MTR and T_1 measurements in the very preterm brain – Markers for changes in tissue microstructure during early development

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Introduction:

The progression of myelination in the immature brain involves the increase in glycolipids and cholesterol concentrations and the decrease in free and total water content of tissue. These changes are manifested as shortening of T_1 relaxation times and increasing magnetization transfer (MT)[1-4]. However, MT and T_1 reflect distinct biological properties of tissue and need not be related. To investigate these two markers of maturation we correlated MT and T_1 measurements in the very preterm brain. Comparing these quantities without reference to age allows for delays in development that may be associated with pathology.

Methods:

Subjects: The study cohort included 15 preterm neonates born between 24 and 31 weeks gestational age (mean, 28.4 ± 2.0 weeks) and scanned between 26 and 32 weeks (mean, 29.9 ± 2.0 weeks). All infants were scanned within 2 weeks after birth. Informed, written consent was given by the infants' parents; the study was approved by the hospital's research ethics board. Infants presented with normal findings (n=5) as well as pathologies such as Grade I germinal matrix haemorrhage (GMH-I) only (n=2), Grade II intraventricular haemorrhage (IVH-II) only (n=3), white matter injury (WMI) only (n=3), GMH-I + WMI (n=1) and IVH-II +WMI (n=2).

MR Acquisition: MR scans were performed on a 1.5T GE Signa Excite HD scanner (GE, Milwaukee, WI) using an MR-compatible incubator and neonatal head coil (AIR Inc., Cleveland, OH). High resolution axial T_1- and T_2-weighted (T_1w and T_2w) volumes were acquired using 3D spoiled gradient recalled (SPGR) (TR/TE/FA=23ms/4ms/19º, BW=15.63kHz, FOV=12.8cm, matrix=128x128, 110 slices of 1mm) and multi-slice 2D FRFSE (TR/TE/ETL=4000/145ms/19, BW=25kHZ, FOV=12.8cm, matrix=128x128, 90 slices of 1mm). MT images were obtained with 1x1x1.5mm voxel size and TR/TE/FA=27ms/4ms/10º by acquiring the sequence twice – once with an off-resonance MT saturation pulse and once without. 3D quantitative T_1 (qT_1) mapping was achieved by acquiring 20 axial slices centered at the level of the basal ganglia using the following experimental parameters: TR/TE=3.9/1.8ms, flip angles of 2^o, 9^o and 19^o, 1.1x1.1x2 mm voxel size and 140 mm FOV[5]. For accurate flip angle calculation, a rapid B_1^+ mapping sequence was employed using 8 shots SE-EPI (TR/TE=4000/15ms), 60° and 120º excitation angles and 120° and 240° refocusing angles, and using the same resolution. Total scan time equalled 25 min.

Image Processing: The Brain Extraction Tool (BET) was used to segment T_2w volumes into brain and non-brain[6]. Images were reviewed on a case-by-case basis and an inter-slice motion correction algorithm based on the MNI AutoReg software package[7] was applied where needed. Structural scans (T_1w and T_2w) were corrected for intensity non-uniformity[8]. The anterior and posterior commissures (AC-PC line) and mid-sagittal plane were manually tagged on T_1w scans. These tag files were then used to align T_1w, T_2w, MT and T_1 relaxometry scans in a Talairach-based orientation with the origin at the AC. MTR images were obtained by computing the percent difference between scans with and without the off-resonance pulse. qT_1 parametric maps were produced using a linear least squares solution[5]. The genu and splenium of the corpus callosum (gCC and sCC, respectively), basal ganglia (BG), thalamus (Thal), posterior limb of internal capsule (PLIC) and posterior periventicular white matter (PVWM) were manually segmented (last 4 structures: left and right) on T_1w scans for each subject; MTR and T_1 values for these structures were extracted.

Analysis: Left/right hemispheric differences in MTR and T_1 values were tested using paired student's t-tests for the BG, Thal, PLIC and PVWM. Multiple comparisons were account for using Bonferroni correction. MTR values were regressed against T_1 using a linear mixed effect model that included T_1, region, and T_1 by region interaction as factors. The interaction factor was used to test for differences in regrasion slope between regions.

Table 1 - Significance of regression results for MTR. *denotes $p < 0.05$.

	T_1	Region	Interaction
All data	<0.0001*	<0.0001*	0.770
Cluster 1	0.005*	0.227	0.891
Cluster 2	<0.0001*	<0.0001*	0.107

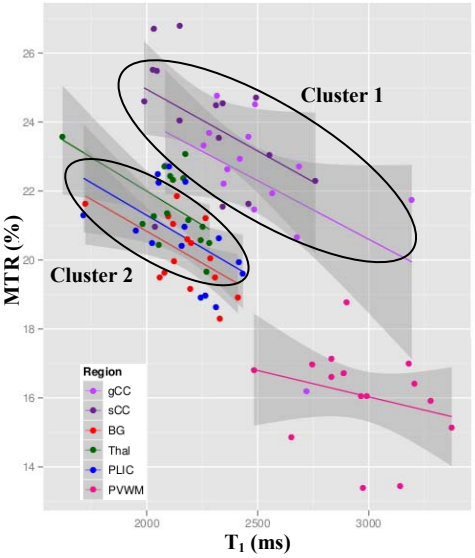

Fig. 1: MTR values as a function of T_1 in the gCC, sCC, BG, thalami, PLIC and P-PVWM. The linear regression line fitted to the data from each region is provided along with and the 95% confidence interval.

Results& Discussion:

Based on paired student's t-tests results, data from left and right hemispheres were pooled for analysis (p>0.0125). Fig. 1 and Table 1 summarize the regression results. MTR varied linearly with T_1 for all regions. The regression slope did not vary between regions, but the intercepts differed significantly. Highest MTR values were shown in the gCC and sCC (no significant difference between those (p=0.227), Table 1 – cluster 1) then, in decreasing order, Thal, PLIC, BG (significantly different, cluster 2) and PVWM. Interestingly, a different order was observed for T_1 as regions in cluster 2 demonstrated the shortest values, then cluster 1 and PVWM the longest. In general, the increase in MTR values with T_1 shortening is attributed to myelination and loss of water content in the developing brain. The different trajectories described here may occur at this age due to the increased rigidity (packing) in tracts such as gCC and sCC resulting in longer T_1 values. This order corroborates recent T_2 relaxometry results and histological findings[9,10]. These findings suggest a means based on T_1 and MT for early and consistent detection of changes in tissue microstructure.

References: **1.** Xydis V et al. *Eur Radiol, 2006; 16: 215-220.* **2.** Engelbrecht V et al. *AJNR, 1998; 19: 1923-1929.* **3.** Van Buchem MA et al. *AJNR, 2001; 22:762-766.* **4.** Williams LA et al. *Radiology, 2005;235:595-603.* **5.** Cheng HL, Wright GA. *Magen Reson Med, 2006, 55: 566-74.* **6.** Smith SM*Hum Brain Mapp, 2002; 17:143-155.* **7.** Collins DL et al. *J Comput Assist Tomogr, 1994; 18:192-205.* **8.** Sled JG et al. *IEEE Trans Med Imaging, 1998; 17:87.* **9.** Leppert IR et al. *J. Magen Reson Imaging, 2009;29:258-267.* **10.** Brody BA et al.*J Neuropathol Exp Neurol 1987;46:283-301.*