ARCHIVAL REPORT

Multimodal Magnetic Resonance Imaging Assessment of White Matter Aging Trajectories Over the Lifespan of Healthy Individuals

George Bartzokis, Po H. Lu, Panthea Heydari, Alexander Couvrette, Grace J. Lee, Greta Kalashyan, Frank Freeman, John W. Grinstead, Pablo Villablanca, J. Paul Finn, Jim Mintz, Jeffry R. Alger, and Lori L. Altshuler

Background: Postmortem and volumetric imaging data suggest that brain myelination is a dynamic lifelong process that, in vulnerable late-myelinating regions, peaks in middle age. We examined whether known regional differences in axon size and age at myelination influence the timing and rates of development and degeneration/repair trajectories of white matter (WM) microstructure biomarkers.

Methods: Healthy subjects ($n = 171$) 14–93 years of age were examined with transverse relaxation rate (R_2) and four diffusion tensor imaging measures (fractional anisotropy [FA] and radial, axial, and mean diffusivity [RD, AxD, MD, respectively]) of frontal lobe, genu, and splenium of the corpus callosum WM (FWM, GWM, and SWM, respectively).

Results: Only R_2 reflected known levels of myelin content with high values in late-myelinating FWM and GWM regions and low ones in early-myelinating SWM. In FWM and GWM, all metrics except FA had significant quadratic components that peaked at different ages ($R_2 <$ RD $<$ MD $<$ AxD), with FWM peaking later than GWM. Factor analysis revealed that, although they defined different factors, R_2 and RD were the metrics most closely associated with each other and differed from AxD, which entered into a third factor.

Conclusions: The R_2 and RD trajectories were most dynamic in late-myelinating regions and reflect age-related differences in myelination, whereas AxD reflects axonal size and extra-axonal space. The FA and MD had limited specificity. The data suggest that the healthy adult brain undergoes continual change driven by development and repair processes devoted to creating and maintaining synchronous function among neural networks on which optimal cognition and behavior depend.

Key Words: Aging, Alzheimer, axial diffusivity, cognition, degeneration, diffusion tensor imaging (DTI), development, fractional anisotropy, magnetic resonance imaging (MRI), myelin, oligodendrocytes, radial diffusivity, relaxation rate (R_2), white matter (WM)

The exceptional myelination of the human brain has imposed especially high metabolic demands that might have belated some maturational processes. Starting from minimal or no myelin at birth, late-myelinating regions such as the frontal lobes might not reach peak myelination until well into middle age. Thus, during the adult lifespan, myelination of the thinner axons of late-myelinating regions in combination with maintenance/repair and degenerative processes combine to create white matter (WM) volume trajectories that are well-approximated by quadratic (inverted U) functions (Figure 1). The interplay of developmental, degenerative, and repair processes have been hypothesized to contribute to developmental diseases such as schizophrenia and bipolar disorder as well as trigger the proteinopathies associated with the pathology of highly prevalent dementing disorders of old age such as Alzheimer's disease (AD) (1,2). It is therefore of great diagnostic and therapeutic importance to define in vivo biomarkers that can track microstructural changes underlying brain myelination and axonal maturation as well as degenerative declines in myelin and axonal integrity associated with aging that result in quadratic trajectories of WM volumes (Figure 1).

We and others have previously used a magnetic resonance imaging (MRI) measure called transverse relaxation rate (R_2) to indirectly assess subcortical myelination in vivo. The R_2 is calculated from the better-known measure transverse relaxation time (T_2) as its reciprocal ($R_2 = 1/T_2 \times 1000$). Calculated R_2 measures are sensitive indicators of myelination, with myelination increasing R_2, whereas age-related myelin breakdown decreases it (3–10). Recently, the relationship between R_2 and myelin breakdown was confirmed in an animal model of genetically induced oligodendrocyte cell death that lacks the inflammatory response that can obscure the underlying myelin-based R_2 changes (11) as well as in a genetically hypomyelinated mouse mutant (12) (see Supplement 1 for prior studies on this subject). Our own prior human studies showed that R_2 reductions track age-related myelin breakdown/loss and are more severe in AD (10,13) as well as healthy individuals at increased genetic risk for developing AD (14,15). Furthermore, in healthy older individuals, increased R_2 is positively associated with better cognitive processing and motor speeds (13,15,16).

The MRI measures derived from diffusion tensor imaging (DTI) have recently become most popular as another way to investigate WM microstructural changes. Diffusion tensor imaging measures the rate of diffusion motion of water molecules on a microscopic spatial scale in a multiplicity of directions. Diffusion tensor imaging produces three standard measures of diffusivity: axial (AxD), along the direction of axons; radial (RD), perpendicular to AxD; and the summary diffusivity measure mean diffusivity (MD), the average of

From the Department of Psychiatry (GB, PH, AC, GK, FF, LLA); Laboratory of Neuroimaging (GB); Department of Neurology (PHL, GJL, JRA); Department of Radiology (PV, JPF), The David Geffen School of Medicine at UCLA, Los Angeles, California; Greater Los Angeles Veterans Administration Healthcare System (GB), West Los Angeles, California; Siemens Healthcare (JWG), Portland, Oregon; and the University of Texas Health Science Center at San Antonio (JM), Department of Epidemiology and Biostatistics, San Antonio, Texas.

Address correspondence to George Bartzokis, M.D., The David Geffen School of Medicine at UCLA, Department of Psychiatry, 300 UCLA Medical Plaza, Los Angeles, CA 90095–6968; E-mail: gbar@ucla.edu.

Received Mar 3, 2012; revised Jun 8, 2012; accepted Jul 1, 2012.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2012.07.010

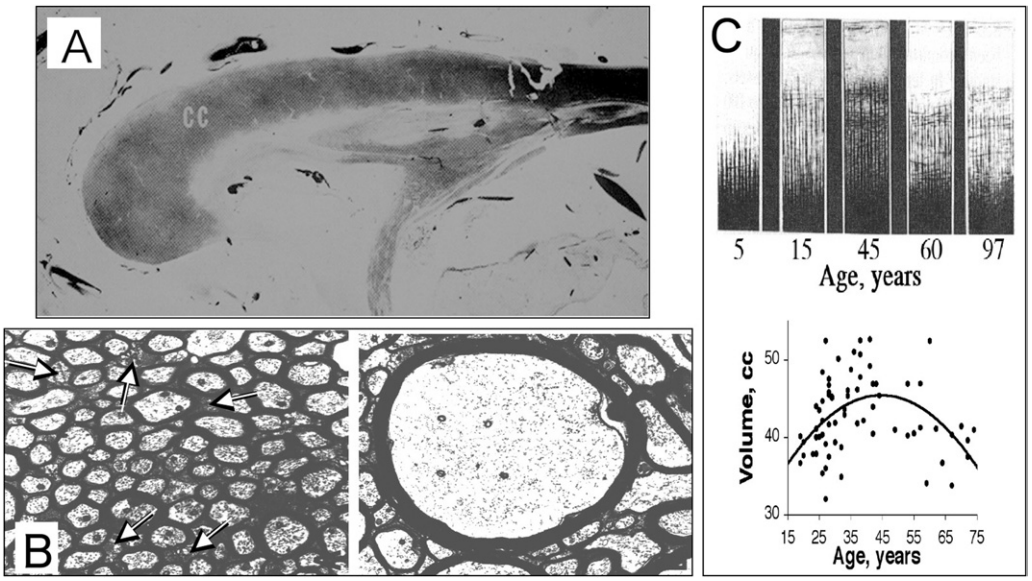

Figure 1. Postmortem assessment of relationships between axonal fiber size, myelin content, and lifespan myelination trajectories of chosen regions of interest. **(A)** Myelin stain of a 1-year-old human brain depicting corpus callosum (CC). Compare early-myelinating caudal end (black myelin stain on right side of the CC) where splenium (SWM) is located with the largely unmyelinated genu (GWM—light gray curved part of the CC on the left side of the panel) (reprinted with permission from Figure 1.3 on page 9 of Kemper [35], adapted from Kaes [68]). **(B)** Left panel: high-magnification myelin stain of adult primate GWM showing preponderance of small myelinated fibers (with some not yet myelinated marked with arrows). Right panel: SWM showing preponderance of very large axon fibers that are almost all thickly myelinated; however, because of the large volume of axonal cytoplasm, the proportion of myelin content is much lower in SWM compared with that of the GWM. Reprinted with permission from Lamantia and Rakic (36). **(C)** Myelination volumes (y axis) versus age (x axis) in frontal lobes of normal human brain. Top panel: postmortem myelin stain data (35) depicting the quadratic lifespan trajectory of frontal lobe intracortical myelin volume peaking at approximately age 45. Lower panel: in vivo magnetic resonance imaging data depicting the similar quadratic lifespan trajectory of frontal lobe myelinated white matter volume of healthy individuals also peaking at age 45. Reprinted with permission from Bartzokis *et al.* (37), copyright © 2001 American Medical Association. All rights reserved.

AxD and RD, as well as another summary variable, fractional anisotropy (FA), encapsulating directional diffusion information (see Supplement 1 for detailed description of these DTI metrics). Restriction in RD is believed to be primarily caused by axonal and myelin membranes making RD potentially sensitive to myelination. That interpretation of the RD metric has been questioned, however (17), and it has been suggested that RD might be most appropriately considered as a marker of tissue integrity (reviewed in [18]). Nevertheless, empirical experiments in animal models (19–23), human postmortem samples of multiple sclerosis brain (24,25), and infant brain development (26) have supported the suggestion that changes in RD might be most closely associated with myelination or loss thereof.

In the current study we assessed the adult lifespan trajectory of R_2 and DTI metrics in a healthy population. We chose a region of interest (ROI) approach to minimize the many pitfalls associated with whole brain DTI analyses, such as nonlinear susceptibility- and eddy current-induced anatomic distortions (27,28). Furthermore, through our three ROI choices, we interrogated: 1) different "types" of myelin, 2) the impact of crossing fibers, and 3) regional differences in vulnerability to age-related myelin breakdown (10) (for details see Supplement 1). Two late-myelinating regions with different fiber orientations were contrasted with one early-myelinating region. Bilateral midfrontal white matter (FWM) regions were chosen as the latest-myelinating regions that contain primarily very thin myelinated fibers with some admixture of large fibers (29,30) connecting it to the rest of the brain with a preponderance of crossing fibers. We also chose two midline corpus callosum (CC) regions that contain essentially only parallel fibers. These two CC regions were also specifically chosen on the basis of their timing/age at myelination and axonal fiber characteristics that produce strikingly different myelin contents: the late-myelinating genu (GWM), which contains almost exclusively small fibers that are thinly myelinated; and the early-myelinating lower splenium (SWM) that contains a preponderance of large primary visual fibers that are thickly myelinated. As can be seen in Figure 1B, these characteristics make the proportion of myelin/voxel volume much higher in the GWM (and FWM) than SWM, because a much larger proportion of the SWM volume is occupied by axonal cytoplasm even though each of those large axons is more thickly myelinated.

The anatomical characteristics of these three ROIs were used to examine the suggestion derived from postmortem and volumetric myelination data (Figure 1C) that over the lifespan there is a dynamic interplay at a microstructural level between developmental/maturational and degenerative/repair processes. To provide cross-validating data on myelin trajectories we examined two different myelination metrics (R_2 and RD). For comparison, we also examined AxD that was expected to track different biological processes (31,32) and the two standard summary measures of overall WM integrity (FA and MD). We assessed the proposition that, although age-related myelin breakdown is a generalized phenomenon, in old age small and thinly myelinated fibers of the late-myelinating regions (FWM and GWM) are most vulnerable to breakdown and loss (10,33,34). In addition, by choosing two CC regions that contain fibers aligned in parallel yet have striking differences in fiber size as well as myelin thickness, content, and vulnerability to breakdown, we tested the hypothesis that—similar to R_2—the RD metric will be most sensitive to an accelerated myelin loss in late-myelinating regions (FWM and GWM). Finally, we examined the proposition that the AxD metric will be most sensitive to axonal size and especially extra-axonal space (31,32).