In vivo assessment of age-related white matter differences using T_2* relaxation

Erika P. Raven[1,2], Peter van Gelderen[2], Jacco A. de Zwart[2], Diana H. Fishbein[3], John VanMeter[1,4], and Jeff H. Duyn[2]

[1]*Georgetown University, Washington, DC, United States,* [2]*Advanced MRI, LFMI, NINDS, NIH, Bethesda, MD, United States,* [3]*University of Maryland School of Medicine, Baltimore, MD, United States,* [4]*Georgetown Center for Functional and Molecular Imaging, Washington, DC, United States*

Introduction: Susceptibility contrast in myelinated tissue is dominated by an abundance of hydrophobic lipid bilayers produced by oligodendrocytes [1]. Myelin bilayers, or sheaths, form concentric wraps around axon processes, dividing water into cellular compartments with distinct susceptibly effects such as local resonance frequency shifts (Δf) and increased R_2* (=1/T_2*) decay rates [2,3]. Experimental data suggest that the susceptibility effects of myelinated axons are best characterized by a three-compartment model, representing water trapped between myelin layers ("myelin water"), within the axonal lumen, and throughout the interstitial space [2,4,5]. The number and integrity of myelin wraps is highly variable, depending on brain region but also on dynamic factors such as age and disease state [6]. By examining cellular specific contributions of each compartment, particularly myelin water, we attempted to examine age-related microstructural white matter differences during two developmental periods, adolescence and adulthood.

Method: Two groups were scanned: (1) Adolescents at Georgetown University (GU), using a 12-channel head coil on a Siemens Trio 3T scanner (n=11 females, n=8 males, ages 13-15, mean age 14), and (2) adults at the National Institutes of Health (NIH), using a 32-channel head coil on a Siemens Skyra 3T scanner (n=5 females, n=4 males, ages 23-49, mean age 29). At both sites, a multi-echo GRE sequence was used to map signal amplitude and phase evolution (9-15 slices, 0.4-0.5 mm gap, 1.5 mm isotropic resolution, FA 60-70°, 3-5 averages, scan time 6-10 min). GU scans used 40 echoes (from positive readout gradient only), TE = 2.9-80.6 ms, echo spacing = 1.92 ms, and TR = 1275 ms. NIH scans used 29 positive-only echoes, TE = 3.3-58.2 ms, echo spacing = 1.92 ms, and TR = 1000 ms. The phase of images was filtered in two steps to remove effects of macroscopic susceptibility differences. First, a linear phase offset term was calculated over time (TE) and subtracted voxel by voxel. Second, to correct for eddy-current effects, a phase map was calculated for each echo independently to remove spatially linear phase variation. Region of interest (ROI) analyses and multi-exponential fitting of multi-echo GRE images were performed using IDL. Three white matter ROIs were manually selected, including two midline corpus callosum regions, the splenium (SCC) and genu (GCC), and one bilateral mid-frontal region (FLWM). Parallel fibers of SCC and GCC were analyzed to minimize known orientation effects to the magnetic field (B_0), while FLWM contained fibers of mixed orientation.

Results: Results of the multi-exponential fitting model for adolescents (Table 1a) and adults (Table 1b) are shown for each ROI. Artifact precluded the analysis of GCC and FLWM in one adolescent. There were no significant group differences in myelin water amplitude, R_2*, or frequency shift for any region. In adolescents, axonal water amplitude and R_2* were significantly increased for SCC, while frequency shift was smaller (less negative) for SCC and GCC. Conversely, interstitial water amplitude was significantly decreased for SCC in adolescents.

Discussion: Myelination follows an inverted U-shaped trajectory with age, with early- (SCC) versus later- (GCC, FLWM) myelinating regions peaking throughout development and into middle age [6]. We predicted that adolescents would have lower myelin water fractions in GCC and FLWM, with SCC being comparable to adults. The current sample did not detect significant differences in *myelin water amplitude* while a 95% confidence interval indicated the difference between groups as less than ~ 22% (SCC), ~ 41% (GCC), and ~ 28% (FLWM) – ranges too broad to distinguish any expected age-related changes in myelination. The inability to detect group differences is potentially related to a lack of sensitivity of the method. This may be due to limitations such as reduced susceptibility contrast at 3T (compared to 7T used in previous work), unpredictable frequency offsets in regions of mixed fiber orientation (i.e., FLWM), and the presence of susceptibility-induced image artifacts (e.g., intravoxel dephasing) in anterior brain regions.

1a. Adolescents		**Myelin Water**			**Axonal Water**			**Interstitial Water**	
ROI	n	A_1 (%)	R_2*$_{,1}$ (Hz)	Δf_1 (Hz)	A_2 (%)	R_2*$_{,2}$ (Hz)	Δf_2 (Hz)	A_3 (%)	R_2*$_{,3}$ (Hz)
SCC	19	11.9 (0.4)	80.1 (2.2)	10.2 (0.3)	52.0 (0.4)**	14.7 (0.2)**	-4.2 (0.1)**	36.2 (0.3)**	19.8 (0.5)
GCC	18	9.7 (0.8)	78.2 (3.4)	13.7 (1.5)	53.7 (0.5)	16.4 (0.4)	-4.5 (0.1)**	36.6 (0.6)	19.2 (0.9)
FLWM	18	8.9 (0.5)	71.1 (2.7)	5.0 (2.0)	54.4 (0.5)	16.3 (0.5)	-4.2 (0.1)	36.6 (0.7)	17.2 (1.0)
1b. Adults		**Myelin Water**			**Axonal Water**			**Interstitial Water**	
ROI	n	A_1 (%)	R_2*$_{,1}$ (Hz)	Δf_1 (Hz)	A_2 (%)	R_2*$_{,2}$ (Hz)	Δf_2 (Hz)	A_3 (%)	R_2*$_{,3}$ (Hz)
SCC	9	12.6 (0.5)	83.2 (1.7)	11.1 (0.4)	48.3 (0.5)**	11.6 (0.4)**	-4.6 (0.1)**	39.1 (0.3)**	20.7 (0.5)
GCC	9	9.9 (0.6)	78.5 (3.1)	11.9 (1.3)	52.7 (0.5)	15.3 (0.3)	-5.1 (0.1)**	37.4 (0.5)	18.8 (0.9)
FLWM	9	9.3 (0.4)	78.6 (3.3)	7.2 (0.9)	53.6 (0.2)	15.6 (0.2)	-4.6 (0.1)	37.2 (0.5)	15.9 (0.4)

Table 1a-b. Mean and standard error (SE) are reported for ROI-based three-component fitting results of adolescents (1a) and adults (1b). A_n is the relative amplitude, R_2*$_n$ the relaxation rate, and f_n the frequency shift of component *n*. Myelin and axonal water frequency shifts were calculated relative to a fixed interstitial water frequency of 0 Hz [2]. Results of two-tailed Student's *t*-tests that reached a p<0.05 cut off when comparing adolescents and adults for each variable are highlighted in blue (key for p: <0.01**).

References: [1] Li, T.-Q. *et al. Magn. Reson. Med.* (2012). [2] Sati, P. *et al. Neuroimage* (2013). [3] Wharton, S. & Bowtell, R. *Proc. Natl. Acad. Sci.* (2012). [4] Van Gelderen, P. *et al. Magn. Reson. Med.* (2012). [5] Lancaster, J. L. *et al. J. Magn. Reson. Imaging.* (2003). [6] Bartzokis, G. *et al. Biol. Psychiatry* (2012).