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BACKGROUND AND PURPOSE: **Clinical validation of magnetization transfer (MT) imaging is important for investigating clinical disease and organization of normal brain function. We determined whether an in vivo quantitative measure sensitive to white matter is distributed in functionally important ways.**

METHODS: **Axial 1.5-T MR images with and those without MT were obtained. MT ratios (MTRs) were computed for 33 regions of interest (ROIs) in 27 healthy adults (aged 18–69 years) without evidence of cognitive or radiographic abnormalities. Three tests of reliability yielded coefficients above 0.97. MTRs for the whole brain, groups of structures, and individual ROIs were calculated. Low standard errors confirmed the consistency of the technique.**

RESULTS: **Age, education, sex, and hand dominance were not correlated with whole-brain MTR (mean = 37.35, SD = 1.25), but age was associated with the cerebellum and some lobes at a trend level. MTRs were as follows, in descending order: corpus callosum, cingulate, white matter, brain stem, subcortical nuclei, and cerebellum. MTRs were selectively higher in the prefrontal lobe versus the posterior frontal lobe and in the lateral temporal lobe versus medial temporal lobe. MTR was higher in the left hemisphere than in the right hemisphere for the whole brain, frontal and temporal lobes, and lenticular nuclei.**

CONCLUSION: **MT imaging showed selective age, medial-lateral, and hemispheric differences, giving evidence of normal aging effects on the white matter in the absence of T2- weighted hyperintensities. These differences support neurocognitive theories of the organization of brain function. MT imaging appears to be a robust technique for use in cognitive neuroscience.**

There is burgeoning interest in understanding the white matter (WM) of the brain, how to measure it quantitatively, and its functional importance (1–6). Studies have shown that WM is primarily responsible for aging-related brain loss based on the greater volume reduction of myelinated nerve fibers than of nerve cells (7–10). In this study, we sought to examine the functional implications of regional differences in the distribution of myelin in the brain by using magnetization transfer (MT) imaging. Previous studies of healthy cohorts analyzed the MT ratio (MTR) histograms of the WM for the whole brain by using semiautomated segmentation methods (11–14) or hand-placed, small, circular, or regular regions of interest (ROIs) (15–18). We sought to measure in greater detail the regions of the brain most vulnerable to ischemic and demyelinating damage, for the original purpose of comparing the findings with those of patients who received brain radiation therapy. We included a greater number of ROIs than previous studies did and sampled structures more completely to examine the clinical validity of MTR for its sensitivity to WM and cognition.

MT imaging is a technique that is sensitive to the exchange of magnetization between a pool of free protons and a pool of protons that are bound to macromolecules. The amount of this exchange can be quantified by calculation of the MTR (19), defined as

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a value of percentage. Exogenous cellular components are the major contributors to the MT effect in brain tissue, and therefore the concentration and integrity of myelin is reflected in MTR values (16, 20, 21). The MTR is the quantitative measure of the amount of MT that occurs between the bound and the mobile water molecules in a given ROI. Normal WM, because of its dense structure of primarily lipids, has a higher MTR than GM, which is about 10% of WM structures (12) and not different from unmyelinated WM in the pediatric brain (17).

Several studies of regional variations in MTR in healthy subjects have been done. Higher MTR is hierarchically distributed with highest values in the corpus callosum; the central and subcortical U fibers of the frontal, temporal, parietal, and occipital lobes; the pons; and the subcortical structures that contain myelinated WM fibers (15, 18). The subcortical nuclei (ie, basal ganglia and thalami) have reliably lower MTR. In the study by Mehta et al (15), the thalamus had the highest value of the gray matter (GM) structures (cortical and subcortical) because of the presence of myelinated WM fibers related to its cortical connectivity. To our knowledge, lateralization of MTR has been examined only once previously (18), and although not significant, values were consistently higher in left than in right WM regions. No hemispheric lateralization of MTR was found in relation to hand preference.

Although the greatest regional differences in WM reflect lesion burden, normal aging effects in MTR are greater in children than in adults, and they have been related to myelination and, more specifically, to the concentration of galactocerebrocides (17). MT can measure the increasing heterogeneity of the maturing brain (22), and greatest regional differences are found in the tracts projecting to the primary cortical areas (16). Age-related differences in adults are more controversial. Mehta et al (15) reported no age-related differences in the MTR of any brain structure among adult age-defined groups, although the data show increasing values in their group of adults aged 21–78 years whose MR images did not show hyperintensities. In contrast, other studies have reported a decrease in MTR with age in older adults (11–13, 18).

In studies that examined MTR in relation to cognitive function (13, 14, 23), the MTR was sensitive to cognitive burden (14) or more sensitive than cognitive measures to normal aging effects (13). MTR was sensitive to early neurodegenerative changes in the temporal lobe, as it was indistinguishable in older adults with mild cognitive impairment and in patients with Alzheimer disease, and values for the whole brain and frontal lobe were generally between those of the Alzheimer and healthy control groups (14). If MTR is sensitive to relatively small differences in cognition, differences in myelin integrity might be discernable in brain structures that are instrumental for rapid sequential processing, such as language and movement.

In this study, we reexamined demographic variables, hemispheric differences if any, and possible differences between the mesial and lateral regions of the WM of the cerebral lobes. We expected any differences found to be consistent with the known neurocognitive functions of the implicated brain regions. We hypothesized that regions of the left cerebral hemisphere that are dominantly involved in language processing would have a higher MTR because of their reliance on the rapid temporal variations of language sensory signals (24) and also because of the sequencing demands of processing language at other levels (morphologic, sentence level). Histologic evidence of this notion (1, 25) is that the increased length of the left posterior superior temporal gyrus, associated with dominant linguistic functions, is due to thicker myelin rather than to increased glial proliferation, neural density, or axonal diameter. Finally, we compared central areas of subcortical WM with lateral areas and hypothesized that MTR is higher in lateral areas because of relatively greater volume of WM from cortical-cortical fiber associations than the lesser cortical-subcortical connectivity of the limbic areas of the central or mesial portions of the lobes.

Methods

Subjects.—Adults were screened by using a neurodiagnostic interview with health history, neuropsychological, and neuroradiologic examinations to serve as healthy control subjects in studies of patients with brain tumors. Relatives of patients and known members of the community were recruited. To prospectively examine the dependence of the MTR on demographic variables and its validity for studying WM based on regional variations, we used highly selective inclusion criteria to identify healthy subjects. Exclusion criteria included the following: 1) structural abnormalities on T2-weighted or other MR images, 2) history of neurologic comorbidity, 3) psychiatric comorbidity, 4) learning disability, 5) history of head injury, 6) cardiovascular disease, 7) pulmonary disease, 8) use of medications 9) diabetes, 10) history of cancer, 11) history of substance abuse, 12) autoimmune disorder, and 13) renal failure or any other disorder that could cause cerebral ischemia. One subject was excluded because of poor memory performance on examination and a history of mild head injury in his youth, although his MR images were normal. Another subject had a benign pineal cyst but was not excluded. This process resulted in a group of 27 healthy subjects aged 18–69 years (mean, 41.07 years; SD, 15.80; median, 41 years). The age distribution by decade was as follows 18–19 years, $n = 2$; 22–29 years, $n = 7$; 31–38 years $n = 4$; 41–49 years, $n = 6$; 52–57 years, $n = 3$; and 61–69 years, $n = 5$. Education ranged from 10 to 20 years (mean, 16.33 years; SD, 2.96), 44% were male and 56% were female, and 89% were right-hand mixed dominant versus 11% left-hand mixed dominant (as determined by interview).

Image Acquisition—All MR studies were performed by using a 1.5-T whole-body system (Vision; Siemens Islin, NJ) with a standard quadrature head coil. For the magnetization studies, two image sets were acquired. These were identical except for the the standard magnetization pulse. The first set of images was completed with the magnetization pulse on, and the second set was acquired with the pulse turned off. Parameters were as follows: gradient-echo sequence (fast low-angle shot [FLASH]), TR/TE = 1200/10; flip angle = 30°; 31 sections 3-mm thick; section gap, 1.5 mm; and matrix, 128 × 256). The field of view was adjusted to give the best resolution for the particular patient and was in the range of 220–230 mm. The MT pulse was the standard MT pulse, which consisted of a 1.5-m/s pulse applied 1.5 kHz off-resonance.

Regions of Interest.—ROIs were chosen on the basis of vulnerability to ischemic injury and demyelination, as related to

the parent study of the damaging effects of radiation therapy on the brain (26, 27). The boundaries for cerebral structures were defined by Brodmann areas (BAs) by using Damasio and Damasio's templates (28) with cytoarchitectonic markings corresponding to the horizontal plane (parallel to the inferior orbitomeatal line). This was useful to differentiate the limbic areas of the temporal and parietal lobes that defined the mesial and lateral portions of these lobes and also the motor and prefrontal areas of the frontal lobe that defined the posterior and prefrontal lobes, respectively. The selected ROIs were the WM of the left and right hemispheres and subcortical structures, as follows: 1) Prefrontal, anterior to frontal horns of lateral ventricles (BAs 8–12, 25, 32, 46, 47); 2) posterior frontal, the remainder of frontal lobes and centrum semiovale (BAs 4, 6, 44, 45); 3) anterior cingulate cortex (BAs 24, 33); 4) posterior cingulate cortex (BAs 23, 31); 5) medial temporal lobe, mesial to the temporal horn of the lateral ventricle, including hippocampus (BAs 27, 28, 34, 38); 6), lateral temporal lobe, lateral to the temporal horn of the lateral ventricle (BAs 20–22, 35–37, 41, 42); 7) medial parietal lobe, medial to lateral ventricles (mesial areas of BA in lateral parietal lobe and 26, 29, 30); 8) lateral parietal lobe, lateral to the lateral ventricles (BAs 1–3, 5, 7, 39, 40); 9) occipital lobe (BAs 17–19); 10) lentiform nucleus (globus pallidus and putamen); 11) head of the caudate; 12) thalamus; 13) internal capsule; 14) genus of the corpus callosum (not hemispheric); 15) body of the corpus callosum (not hemispheric); 16) splenium of the corpus callosum (not hemispheric); 17) cerebellum; and 18) brain stem. CSF was also measured.

A whole-brain MTR was computed by using the means of all ROIs. The ROIs were weighted by region size. For analyses, ROIs were grouped into WM structures (frontal, temporal, parietal, and occipital regions); anterior and posterior portions of the cingulate; segments of the corpus callosum; subcortical nuclei and related structures (basal ganglia, thalamus, and internal capsule); cerebellum; and brain stem. Bonferroni corrections were made for all multiple comparisons. Results were significant when $P < .05$ was divided by the number of regions in a comparison.

Image Postprocessing.—Images were transferred to a workstation (Sparc 1300; Sun Microsystem Santa Clara, CA), where processing was performed by using programs written with programming language IDL (Research Systems Inc, Boulder CO). Both a neuroradiologist (E.T.) and a research fellow (G.L.) trained by a licensed neuroradiologist (J.H.) observed and outlined the images. Outlining the ROIs was done on the non-MT, T2-weighted images. The T2-weighted (spin-echo) images were used to position the ROIs on the data matrix, and the ROIs were then automatically translated to the MT images for computation of MTR by using an in-house software routine. We included only the WM, avoiding sulci and leaving a surrounding rim of WM/GM gradation to minimize the partial volume effect from GM or CSF (Fig 1). While prior groups used regular ROI shapes, we outlined the form by keeping to WM boundaries or the boundary of the subcortical GM nucleus.

Inter-rater reliability was calculated as an intraclass correlation coefficient of 0.999, revealing no significant difference between the observers in this study. Because the outlining was dependent on subjective observation, we also examined the potential differences in the observer's perception of the boundary of WM. We examined inter-rater reliability by postprocessing the data twice, by one observer using a more liberal approach to defining an ROI (including smaller margins around ROIs and therefore a greater amount of WM area sampled from the ROI), and another observer using a more conservative approach (including a larger rim around WM at the expense of total area sampled) to avoid partial-volume effects. This comparison was made for 132 ROIs; that is, all ROIs for two cases. Results again did not differ (intraclass correlation coefficient = 0.999). A third reliability study was conducted to determine if equivalent values could be calculated by using the MT sequence in the same individual on two dates. One subject was re-imaged a few weeks after an initial session, and the intraclass correlation coefficient of 0.977 was considered acceptable.

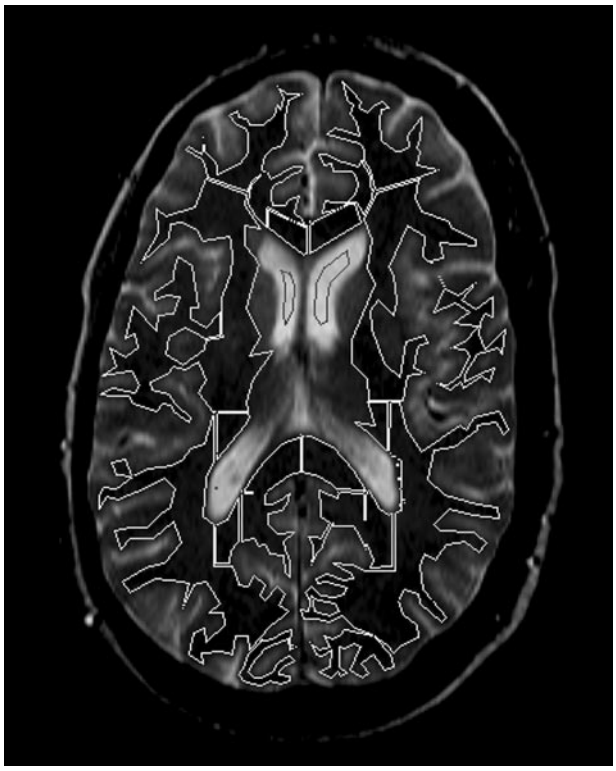

FIG 1. ROI outlining method.

MTRs were calculated as percentages on a pixel-by-pixel basis from the intensities of the images with (Im) and those without (Io) the MT pulse by using this equation: MTR = 100 (Io – Im)/Io. Although any of the three images (Io, Im, MTR) could have been used to define ROIs from which the program calculates the mean, SD, and area of the MTR, both technical processors consistently used the Io image.

Mean MTR and its SD were calculated for an ROI on each imaged section where the ROI was visible, for up to 28 sections of 3-mm thickness. Ultimately, the MTR means and SDs used for analyses represented all calculated pixel values for an ROI or those weighted by area for individual and combined ROIs.

Analysis.—We computed association of mean signal intensity and area of each ROI with age, stratified age, education, hand dominance, and sex by means of either correlation coefficients or *t* tests, as appropriate. The ROIs were grouped into six sets of related regions and a multivariate analysis of variance (MANCOVA) was run to compare the sets. Lastly, we checked for medial-lateral, anterior-posterior, and hemispheric effects between ROIs by use of paired *t* tests. Bonferroni adjustment of the test level was incorporated to avoid excessive false-positive results.

Results

Associations of Demographic Variables with MTR for Brain Regions.—The whole-brain MTR was normally distributed, with a mean of 37.35 (SD = 1.25) and a range of 35.3–40.23. Age was not significantly correlated with the MTR mean for the whole brain ($r = 0.06$, $P = .78$). To further examine age effects, subjects were stratified into a younger group (age 18–38

years; $n = 13$; five male, eight female) and an older group (age 41–69 years; $n = 14$; six male, eight female). Student t tests demonstrated no differences in either the mean MTR for all ROIs (younger mean = 39.31, SD = 4.67; older mean = 40.90, SD = 5.12; not significant) or the mean for the WM ROIs (younger mean = 39.98, SD = 3.71; older mean = 40.90, SD = 3.16; not significant). However, the two groups were different in the mean WM ROI area, as observed by a single neuroradiologist (E.T.) who was blinded to the subject's age (younger mean = 57.99 mm^2, SD = 20.94; older mean = 39.19 mm^2, SD = 14.02; $P = .005$). In addition, age was not significantly associated with the major groupings of WM and subcortical ROIs, with the exception that older age was significantly associated with lower MTR in the cerebellum ($r = -0.48$, $P = .01$). However, trends for positive correlation of age and MTR were found in the cingulate ($r = 0.42$, $P = .03$) and cerebral WM ($r = 0.37$, $P = .06$). Among the cerebral WM regions, trends for positive correlations with age were found for the left ($r = 0.41$, $P = .04$) and right ($r = 0.40$, $P = .04$) occipital lobes and for the right temporal lobe ($r = 0.36$, $P = .06$).

Education was unrelated to whole-brain and other regional groups of ROIs, except for a moderate correlation of higher education with higher MTR in the cerebellum ($r = 0.49$, $P = .01$). Hand dominance showed no association with whole brain, cortical, corpus callosal, subcortical, cerebellar, or brain stem MTR values, although there were only three of 27 lefthand- or mixed-dominant individuals. We also examined whether hand dominance was related to higher contralateral MTRs. No effect of hand dominance was found: The right-hand–dominant group had nonsignificantly higher left than right whole -pain and cortical MTRs, as did the small non–right-hand–dominant group. No significant sex differences were found in MTR for whole brain or for groupings of ROIs.

Hierarchy of MTR among Anatomic Structures.—The brain was segmented as described earlier and grouped into six sets of related structures: 1) segments of the WM of the cerebral lobes combined (frontal, temporal, parietal, occipital), 2) segments of the corpus callosum combined (genus, body, splenium), 3) WM of the anterior and posterior cingulate gyrus combined, 4) subcortical nuclei and structures combined (lentiform nuclei, heads of the caudates, thalami, and internal capsules), 5) cerebellum, and 6) brain stem. MANOVA confirmed that these groups varied significantly in MTR value, with F (4, 104) = 181.02 and $P < .0001$. Mean MTRs ± SDs were as follows, from highest to lowest: corpus callosum, 39.99 ± 1.51; cingulate gyri, 39.87 ± 1.89; WM, 38.61 ± 1.47; brain stem, 37.62 ±1.36; subcortical nuclei and GM, 36.58 ± 1.26; and cerebellum, 31.93 ± 1.66 . MTRs for the WM of the cerebral lobes were also hierarchically distributed, with F (3, 78) = 8.08 and $P < .0001$. Values were as follows: frontal, 38.93 ± 1.51; parietal, 38.87 ± 2.09; occipital 38.67 ± 1.65; and temporal, 38.06 ± 1.47. The subcortical structures varied significantly, with F (3, 78) = 334.75 and $P < .0001$. Values from highest to lowest were in the internal capsules, thalami, and caudate, to the lentiform nuclei (Table 1).

TABLE 1: Mean magnetization transfer ratios and analysis of variance for substructures of cortical and subcortical regions

Region	Mean	SE	Significance (F)
Mesial temporal	37.35	0.10	$P = .0005$
Lateral temporal	38.21	0.10	
Prefrontal	39.63	0.16	$P = .0005$
Medial frontal	38.36	0.16	
Mesial parietal	38.97	0.14	$P = .61$
Lateral parietal	38.87	0.14	
Genu	40.98	0.22	$P = .0005$
Body	39.52	0.22	
Splenium	39.62	0.22	
Anterior cingulate	39.46	0.26	$P = .11$
Posterior cingulate	40.09	0.27	
Lentiform nucleus	35.11	0.13	$P = .0005$
Head of caudate	35.22	0.13	
Thalamus	38.07	0.13	
Internal capsule	39.80	0.13	

Medial-Lateral and Anterior-Posterior Differences in MTR.—Medial or central versus lateral areas of three of the cerebral hemispheric WM regions were compared (Table 1). MTRs were significantly higher in the prefrontal versus posterior part of the frontal lobes, with F (1, 26) = 30.37 and $P < .0001$, and in the lateral versus medial part of the temporal lobes, with F (1, 26) = 35.08 and $P < .0001$. However, no difference was found in the lateral versus medial part of the parietal lobes; F (1, 26) = 0.271 and $P < .61$. No significant difference in MTR was found in the anterior versus posterior cingulate; F (1, 26) = 2.74 and $P < .11$. In the corpus callosum, values were significantly higher in the genu, with F (2, 52) = 13.99 and $P < .0001$, than in the body and splenium which did not differ from each other (Table 1).

Hemispheric Differences.—The entire left hemisphere mean MTR was significantly greater than that of the right hemisphere, with paired t (26) = 5.41 and $P < .0001$, although the left hemispheric augmentation of MTR was significant only for the cerebral WM, with paired t (26) = 5.60 and $P < .0001$ (Table 2). Left-hemispheric MTR augmentation was found in the frontal and temporal lobes primarily, a trend was found for the parietal lobes, and the occipital lobes showed no hemispheric effect (Table 2). Higher MTR for the posterior frontal and lateral temporal areas accounted for most of this left-hemispheric effect: posterior frontal paired t (26) = 4.52 and $P < .0001$, prefrontal, lateral temporal paired t (26) = 8.24 and $P < .0001$, and mesial temporal not significant (Table 2). The intraindividual left-hemispheric superiority in MTR for the posterior frontal region was found in 78% of cases, for the prefrontal region in 48% of cases, for the lateral temporal region in

TABLE 2: Hemispheric differences in magnetization transfer ratio of regions as measured by paired *t* tests

Region	Left Mean	SD	Right Mean	SD	Paired *t*	*P*	Significance*
Hemisphere mean	37.55	1.25	37.25	1.31	5.41	.0005	*
Cortical regions	38.77	1.44	38.45	1.52	5.57	.0005	*
Cingulate	39.79	2.04	39.92	1.79	1.08	.287	
Subcortical	36.65	1.29	36.52	1.25	2.30	.030	
Brain stem	37.64	1.42	37.61	1.34	0.44	.666	
Cerebellum	31.85	1.61	32.01	1.76	1.25	.222	
Frontal	39.06	1.50	38.81	1.54	3.42	.002	*
Prefrontal	39.90	1.60	40.05	1.67	1.35	.188	
Posterior frontal	38.86	1.59	38.54	1.63	4.52	.0005	*
Parietal	38.97	1.96	38.76	2.23	2.32	.029	
Lateral parietal	38.98	2.00	38.76	2.29	2.25	.033	
Mesial parietal	39.03	1.99	38.90	2.14	1.29	.207	
Occipital	38.69	1.61	38.65	1.75	0.34	.733	
Temporal	38.35	1.41	37.77	1.55	7.52	.0005	*
Lateral temporal	38.54	1.42	37.87	1.59	8.24	.0005	*
Mesial temporal	37.48	1.74	37.25	1.63	1.14	.267	
Internal Capsule	39.95	1.50	39.67	1.58	1.94	.063	
Thalamus	38.02	1.33	38.11	1.30	1.40	.174	
Head of the caudate	35.32	1.30	35.11	1.33	1.25	.221	
Lentiform nucleus	35.21	1.43	35.01	1.27	2.86	.008	

* Significance indicates those results that reach an accepted α of $P < .0036$ after applying a Bonferroni correction.

96% of cases, and for the mesial temporal region in 56% of cases. Subcortical structures together showed a similar trend, with paired t (26) = 2.3 and $P < .03$. In the subcortical ROIs (internal capsules, thalami, heads of the caudate, lenticular nuclei), the lentiform nucleus showed a significant left-hemispheric effect (Table 2), which was found in 78% of the cases: paired t (26) = 2.86 and $P < .008$.

Discussion

We found selective differences in MTR of the WM of the brain and subcortical nuclei. This observation suggests organization of regions by WM density consistent with inherent adaptive brain functions, most notably those of motor functions, language, and executive functions. This study reproduced the hierarchical organization of myelin density found in prior studies that used MT imaging to examine normal brains and expanded on these prior findings with evidence of hemispheric effects and mesial versus lateral differences. We also revisited the question of how demographic variables might account for differences in myelination.

Demographic variables had no effect on the mean MTR of all regions, but specific ROIs showed borderline significant correlations with age. The lack of association of handedness and sex with MTR of the WM is consistent with prior imaging results (18), which are further supported by those of a diffusion tensor imaging study reporting a lack of sex effect in healthy aging men and women (29). Prior pathologic studies that directly examined myelin in adults reported no sex differences in the myelination of the hippocampal formation or WM beyond early adulthood (30) until late adulthood (8). Education was positively correlated only with cerebellar results ($P <$ .01), although this finding is brought into question with Bonferroni correction. Without other studies for comparison, this finding remains in isolation.

The finding of nearly significant positive correlation of age with MTR in the occipital and right temporal lobes (with trends for other WM structures) and the equivalent MTRs for our younger and older subjects deviates from reports of negative correlations of age with WM (11–13, 18). To our knowledge, only one study besides ours reported a positive (though nonsignificant) correlation of age and MTR (15), but the presence of WM hyperintensities appears to account for these differences in the age effect. In all of the studies showing a negative correlation of age and MTR, WM hyperintensities were not screened out. Age was strongly and negatively correlated with these hyperintensities in one study (13). In the studies finding some positive correlation, subjects with WM hyperintensities were prospectively excluded. We also found that the total gross volume of WM (multiple sections $\times$ area) of the older age group was 68% that of the younger group. While multiple mechanisms have been examined for age-related shrinkage of the WM such as loss of smaller diameter axons, structural age-related changes in both primates and humans evidence no loss of glial cells, relative reduction of the number of small diameter nerve fibers, and ubiquitous increases in myelin though myelin integrity degenerates (6).

Pathologic findings of aging effects on myelin suggest that a slow progression of MTR, which indicates increasing density of myelin, is expected in adulthood before old age, followed by a precipitate decline (8, 9). The positive correlations of age with MTR we found in some cerebral structures is consistent with the increases in WM reported in pathologic until the seventh or eighth decade. At that point, myelin breaks down rapidly (8), resulting in a change in conduction rates, loss of synchrony in cortical neuro-

nal circuits, and cognitive impairment. Cognitive impairment in old age may be more related to a breakdown of myelin integrity or thinning of myelin in the normal aging brain (including more accelerated loss of WM chemistry) than to loss of cortical neurons or synapses (7–9, 31). Some morphographic studies show regional WM increases until the fifth decade and decreases thereafter (32). However, pathologic studies show increases in myelin until age 60 or 70 years as a result of accumulated myelin without axonal loss; this partly reflects damage to and repair of myelin causing increasing numbers of myelin laminae, ballooning of sheaths, redundancy of myelin, and splitting of myelin (9, 33). Furthermore, larger-diameter axons have thicker myelin sheaths (33), and small-diameter nerve fibers have a greater reduction with age (6). Thus, the stability of MTR across age groups and the positive association with age that we found in some cortical WM areas (occipital and right temporal lobes) may represent the accumulation of myelination described in studies of normal aging before the onset of the morphographic abnormalities or cognitive impairment (which were eliminated in our screening process). The adults selected for this study permitted an examination of aging effects that was not dominated by the rapid changes that occur after age 70 in both neuronal structure and chemistry or by the heightened risk of latent brain abnormalities in late aging.

Findings in the cerebellum demonstrated a negative association with age; this is consistent with results demonstrating early age-related sensitivity of the cerebellum beginning at age 50 years (34, 35). Although this age-related loss was associated with the GM in one study (35), our findings suggest that the cerebellar WM is also sensitive to age-related loss. The cerebellum, comprising micromodules that process in a parallel array, results in a network capable of execution and learning at exceptionally high speed (36). Our results may suggest that the cerebellum—with its different cytoarchitecture that is less reliant on serial neural transmission than on parallel processing—may tolerate more thinning of myelin before cognitive impairment results. The parallel network of neural transmission in the cerebellum may be sufficiently efficient to compensate for a reduction in the speed of short transmissions when myelin is lost. This could account for a negative aging effect on MTR without corresponding cognitive impairment. Alternately, whether the cerebellum is less prone to WM chemical disintegration than the cerebral areas is untested, as is the idea of whether the cerebellum is more dependent on neuronal loss in aging than is the cerebrum.

Hemispheric effects were found for the cortex, specifically the frontal and temporal lobes, and a trend was found for the lentiform nucleus. The frontal findings were predicted on the basis of the dominance of motor processing in the frontal lobe and were supported by the left hemispheric superiority only in the posterior, or motor, portion of the frontal lobe. The prediction was that the temporal lobe would also show left-hemispheric superiority in MTR due to the language specialization of the left temporal lobe, especially of the superior (and transverse superior), inferior temporal, and supramarginal temporal gyri (37). As expected, the hemispheric effect was due to the greater MTR in the left lateral rather than mesial and limbic portion of the temporal lobe.

The basal ganglia—lentiform nucleus (putamen and globus pallidus) and caudate—have been associated with fluent speech and, possibly, with language, although whether extensive disruption of cortical tracts are necessary for a language disturbance remains controversial (38). Speech problems due to defects in motivation have been excluded (38). However, the head of the caudate and the globus pallidus are closely related elements in Crosson's proposed mechanism for release of preformulated language (39), and both have been frequently implicated in subcortical aphasia. Therefore, a left hemispheric specialization for the lentiform nucleus and not the head of the caudate is difficult to explain. One possible explanation is that the caudate appears to be bihemispherically involved in several functions of language and memory (40–43), whereas the language-dominant left globus pallidus and putamen may be more specifically involved in subcortical aphasic disorders involving speech production (38). The putamen is involved in motor production circuits, and it may also contribute to the hemispheric effect in MTR for the lentiform nucleus due to left-hemisphere motor dominance. A left-hemispheric effect for the lentiform nucleus is also consistent with the robust left-hemispheric effect found in the left posterior frontal region, as speech production is dependent on the connectivity of the left basal ganglial–posterior frontal loop.

An aphasic syndrome sometimes occurs after lesions of the dominant thalamus, and thus, we might question why the thalamic MTR did not demonstrate a language-based hemispheric laterality effect. Both right and left thalamic aphasias are characterized by failure of semantic, attention, or visuoperceptual (rather than phonemic) contributions to reading and speech (44–46). Therefore, the thalamus may not be as dependent on speeded sequential processing dominantly processed in the left hemisphere, and it may be more dependent on bihemispheric cortical processing. Indeed, intrathalamic organization shows multiple corticothalamic and thalamocortical connections associated with aphasias because of widespread connections with the frontal, temporal, and parietal lobes (45).

Our sample differed from that of prior regional studies of MTR in healthy adults because our subjects were screened by means of neurodiagnostic interview, MR imaging, and neurocognitive testing. In their study of regional differences, Mehta et al (15) relied on a sample with "single, isolated complaints" of cognitive function for whom MR imaging was requested to rule out correlative structural abnormalities and in whom no abnormalities were found. Our adult group did not extend to old age; thus, we eliminated the unequivocal "normal" aging abnormalities of that period and some degree of noise, but this

limitation also precluded an examination of an expected decline in MTR after age 70 years. Furthermore, our small sample prevented a closer examination of age effects.

The lack of change in MTR with age in this group up to age 69 years with a corresponding loss of WM area is a paradoxical effect that could not be resolved in this study. To examine this paradox, a systematic study of age throughout the adult age span in *superhealthy* individuals is needed of MT and volumetric studies of WM.

Conclusion

In this study, a quantitative measure of the WM of the brain was distributed in functionally important ways. The relevance of myelin density to brain function may be an ontologic or an adaptive function or both, as suggested by published work (47). MT is a structural imaging technique with which we can understand the role of myelin. There was a lack of MTR change with age, yet smaller WM volume was associated with older age in our study sample as screened for WM hyperintensities on MR images. This suggests that the WM atrophy is salient even in very healthy individuals without cognitive impairment before old age and is therefore not due to thinning of myelin.

MT imaging may also be a technique to evaluate the role of myelin in studies of cognition. It is sensitive to cognitive impairment or clinical symptoms in disease models, including multiple sclerosis (23, 48, 49), schizophrenia (50), and dementia (14). Although not yet tested, MT imaging may also be relevant to studies of normal cognitive function because of its capacity to measure the small variations in myelin and axonal integrity in studies of healthy individuals prior to major changes from myelin loss due to old age.

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