ORIGINAL CONTRIBUTION

White Matter Structural Integrity in Healthy Aging Adults and Patients With Alzheimer Disease

A Magnetic Resonance Imaging Study

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Background: Imaging and postmortem studies suggest that frontal lobe white matter (FLWM) volume expands until about the age of 44.6 years and then declines. Postmortem evidence indicates that the structural integrity of myelin sheaths deteriorates during normal aging, especially in late myelinating regions such as the frontal lobes.

Objectives: To assess the integrity of FLWM by magnetic resonance imaging and, thus, to provide an important index of brain aging and its relationship to Alzheimer disease (AD).

Design: Cross-sectional study.

Setting: Two metropolitan university hospitals and AD research centers.

Participants: Two hundred fifty-two healthy adults (127 men and 125 women), aged 19 to 82 years, and 34 subjects with AD (16 men and 18 women), aged 59 to 85 years.

Main Outcome Measure: Calculated transverse relaxation rate (R_2) of the FLWM (an indirect measure of the structural integrity of white matter).

Results: As expected from prior imaging data on FLWM volume, the quadratic function best represented the relationship between age and the FLWM R_2 ($P<.001$). In healthy individuals, the FLWM R_2 increased until the age of 38 years and then declined markedly with age. The R_2 of subjects with AD was significantly lower than that of a group of healthy control subjects who were of similar age and sex ($P<.001$).

Conclusions: The R_2 changes in white matter suggest that the healthy adult brain is in a constant state of change, roughly defined as periods of maturation continuing into middle age followed by progressive loss of myelin integrity. Clinically diagnosed AD is associated with more severe myelin breakdown. Noninvasive measures, such as the determination of the R_2, may have the potential to track prospectively the trajectory of deteriorating white matter integrity during normal aging and the development of AD and, thus, may be a useful marker for medication development aimed at the prevention of AD.

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MAGNETIC resonance imaging (MRI) studies[1,2] can investigate the structural manifestation of myelination in vivo through imaging sequences that provide accurate measures of white matter volume. By using this approach, it was demonstrated recently that frontal lobe white matter (FLWM) volumes of healthy men continue to increase into the fifth decade of life, reaching a maximum volume at the age of 44.6 years and then declining.[3] These results are consistent with postmortem data showing that, in humans, white matter myelination of frontal regions continues into middle age,[4,5] followed by a breakdown in the myelin sheaths, which seems to begin in the fiber systems that were myelinated later in development.[5]

Oligodendrocytes are heterogeneous based on when in the process of brain development they underwent differentiation and produced their myelin sheaths. The later-differentiating oligodendrocytes ensheath many more axons with smaller axon diameters, have different lipid properties, and may have a slower rate of myelin turnover with a reduced ability for myelin repair than earlier differentiating cells.[6,7] This developmental heterogeneity may increase the vulnerability of late myelinating regions, such as the frontal and temporal lobes,[3,4] to myelin breakdown.[5] In addition, oligodendrocytes are more sensitive than neurons and astrocytes to various insults, including chronic hypoperfusion,[8-11] toxic products of activated microglia, such as nitric oxide,[12-14] and excitotoxicity.[15-17]

Changes in the structural integrity of myelin can be measured with MRI. In addition to increasing white matter volume, myelination reduces water content in white matter[18,19] and, conversely, myelin breakdown increases it.[20,21] Focal areas of myelin breakdown are easily identified visually on T2-weighted MR images as T2 hyperintensities.[20,21] This sensitivity is because relatively small changes in the amount of tissue water detected by MRI instruments (MRI "visible" water) markedly alter the transverse relaxation time (T2); the T2 of water (such as cerebrospinal fluid) is more than 2000 milliseconds, while the T2 of brain parenchyma is less than 100 milliseconds.[22]

Analysis of relaxation time measurements is facilitated by the convention of transforming T2 (measured in milliseconds) into transverse relaxation rates (R_2) (expressed in seconds^{-1}) using the following formula: $R_2 = [(1/T2) \times 1000 \text{ milliseconds}]/\text{second}$. Calculated R_2 measurements can reveal brain myelination differences not visibly discernible with T2-weighted images, and are a more sensitive indicator of myelination.[18] Myelination increases R_2, while age-related myelin breakdown decreases R_2.[18,20,21,23-25]

Age-related myelin abnormalities visualized on electron microscopy consist primarily of splits in the lamellae of the myelin sheaths (or ballooned sheaths) and loss of myelin staining, in the absence of changes in neurons, axons, or synapses.[5,26,27] In patients with Alzheimer disease (AD), similar myelin abnormalities have been described in the absence of axonal damage.[28] This pattern of myelin breakdown creates microscopic fluid-filled spaces, increases MRI visible water, and, thus, decreases the R_2.[24,29-32] A similar effect can occur when damaged myelin is removed by activated microglia,[14] because removal of myelin also increases the proportion of MRI visible water. This age-related myelin breakdown may underlie the age-related reduction of myelin staining observed in human postmortem samples[5] and the increases in white matter MRI visible water observed in aging individuals and patients with AD.[24,29,31-36]

Based on the observed changes in FLWM volume,[3] we hypothesized that the age-related changes in the white matter R_2 would show a quadratic relationship with age similar to that observed with volume changes. These changes would reflect continued myelination during young adulthood,[4] increasing the FLWM R_2, followed by diffuse myelin breakdown with age,[5,26,27] decreasing the FLWM R_2. Because nonrandom age-related myelin breakdown may contribute to the pathophysiologic mechanisms of AD by accelerating the destruction of late-myelinating projection neurons,[5,37] we further hypothesized that the FLWM R_2 decrease would be larger in subjects with AD than in healthy older (aged 59-85) subjects.

METHODS

SUBJECTS

Healthy adult volunteers were recruited from the community and hospital staff and participated in the study. Potential subjects were excluded if they had a history of a central nervous system disorder or a family history of AD, chorea, or other neurodegenerative disorder. The final healthy population (n=252) consisted of 127 men and 125 women, ranging in age from 19 to 82 years (mean, 54.9 years; SD, 17.5 years).

All participants with AD were originally recruited from clinics associated with 2 metropolitan university hospitals and AD research centers. Patients in these clinics had undergone a complete clinical assessment that includes a review of the clinical history, medical problems, and medication use; a comprehensive neurological and cognitive examination; a blood chemistry analysis; and structural neuroimaging. Participants met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria[38] for probable or possible AD, as diagnosed by center-affiliated physicians. Participants spoke English and had none of the following: ferromagnetic devices or implants, unstable medical illnesses that could cause cognitive deficits, non–AD-related neurological disorders, a history of substance use disorder within the past 2 years, or a history of traumatic brain injury with neurological sequelae.

Healthy subjects were independently functioning and had no evidence of neurocognitive impairment on clinical interview with the study principal investigator (G.B.). Of the healthy subjects who were 55 years and older, 101 of 161 were administered the Mini-Mental State Examination. Their scores ranged between 27 and 30 (mean, 28.6; SD, 1.0). Of the 60 subjects without Mini-Mental State Examination scores, 55 were administered a relatively brief battery of neuropsychological tests, assessing various independent cognitive abilities, including tests of memory for verbal and visual material (the California Verbal Learning Test and the Benton Visual Retention Test), 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 cognitive ability. None of the scores were in the impaired range based on published normative scores.[39-41]

Subjects with AD (n=34) consisted of 16 men and 18 women, ranging in age from 59 to 85 years (mean, 76.3 years; SD, 6.7 years). They had mild to severe AD, with Mini-Mental State Examination[42] scores ranging between 3 and 26 (mean, 18.4; SD, 6.6) and a length of illness (based on caregiver and/or medical record report of when symptoms were first noticed) ranging between 2 and 10 years (mean, 5.0 years; SD, 2.2 years).

Of the 34 subjects with AD, 28 (82%) were white, 3 (9%) were African American, 1 (3%) was Asian, and 2 (6%) were Hispanic. Of the 252 healthy control subjects, 183 (73%) were white, 37 (15%) were Asian, 28 (11%) were African American, and 4 (2%) were Hispanic (percentages do not total 100 because of rounding).

MRI PROTOCOL

All subjects underwent scanning using the same 1.5-T MRI instrument (Picker International, Inc, Cleveland, Ohio), and all scans used the same imaging protocol. 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, 30 milliseconds; and excitations, 1), 10-mm thickness, was acquired and used to align the subsequent sagittal pilot images. The middle slice of the sagittal pilot images was aligned on the coronal pilot to obtain a true midsagittal image of the brain. After the sagittal pilot spin-echo images (repetition time, 550 milliseconds; echo time, 26 milliseconds; and excitations, 2), 5-mm thickness, 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 dual spin-echo sequence (Carr Purcell

Meiboom Gill) (repetition time, 2500 milliseconds; first echo, 20 milliseconds; second echo, 90 milliseconds; and excitations, 2), 3-mm slice thickness, 192 gradient steps, and 25-cm field of view.

The T2 was calculated for each voxel by an automated algorithm from the 2 signal intensities (echo times, 20 and 90 milliseconds) of the dual spin-echo sequence to produce gray scale–encoded T2 maps of the brain.[24]

The T2 measures were extracted using an image analysis workstation (MacIntosh). A single rater, who was blind to clinical information, performed all measurements. The image analysis software permitted the rater to delineate the region of interest (ROI) using a mouse. A circular ROI sample of supraorbital white matter was placed manually by the rater in the FLWM on the second and third contiguous slices above the last image containing the orbitofrontal cortex. The rater then used the gray/white matter contrast of the early (echo time, 20 milliseconds) and late (echo time, 90 milliseconds) echo images to ensure that the ROI did not include gray matter regions, T2 hyperintensities, or other hyperintense structures, such as periventricular halos (**Figure 1**). The ROI was then transferred onto the T2 maps.

To obtain T2 measures of homogeneous white matter tissue and eliminate the possibility that any remnants of a T2 hyperintense lesion was included, all pixels with T2 values that fell above the right side inflection point on the histogram distribution of the ROI were eliminated. This minimized the influence of voxels containing small partial volumes of cerebrospinal fluid, which can markedly increase the T2 of the voxel. Thus, the final measure was the average T2 for the remaining homogeneous region of white matter tissue.[24]

The T2 data for each ROI were obtained from contiguous pairs of slices. The second and third slices superior to the orbitofrontal gray matter were used to obtain the FLWM data. The R_2 was calculated as the reciprocal of $T2 \times 1000$. The average R_2 of the 2 slices from both hemispheres were the final measures used in the subsequent analyses.

The test-retest reliability of the R_2 measurement was assessed by computing intraclass correlation coefficients for 2 ratings done at least 1 month apart by the same rater for 13 of the scans. Unlike the usual Pearson product moment correlation (a measure of association, not agreement), which standardizes both measures and, thus, removes any differences in mean or SD, the intraclass correlation counts any within-person variability as an error. It can only reach 1.0 if the measures of the same scan are identical; thus, it is a more stringent measure of reliability. Reliability using the intraclass correlation coefficient was good ($R_{xx}=0.91$, $F_{1,12}=21.3$, $P<.001$).

STATISTICAL METHODS

All statistical analyses were performed using SAS statistical software, version 6.12 (SAS Institute Inc, Cary, NC), and all significance levels reported are 2 sided, with $P<.05$ considered statistically significant. The relationship between the frontal white matter R_2 and age was modeled as follows. First, a quadratic regression function was fit in the group of healthy participants. To check on the relevance of educational level, sex, and race, these variables were entered in separate regression analyses. In each case, the main effect and interactions with the linear and quadratic terms were separately evaluated for each demographic variable. Race was treated as a trichotomy and coded as a classification variable using 2 dummy variables (African American, white, and other) and tested with $df=2$. All main and interaction effects involving race are nonsignificant ($P>.61$). None of the ancillary variables had statistically significant associations with the R_2 ($P>.10$ for all), so they were dropped from the models and are not reported further. The peak of the quadratic regression function was calculated. A check on the fit of the model among individuals older than 60 years was done by testing the residuals from the regression line in this subgroup against 0. To evaluate the R_2 among patients with AD, residuals from the normal regression function were calculated and the mean was tested against 0. The association between the R_2 and duration of illness was evaluated in a multiple regression model among participants with AD, including age and duration of illness.

A subset of 68 men in the present sample had also participated in a previous volumetric study.[3] The estimated peaks of the quadratic age regression curves for volume and R_2 data were compared in this sample using a bootstrap replication analysis.[43]

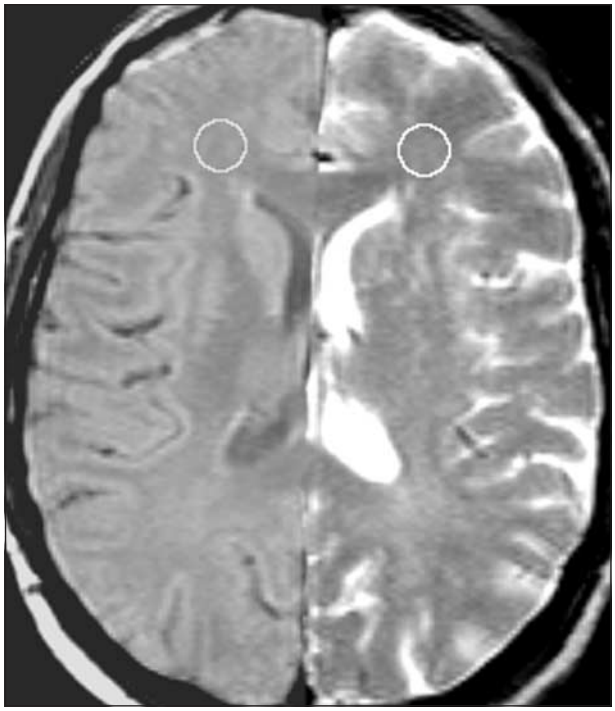

Figure 1. Example of an axial image from a 74-year-old healthy control subject. On the left, the image depicts region-of-interest (ROI) placement on an early echo image (echo time, 20 milliseconds) used to avoid gray matter. On the right, the ROI is placed on a late echo image (echo time, 90 milliseconds) to avoid hyperintensities.

RESULTS

The quadratic regression function of R_2 on age among healthy subjects was highly significant ($R^2_{2,249}=0.34$, $P<.001$). The highly significant quadratic term ($t_{2,249}=-5.84$, $P<.001$) confirmed that the fit was nonlinear. The peak of this function $\{y=15.22+[(0.055\times\text{Age})-(0.00072\times\text{Age}^2)]\}$ occurred at 38.3 years (**Figure 2**).

Among healthy subjects who were older than 60 years, the regression function fit well (mean residual, −0.013; SD, 0.50; $t_{136}=-0.31$; $P=.76$), but the R_2 of individuals with AD was significantly lower than the age-adjusted curve (mean residual, −0.55; SD, 0.72; $t_{33}=-4.51$; $P<.001$). The mean R_2 was 15.59 (SD, 0.53) and 14.65 (SD, 0.73) seconds^{-1} for healthy subjects and subjects with AD, respectively. Thus, participants with AD were approximately 1 SD below the expected value based on the healthy group. The R_2 values were variable, particularly among participants with AD who had a shorter dura-

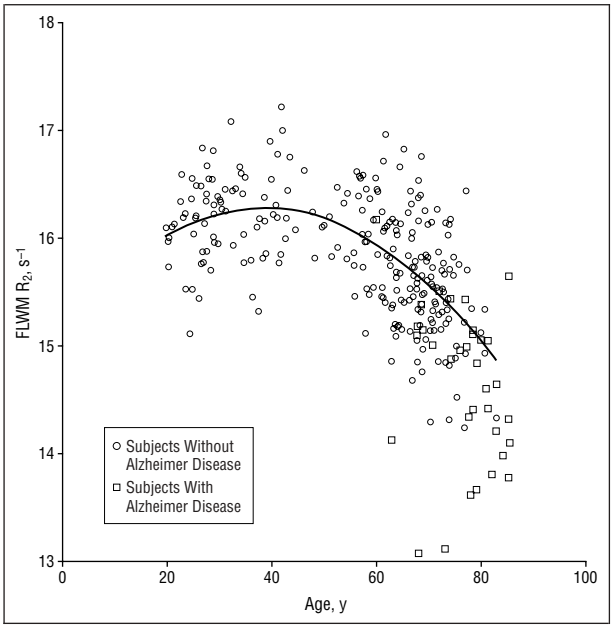

Figure 2. Regression line of the frontal lobe white matter (FLWM) transverse relaxation rate (R_2) on age in a sample of 252 healthy control subjects. The FLWM R_2 values for a group of 34 subjects with Alzheimer disease are also displayed.

tion of illness. Controlling for age, no meaningful association was observed between duration of illness and the FLWM R_2 (partial β, –.027; SE, .06; t_{31}=–0.48; P=.64).

As previously reported[3] in a subsample of 68 healthy men who had also been examined for structural age-related changes, the age at which the FLWM reaches maximum volume, derived from a quadratic curve, was calculated to be 44.6 years. A bootstrap replication analysis[43] confirmed that the maximum FLWM R_2 is reached at an earlier age (36.8 years) than the maximum FLWM volume (z=2.24, 2-tailed bootstrap analysis, P=.02).

COMMENT

The most striking observation of the present study is the inverted U pattern of the FLWM R_2 changes with age, which was modeled as a quadratic function for subsequent analyses. As hypothesized, based on prior results[3] showing a similar quadratic pattern of age-related changes in FLWM volume, the age-related pattern in FLWM R_2 was also well fit by a quadratic model, reaching a maximum at the age of 38 years. The R_2 increase up to the age of 38 years is reflective of continuing myelination of the FLWM.[3,4,18,23] Ono and colleagues,[23] using similar instrument and imaging sequences, observed an R_2 of 15.5 seconds^{-1} in a group of 12 children whose mean age was 10.1 years. Our data, obtained from adults, showed that the most dramatic changes in the R_2 were associated with the subsequent aging process and the diagnosis of AD.

The data for the 68 healthy male subjects for whom FLWM volume and R_2 data were available showed that the beginning of the R_2 decrease predates the age at which volume decreases begin.[3] This pattern is consistent with recently published observations[44] from a primate model of aging showing myelin breakdown while active myelination and myelin volume expansion are still occurring. In the subjects with AD, no clear association between duration of symptoms and the R_2 was observed. In fact, of the 2 participants with AD who had the shortest illness duration (2 years), one had the lowest age-adjusted R_2 value by far, and the 5 lowest age-adjusted scores were all in individuals with illness duration of 6 years or less. Although these are small numbers from which to attempt any generalization, it is clear that dramatic reductions in FLWM R_2 values may be observed early in the course of AD.

The significantly decreased FLWM R_2 values observed with aging and AD could be manifestations of either increased MRI visible water[30,45] or decreased tissue iron.[31] The latter possibility is unlikely, given previous studies[3,24,31] that showed iron levels in the FLWM to be unchanged during this age range in healthy controls or in patients with AD. Therefore, the significantly decreased white matter R_2 value observed in healthy aging individuals and in patients with AD is most consistent with myelin pathologic changes demonstrated in postmortem studies.[5,26-28,35,46-52] In addition, the R_2 reductions observed in patients with AD may be specific to this age-related neurodegenerative disease because a study[53] of older individuals with Parkinson disease showed no decrease in FLWM R_2 values and no differences in FLWM tissue iron level when compared with the values of age-matched healthy controls.

The age-related reduction in R_2 values occurring in healthy subjects after about the age of 38 years is consistent with the view that myelin degeneration may be a major factor in the cognitive decline associated with aging itself.[20,26,54] Neuronal loss is minimal during normal aging,[55-58] making wallerian (axonal) degeneration an unlikely explanation for the myelin loss. Postmortem data indicate that myelin pathologic changes are not accounted for by neuronal pathologic changes in AD either; thus, as in normal aging, wallerian degeneration is probably not the factor that explains axonal myelin changes.[28,35,47,48]

The possibility that myelin breakdown may be a contributing factor to AD has been suggested previously.[28,37,46,48] The neurodegeneration of AD is not global[37,58-60]; rather, the neurons most susceptible to neurodegeneration in patients with AD extend small-diameter axons that myelinate late in life.[5,37,51] The susceptibility of this subset of axons to myelin breakdown[5-7,49,51] may provide a mechanism through which the apparent progression of cortical AD pathologic changes could occur in a predictable order that seems to be the reverse of myelination, as suggested by Braak and Braak.[61]

Myelin breakdown is also observed in patients with AD.[28,35,46,47,52] Widespread and diffuse myelin breakdown has been reported to occur in more than half of subjects with AD, despite the lack of evidence of infarction or white matter amyloid angiopathy.[35,47] The exact mechanism of this myelin breakdown is unknown and could be multifactorial. Some investigators[52] attribute it to ischemia, while others[28] attribute it to a primary disease process. In addition, the prevalence of β-amyloid deposition, one of the hallmarks of AD, is age dependent[62] and has been associated with myelin destruction.[63,64] β-Amyloid can be produced by oligodendro-

cytes and neurons,[65] and increases lipid peroxidation.[66] Increased levels of lipid peroxidation have been demonstrated in the myelin of brains with AD.[46] The loss of myelin would require an approximately 5000-fold increase in neuronal energy expenditure to maintain neurotransmission levels.[6,7] Because approximately 2% to 3% of the oxygen consumed during normal mitochondrial respiration is obligatorily transformed into free radicals,[8,67] the tremendous increase in free radical production could contribute to AD neuronal changes.[68-70]

Regardless of the exact mechanism, the normal age-related progression of myelin breakdown[5,26,27] could contribute to the age-related increase in the incidence of AD.[71] The present data indicate that, on average, myelin breakdown becomes apparent late in the fourth decade of life as a part of normal aging. This process may increasingly create conditions for the progressive nonrandom neuronal damage characteristic of AD.[36,37,58,59] The lack of association between length of illness and R_2 reduction in subjects with AD is consistent with this model. The data suggest that a low R_2 may be a marker for the subsequent development of AD, and confirm that considerable R_2 decreases can be present early in this illness. Whether R_2 values start to decline earlier in patients with AD or whether patients with AD have an accelerated decline in R_2 can only be answered through in vivo prospective studies.

Important additional limitations of this study need to be considered. Although reproducible,[24,32] the 2-echo R_2 measure can only be an approximation of the absolute R_2 values. The cross-sectional design could reduce some of the changes observed with aging and AD if R_2 decreases are associated with the mortality or debility that caused potential subjects to be excluded from the study. In addition, we excluded healthy subjects with known family histories of AD who would be at greater risk for having incipient AD themselves. Our findings pertain to a specific delimited region of the frontal lobe. However, this region was chosen for study because it has been shown to myelinate late in adulthood[3,4] and has been reported to be the most susceptible region of the prefrontal cortex in patients with AD.[72] Finally, in a cross-sectional study,[73] interpretation of age-group mean differences as changes or increases/decreases must be made with caution.

If a causal relationship is established between premorbid white matter R_2 and age-related cognitive impairments and AD through prospective studies, new avenues of treatment and prevention may be possible. Serial evaluations of white matter R_2 could be used to monitor the effects of possible new treatments,[74] and available treatments,[75-77] that could affect the process. Because myelin breakdown begins to occur during early middle age, there is a decade-long period during which therapeutic interventions could alter the course of brain aging and possibly of neurodegenerative disorders such as AD, before clinical evidence of neurocognitive decrements appears.[58] Thus, medication development targeted toward preventing age-related cognitive decline and AD may be possible using noninvasive in vivo neuroimaging markers.

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