates several cognitive processes including psychomotor speed, visualspatial scanning, and simple constructional ability (57). The score reflects number of symbols copied after 90 sec.

CPS

A composite measure of CPS was obtained by standardizing the scores from Trails A (log transformed owing to positive skew) and Digit Symbol and averaging them. Higher CPS score represents faster/better performance on this measure. Because a lower score on Trails A represents faster performance (as opposed to a higher score being better on Digit Symbol), Trails A scores were inversed (multiplied by -1) before being averaged with the Digit Symbol scores in order to achieve the same direction for both measures. Higher CPS score thus represents faster/better performance.

Verbal Memory

The California Verbal Learning Test (CVLT) (58) was obtained to serve as the contrast measure in assessing the specificity of the CPS findings. The CVLT consists of five learning trials of 16 words (Monday list A), providing a measure of immediate memory span as well as a learning curve. Subjects are asked to recall as many words as possible from the first list, after an interference trial consisting of a different list, then after a 30-min delay. The total number of words recalled after the 30-min delay serves as a measure of memory for unstructured verbal material.

MRI Protocol

All subjects were scanned with the same 1.5 tesla MRI instrument, all scans used the same imaging protocol, and scan timing was irrespective of demographic (e.g., age, gender) or genotype variables. Details of the protocol have been published previously (3,10,59) and are only summarized here. Two pilot sequences were obtained to specify the location and spatial orientation of the head and the position of the axial image acquisition grid. The axial image acquisition sequence acquired interleaved contiguous slices with a Carr Purcell Meiboom Gill dual spin-echo sequence 2500/20,90/2, 3-mm slice thickness, 256×192 view matrix, and 25-cm field of view.

Image Analysis

Transverse relaxation time (T_2) was calculated for each voxel by an automated algorithm from the two signal intensities (echo time = 20 and 90) of the robust dual spin-echo sequence that used 90° refocusing pulses to produce gray-scale encoded T_2

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