Investigating the Relationships Between T1 and T2 Relaxation Times and Myelin Water Fraction During Neurodevelopment

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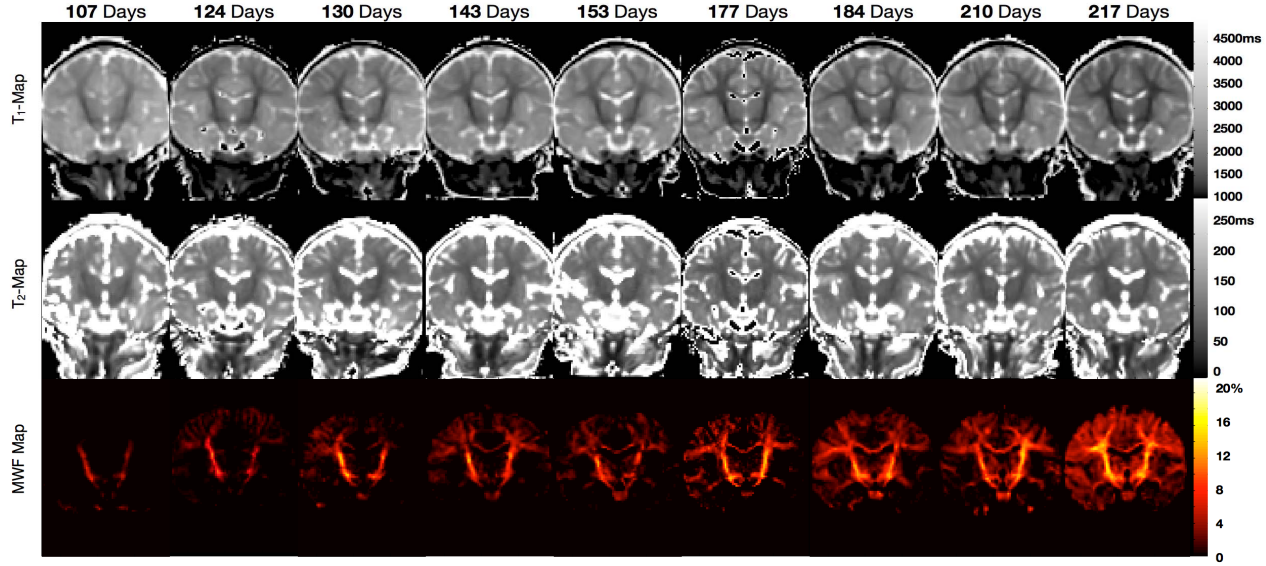
INTRODUCTION: Human neurodevelopment is punctuated by several essential processes, amongst them are dendritic growth; synapse generation and subsequent pruning; and myelination. The establishment of the lipid myelin layer surrounding neuronal axons is necessary for the efficient and coordinated flow of information across the complex integrated neural systems responsible for cognitive, emotional and behavioural functioning. Given the crucial role myelin plays, and the emerging hypothesis that abnormal or aberrant myelination contributes to the etiology of several neurological and psychiatric disorders (i.e. autism), investigation of the spatio-temporal dynamics of myelination is necessary. To this end, several magnetic resonance imaging techniques have been used to provide information related to myelin. For example, the gradual onset of 'adult-appearing' grey / white matter contrast in T_1 and T_2-*weighted* images broadly follows the the established myelination time-course derived from serial post-mortem histological studies. However, T_1 and T_2-*weighted* images are *qualitative*, limiting objective comparisons between subject groups. Diffusion-weighted imaging (and, by extension, diffusion tensor imaging, DTI) is sensitive to fibre architecture, coherence, and density. DTI-derived metrics, including fractional anisotropy (FA), mean and radial diffusivity (MD and RD), provide complementary indices of neuronal maturation, however, as significant FA and RD are noted in non-myelinated nerve [1,2], these metrics are not myelin-specific. Quantitative T_1 and T_2 evaluation is also cited as a surrogate measure of myelin [3.4], as T_1 and T_2 decreases during neurodevelopment are believed to reflect the increased presence of myelin precursory proteins and macromolecules, development of the myelin bilayer, and loss of free water. While not myelin-specific, the relationships between T_1 and T_2 and myelin content, and therefore their surrogate suitability, remains unknown. In this work, we investigated these relationships through comparison of T_1 and T_2 with myelin content, quantified through evaluation of the myelin water fraction (MWF) derived using multi-component Driven Equilibrium Single Pulse Observation of T_1 and T_2 (mcDESPOT) [5].

METHODS: Quantitative DESPOT [6] T_1 and T_2, and mcDESPOT MWF data were acquired of 9 healthy infants (4 female) between 3 and 8 months of age during non-sedated natural sleep. Acquisition parameters were: SPGR: TE/TR = 4.1/11.2ms, α = {3,4,5,6,7,9,11,14}°, BW = 93Hz/voxel; SSFP: TE/TR = 5.6/11.2ms, α = {14,20,25,30,37,46,58,80}°, BW = 244Hz/voxel. SSFP data were acquired with phase-cycling increments of 0 and 180° to allow correction for off-resonance effects [7]. Scan time was minimized through partial k-space acquisition (NEX=0.5) and parallel imaging (G factor = 1.5). Total acquisition time was 10 minutes on a GE Signa 1.5T clinical scanner with an 8-channel head RF coil. Following acquisition, each infant's data were linearly co-registered and non-brain signal removed. Voxel-wise T_1 estimates were derived from the SPGR data; T_2 from the SSFP data; and MWF from both as detailed in [5,6]. All infant data was then non-linearly co-registered and developmental trajectories (T_1, T_2 or MWF vs. age) were calculated for the genu, body and splenium of the corpus callosum; internal capsule; frontal, temporal, parietal, and occipital lobe white matter. Correlations between T_1 and T_2; T_1 and MWF; and T_2 and MWF were then investigated over these regions to determine the relationships between them.

RESULTS: A comparison of coronal T_1, T_2 and MWF maps through each of the infants over the age range is shown in Fig. 1. As noted in previous studies, T_1 and T_2, particularly within the major white matter pathways, decrease dramatically over the first 8 months of life. The data also reveal the dynamic increase in myelin as the white matter pathways become established. Corrected for multiple comparisons, statistically significant (p<0.05) correlations were found between T_1 and T_2 in bilateral frontal WM, left genu and right splenium of the corpus callosum; between T_2 and MWF in the right splenium of the corpus callosum; and between T_1 and MWF in bilateral frontal occipital and cerebellar WM, left temporal WM, and genu and splenium of the corpus callosum.



DISCUSSION / CONCLUSIONS: Visualization and quantitative evaluation of white matter maturation and myelination has tremendous research and clinical applicability. While MRI has provided a non-invasive window into the process of neurodevelopment, quantitative analysis of specific development processes have been difficult given the dearth of appropriate and specific imaging techniques. In this work, we investigated the relationships between relaxation times and myelin water fraction. In general we found that T_1 was generally well correlated to MWF, likely owing to the strong influence of lipids, proteins and macromolecules (the very substrates of myelin) on T_1. In contrast, T_2 was poorly correlated with MWF, likely due to the greater dependence of T_2 on free water content and paramagnetic atoms (not greatly affected during early myelination). Thus, contrary to existing reports [4], changes in T_2 should not be immediately interpreted as variations in myelin content. In general, however, quantitative evaluation of MWF, through mcDESPOT or other technique, is preferable to surrogate markers.

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