Inhomogeneous Magnetization Transfer: Developmental changes during childhood

Alyssa Mah[1], R Marc Lebel[2,3], David C Alsop[4], Gopal Varma[4], and Catherine Lebel[3]

[1]Biomedical Engineering Program, University of Calgary, Calgary, AB, Canada, [2]General Electric Healthcare Canada, Calgary, AB, Canada, [3]Radiology, University of Calgary, Calgary, AB, Canada, [4]Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

Introduction: Myelin forms an insulating layer around axons and facilitates efficient neural connections. Changes in myelination occur during childhood and adolescence; various MRI techniques including anatomical imaging, diffusion tensor imaging (DTI), myelin water imaging, and magnetization transfer (MT) imaging have been used to study healthy white matter (WM) development in vivo. With these methods, rapid WM changes have been shown during infancy [1, 2] and continued development has been reported during childhood and adolescence [3-7]. These reports are suggestive, but not indicative, of increased myelination throughout development because they are sensitive to multiple processes. Imaging techniques more specific to myelin have not been used in late childhood/adolescence.

Inhomogeneous magnetization transfer (ihMT) is able to virtually eliminate signal from unmyelinated tissues and provides a quantitative measure attributed to motion-restricted lipid chains in membranes that are far more dense in myelinated tissues [8], while MT indirectly probes all macromolecular components [9]. ihMT may provide a biomarker specific to myelin and allow further characterization of WM development. Here, we use MT and ihMT to characterize WM in children. Understanding healthy development can help identify critical periods of maturation, and may ultimately assist with identification and treatment of developmental disorders.

Methods: (ih)MT and DTI data were collected from 16 healthy children (9 2-4 years; 7 8-13 years). Subjects were scanned on a 3T MR system (Discovery 750w; General Electric, Waukesha, WI) using a 32-channel head coil. Two slightly different protocols were used for the two age groups; key contrast generating elements were the same. The (ih)MT sequence collected both ihMT and MT data using a whole brain 3D spoiled gradient echo (SPGR) sequence with a 5 ms Fermi pulse with peak B1 of 45 mG and ±5 kHz offset prior to excitation. In the younger children: TR/TE = 10.18ms/2.04ms, 2.4 mm^3 isotropic resolution, total scan time of 5:04 m:s. In the older children: TR/TE = 10.46ms/2.176ms, 2.2 mm^3 isotropic resolution, scan time of 5:12 m:s. DTI protocol: single spin echo, 2.2 mm slices, 30 directions; for young children: b=750 s/mm^2, 5 b=0 s/mm^2, scan time = 4:03; for older children: b=900, 2000 s/mm^2, 10 b=0 s/mm^2, scan time 14:24 m:s. All data quality was good, with very little motion from either the preschool or childhood groups.

Quantification of MT and ihMT measurements was performed using inverse subtraction methods and a high tip angle reference scan. With an SPGR sequence in the short TR/low-tip regime, the difference in longitudinal relaxation rates observed with different MT pulse conditions was approximated by: $\Delta(R_1^*) = \frac{C\alpha^2}{2T_R} S_C \Delta\left(\frac{1}{S^*}\right)$ Eq. 1

In Eq. 1, R_1* is the longitudinal relaxation rate during a particular MT state; S* is the measured signal during this state. C is the flip angle scale factor for the high tip angle reference, α is the flip angle, and S_c is the measured reference signal. In conventional MT, $\Delta(R_1^*)$ and $\Delta(1/S^*)$ are the rate and inverse signal differences when an off-resonant pulse is applied vs when no pulse is applied. In ihMT, the differences are between conditions with single-frequency off-resonant pulses applied at ±5 kHz, and dual-frequency off-resonant pulses with power split between +5 kHz and -5 kHz. The rate differential in Eq. 1 provides a simple, quantitative measure correlated to the concentration of the targeted pool (i.e., all macromolecular content or myelin).

DTI data was processed in Diffusion Toolkit and 7 WM tracts were delineated in TrackVis [12], and normalized to the (ih)MT images for use as volumes of interest: the cingulum (CG), corticospinal tract (CST), genu and splenium of the corpus callosum (GCC, SCC), inferior fronto-occipital fasciculus (IFO), and superior and inferior longitudinal fasciculi (SLF, ILF). Mean qMT and qihMT were calculated for each tract for each subject. Groups were compared using independent-sample T-tests.

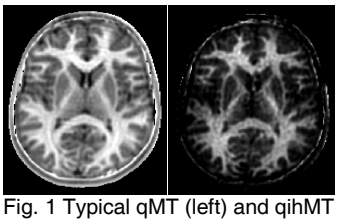

Fig. 1 Typical qMT (left) and qihMT (right) images from a 9-year old.

Results: Fig. 1 shows sample axial images. Signal intensity in the images is related to myelin concentration (qihMT), and all macromolecular contributions (qMT). Mean values of qMT and qihMT for each tract are shown in Fig. 2. Significant differences were observed in qMT between groups for all tracts except the CST and SLF, while only the CG and GCC had significant qihMT differences. The average difference in qihMT magnitude across all WM tracts was 18%, while the average difference qMT magnitude was 8%.

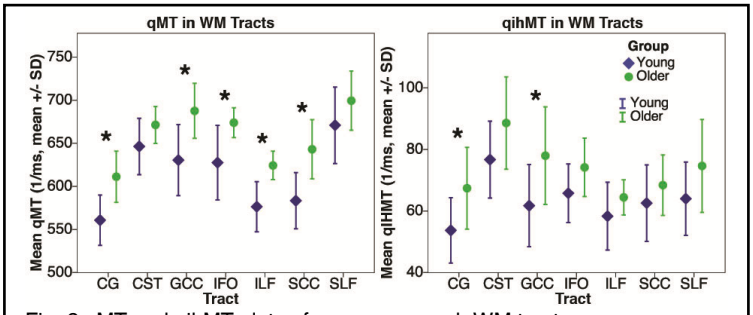

Fig. 2 qMT and qihMT plots of means per each WM tract. (*: $p < 0.05$ from independent-sample T-test between groups)

Discussion/Conclusion: qMT and qihMT quantify $\Delta(R_1^*)$ due to the exchange of magnetization from the macromolecular pool. qMT has greater magnitudes because it encompasses all macromolecules, while qihMT is more specific to the a restricted pool of macromolecules. Significant differences in qihMT indicate measurable myelin increases during childhood in the CG and GCC. Non-significant increases of qihMT were observed for all other tracts, suggesting that myelination is occurring elsewhere; increased power is needed to test this. DTI studies have consistently noted increased fractional anisotropy in all of these areas during childhood [3], though this may reflect processes other than just myelination. Post mortem studies demonstrate a posterior-to-anterior progression of myelination [13], which is consistent with our findings of increased myelin in the frontal tracts during childhood. Qualitatively, it is interesting to note the increased ihMT in the CST relative to other tracts, a contrast that is not apparent in the qMT image or data plot. In conclusion, qMT and qihMT provide unique information about WM development during childhood that may be used to more specifically understand the physiological processes occurring during this time.

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