In Vivo Imaging of Myelin Development in Young Males using T_2 Relaxation

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INTRODUCTION: Yakovlev and Lecours showed in 1967 that the myelination of certain structures of the central nervous system (**CNS**) such as the corpus callosum (**CC**), fornix and the reticular formation continues into the second decade [1] but until recently there has been no way of corroborating this research in normal children due to the lack of a non-invasive, *in vivo* technique to assess the quantity of myelin. However, analysis of the $\mathbf{T_2}$ of water in white matter allows for the calculation of a myelin water fraction (**MWF**) which has been shown to correlate strongly with myelin staining of formalin fixed multiple sclerosis brains [2]. The MWF represents the relative signal from the water trapped between the myelin bilayers (defined as having T_2 <50ms and referred to as myelin water) to the total signal from all water environments in the CNS: myelin water, intra and extra cellular water (T_2 approximately 80ms) and water in cerebrospinal fluid (**CSF**) which has T_2 greater than 1s [3, 4]. This study is the first to image the development of myelin of the CC across a narrow age range of normal males using this technique.

METHODS: *MR Acquisition*: Eight normal male children aged between 9 and 12 years (mean 10.9 years) were scanned on a 1.5T GE scanner in the midsagittal plane. T_2 data from three volunteers was not usable due to motion artefact. T_2 relaxation data was acquired using a modified 32 echo Carr-Purcell-Meiboom-Gill (**CPMG**) sequence which utilised crusher gradient pulses to eliminate the signal from tissue outside the selected slice. (TR = 3 s, echo spacing = 10 ms, slice thickness = 5 mm, field of view = 22 cm, 256 x 128 matrix). Each voxel measured 0.86mm x 0.86mm x 5mm.

Data Analysis: The 32 echo decay curves were decomposed into an unspecified number of exponential components using a regularised non-negative least squares algorithm [5]. The MWF was defined as the fraction of the T_2 signal below 50ms relative to the total T_2 signal. A myelin water map of the midsagittal slice was created representing the MWF for each individual voxel. A region of interest (**ROI**) was drawn around the CC on the first echo of the CPMG sequence, which has high in-plane anatomic resolution, in order to identify the voxels representing the white matter of the CC. An average MWF was calculated from the entire signal within this region.

The myelin water map was filtered for voxels which exhibited a poor fit to the T_2 decay curve. Images were filtered such that voxels with a signal to fit ratio (**SFR**, which is analogous to SNR, but compares the signal density to the standard deviation of the residuals of the T_2 decay curve), less than 100 were excluded from the analysis. Figures 1, 2 and 3 show an unfiltered myelin water map, the SFR map for the myelin map in Figure 1 and the filtered myelin map respectively.

Ranking Myelin Development: The voxels representing the white matter of the CC were isolated and their MWFs were superimposed onto the first echo of the T_2 sequence. The 5 images were then ranked from that exhibiting the least myelin development to most the developed by 4 informed investigators.

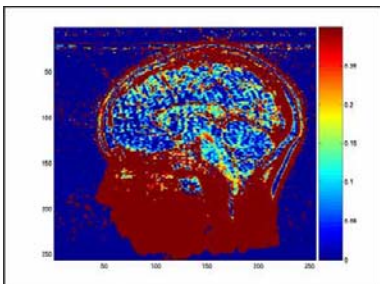

Figure 1: Unfiltered myelin map of the midsagittal plane of a male aged 12 years

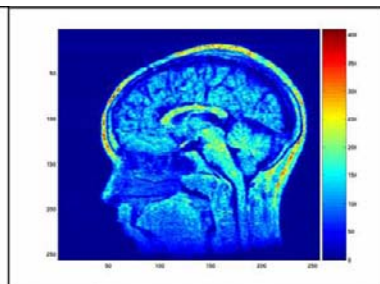

Figure 2: Signal to fit ratio (SFR) map for each voxel illustrated in Figure 1.

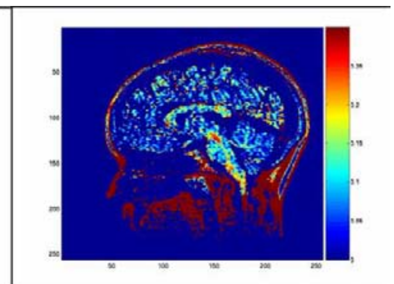

Figure 3: Filtered myelin map from Figure 1 excludes voxels with SFR less than 100

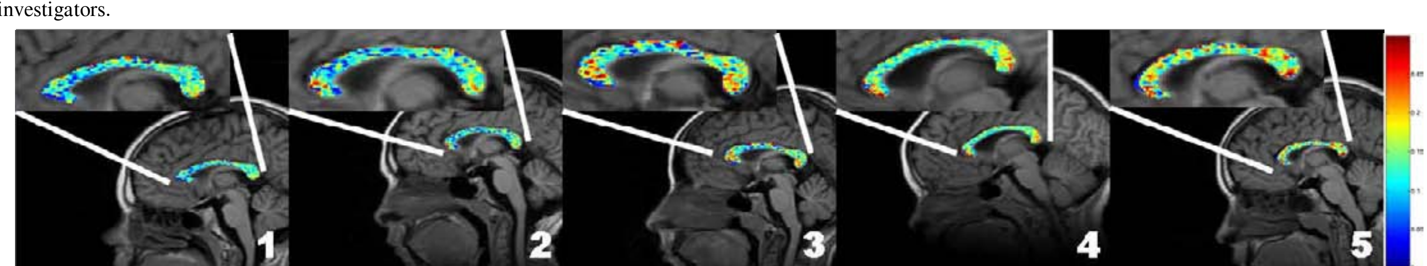

Figure 4: The filtered myelin water maps ranked by independent judges from least to most myelin. The colour bar represents the myelin water fractions of each voxel.

RESULTS: The maps are illustrated in Figure 4 ordered by their mean ranking. The investigators had an inter-rater spearman's rank correlation of 0.975. The ranking did not correlate with the subject's age. The ranking correlated perfectly with the average MWF.

DISCUSSION: The filtered maps clearly show the myelination of the corpus callosum beginning at the genu and splenium and continuing into the main body of the CC which agrees with Yakovlev and Lecours findings. The investigators were evenly split when ranking the scans illustrated above as 3 and 4. This was due to the similarities between the two scans and the subjective nature of the ranking. However, the investigators did have a very high inter-rater correlation and, with the exception of the reversal of order for these two scans, ranked the other scans exactly the same. The scans ranked perfectly with the average MWF illustrating that these images we view are well represented in the calculations performed using average MWF. The lack of a correlation with age indicates that age is not the only factor affecting the myelination of the CC in young males.

The SFR filter successfully isolated and excluded voxels with falsely high MWF found in the CSF due to flow effects since these voxels showed very large residuals from T_2 decay curve fits. The uniformity of the correlations across a large range of minimum values allows us to conclude that the exact minimum SFR value is not significant but that any value within this range is acceptable.

CONCLUSION: These results show that T_2 relaxation analysis provides a non-invasive, *in vivo* method for quantifying myelin development which will allow the myelination process to be better understood than has previously been possible. Further studies using this technique will be able to show, for the first time, the myelination of the normal adolescent brain over the course of time.

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