Early myelination in the very preterm brain – A combined MTR-DTI study

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Introduction:

Magnetization transfer (MT) and diffusion tensor imaging (DTI) have been used in the past to investigate maturation in the paediatric population including term and preterm neonates[1-4]. MT is thought to be sensitive to myelination, whereas DTI parameters manifest restriction of water movement in tissue. We compare these modalities to quantify brain maturation-myelination in very preterm neonates (<32 weeks gestational age (GA)) using voxel based analyses (VBA).

Methods:

Subjects: The study cohort included 22 preterm neonates born between 27 to 31 weeks GA (mean 29.4 ± 1.0 weeks) and scanned between 28 to 32 weeks (mean 30.8 ± 1.0 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=19, including 1 with non-specific basal ganglia hyperintensity), Grade I germinal matrix haemorrhage only (n=2) and Grade II intraventricular haemorrhage only (n=1).

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. Twice refocused spin echo planar DTI was acquired with 3 non-diffusion and 15 non-collinear diffusion weighted volumes and b=700 s/mm^{2}using: 2D axial oblique slices, FOV=205mm, with 1.6mm cubic voxels, TR/TE/FA=15s/85ms/90°. Total scan time equalled 30 min.

Image Processing: The Brain Extraction Tool (BET) was used to segment T_2w volumes into brain and non-brain[5]. Three structural scans (T_1w, T_2w and proton density (MT without the off-resonance pulse)) were corrected for intensity non-uniformity[6] and used to segment the brain anatomy into white matter (WM), grey matter (GM), and cerebral spinal fluid (CSF)[7]. Magnetization transfer ratio (MTR) images were obtained by computing the percent difference between scans with and without the off-resonance pulse. DTI data were processed using the DROP-R algorithm[8] and fractional anisotropy (FA) and mean diffusivity (MD) maps were produced. Rigid body registration of T_2w volumes was accomplished using a target model, a 30 week neonate not included in the present cohort[9]. Subsequently, all volumes were co-registered using all possible pair-wise affine registrations to create a linear average of the entire data set[10]. Affine transformation matrices were applied to all individual scans to produce average volumes. A threshold of >50% representation across subjects was applied to the segmented averaged WM and GM volumes to construct the corresponding masks.

Analysis: Voxel based linear regressions of FA and MD values against MTR across subjects were calculated to produce volumetric maps of slope and intercept. At each voxel this analysis included only the subset of subjects where the tissue classification (GM or WM) matched the classification of the group average.

Results& Discussion:

Fig.1 depicts the averaged MTR, FA and MD maps. The MTR map (a) demonstrates clear myelination in the genu and splenium of the corpus callosum (gCC and sCC, respectively) and thalamus with evidence of early myelination in the anterior and particularly the posterior limb of the internal capsule (ALIC and PLIC, respectively) as well as the globus pallidus. Histological findings describe myelination in the ventrolateral thalamus under 36 weeks GA, PLIC around 36 weeks and ALIC and globus pallidus close to term[11]. Interestingly, myelination in the gCC, and sCC is observed only after term. The MD map (d) shows a decreased diffusion coefficient, suggesting increased restriction, in all those areas, whereas, the FA map (b) delineates WM tracts with the highest values in the sCC, then (in decreasing order) gCC, PLIC, ALIC and the external capsule. The slope parametric volumes presented in Fig. 1e,f extracted from the correlation between FA / MD and MTR reveal different trends across brain regions showing negative correlation between MTR and FA values in the basal ganglia (BG) while a positive correlation is observed in myelinated as well as pre-myelinated WM areas, though to different extents. A tenfold lower positive slope is observed in ventrolateral thalamus compared to the WM. Interestingly, in a previous study we have shown a similar maturation rate in the BG and thalamus using MTR measurements with significantly higher values in the latter[12]. The above results suggest DTI parameters to be sensitive to axonal packing and the development of order in tissue rather than myelination, while MTR maps detect early myelination in GM as well as WM structures. Therefore, a multi-modal approach is suggested to achieve a more complete description of the components of maturation-myelination processes and gain fuller understanding of the timing of these developmental changes in the immature brain using MRI.

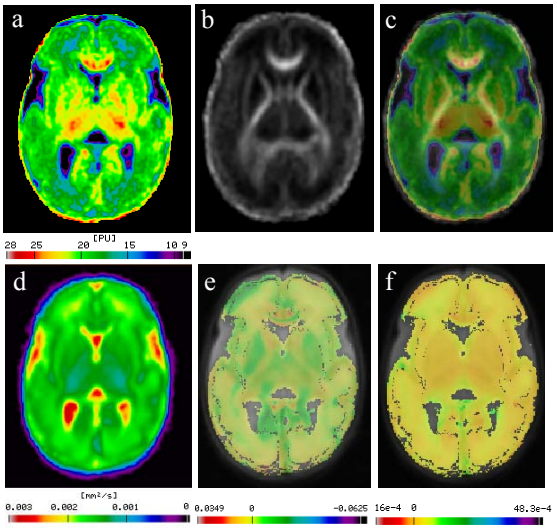

Fig. 1: Average MTR (a) and FA (b) maps, overlay of both (c), average MD map (d) and the slope map for FA (e) and MD (f) regression against MTR, overlaid on average T_2w volume.

References: **1.** Xydis V et al. *Eur Radiol, 2006; 16:215-220.* **2.**. Engelbrecht V et al. *AJNR, 1998; 19:1923-1929.* **3.** Mukherjee P et al. *Radiology, 2001;221:349-358.* **4.** Partridge SC et al. *J Magen Reson Imaging, 2005;22:467-474.* **5.** Smith SM*Hum Brain Mapp, 2002; 17:143-155.***6.** Sled JG et al. *IEEE Trans Med Imaging, 1998; 17:87-97.* **7.** Tohka J et al. *NeuroImage,2004; 23:84-97.* **8.** Morris D et al. *ISMRM, 2010; 18:4040* .**9.** Collins DL et al. *J Comput Assist Tomogr, 1994; 18:192-205.***10.** Spring S et al. *NeuroImage*, *2007*; 35:*1424-1433.* **11.** Brody BA et al.*J Neuropathol Exp Neurol 1987;46:283-301.***12.** Nossin-Manor R et al.*ISMRM, 2010; 18:4383.*