T2 Relaxation Illustrates Correlation Between Myelin Development and Verbal IQ Scores in Young Males

K. Whitaker[1], C. M. Clarke[2], and A. L. MacKay[1,3]

[1]Physics and Astronomy, University of British Columbia, Vancouver, BC, Canada, [2]Psychiatry, University of British Columbia, Vancouver, BC, Canada, [3]Radiology, University of British Columbia, Vancouver, BC, Canada

INTRODUCTION: Until recently the investigation of the myelination cycle has been hampered by the lack of a non-invasive, *in vivo* technique for assessing the quantity of myelin. However, analysis of the $\mathbf{T_2}$ decay of water in the central nervous system (**CNS**) allows the measurement of a myelin water fraction (**MWF**) which has been shown to correlate strongly with myelin staining of formalin fixed normal and Multiple Sclerosis brains [1]. 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 healthy CNS: myelin water, intra and extra cellular water (T_2 approximately 80ms) and water in cerebrospinal fluid (**CSF**) which has T_2 about 3s [2, 3].

The Wechsler Intelligence Scale was developed based on the philosophy that intelligence is "the global capacity to act purposefully, to think rationally, and to deal effectively with [one's] environment" [4]. In 1949 this test was adapted for children and was revised in 1974 to the Wechsler Intelligence Scale for Children – Revised (**WISC-R**). The test comprises a battery of 10 subtests which are compiled to provide verbal, performance and full intelligence quotients (**VIQ**, **PIQ** and **FIQ**). These scores are age corrected but do not account for any other factor which may affect the child's cognitive development.

The myelination of certain CNS structures continues into the second decade [5] and the development of white matter structure in children has been shown to correlate with increased cognitive function and specifically with IQ [6]. However, these studies have only investigated the size of the structures rather than the amount of myelin. The number of myelinated axons in the corpus callosum (**CC**) has been shown to be greater in rats raised in enriched environments [7]. We hypothesised that T_2 relaxation analysis would provide information which would predict the subject's cognitive ability by correlating the quantity of myelin within the CC and their WISC-R scores.

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[8]. The MWF was defined as the fraction of the T_2 signal below 50ms relative to the total T_2 signal. 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. The average MWF was calculated using the entire signal from the ROI and a myelin water map, illustrating the MWF for each individual voxel, was created. Maps 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 a certain minimum value were excluded from the analysis. The minimum SFR values tested ranged from 90 to 110. The voxels with acceptable SFR within the CC of a subject are illustrated in Figure 1.

A novel, voxel based analysis of the MWF, which counted the number of voxels with a MWF greater than a critical SFR value and designated these "highly myelinated voxels" (**HMVs**), was used to create further myelin measures. A range of critical MWF values from 0.01 to 0.25 were investigated.

Cognitive Scores: A trained investigator conducted the ten subtests of the WISC-R and recorded the scores. The VIQ, PIQ and FIQ were calculated from the age corrected and population normalised subtest scores.

Statistical Analysis: The Pearson's product moment of each of the IQ scores against the myelin measures was calculated.

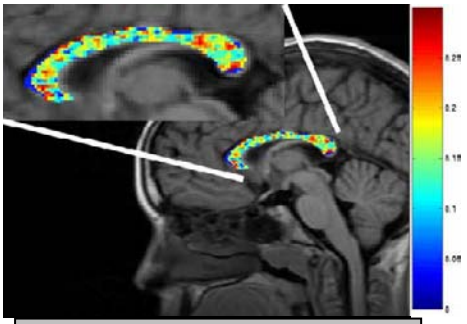

Figure 1: A myelin water map of the myelin water fraction values for each voxel within a region of interest outlining the corpus callosum which has a high signal to fit ratio

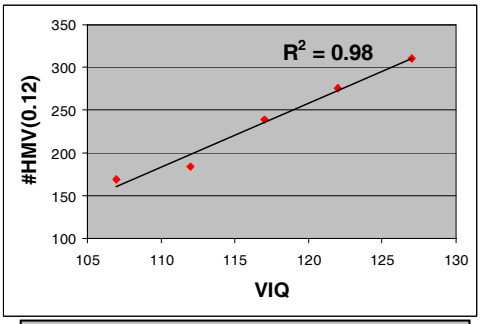

Figure 2: VIQ vs the number of voxels with MWF greater than 0.12 for 5 normal males aged 9 to 12 years

RESULTS: There were no significant correlations between the average MWF and any of the composite IQ measures, nor were there any correlations between the IQ measures and the number of HMVs for the unfiltered myelin maps at any critical point. However, a very strong correlation was found between the number of voxels with MWF greater than 0.12 ($HMV_{0.12}$) and the subject's VIQ for all SFR filtered ROIs ($r^2 = 0.98$, $p < 0.002$, illustrated in Figure 2). Significant correlations were also found between the VIQ and the number of HMVs for critical points 0.10 ($r^2 = 0.93$, $p = 0.009$), 0.11 ($r^2 = 0.96$, $p = 0.003$), 0.13 ($r^2 = 0.96$, $p = 0.004$) and 0.14 ($r^2 = 0.95$, $p = 0.004$). No correlations were found between PIQ or FIQ and any myelin measures. The size of the ROI was not correlated with any of the IQ measures which were, as expected, independent of age.

DISCUSSION: The lack of correlation with the size of the ROI, and therefore cross sectional area of the CC, with any of the composite IQ scores indicates that it is not simply the size of the white matter structure which determines the subject's cognitive ability. The correlation between the VIQ and $HMV_{0.12}$ supports a hypothesis that the myelin development is also a key factor in cognitive ability. The results suggest that the voxel based analysis method may reveal more information regarding the myelin development of CNS structures than an average MWF, which did not correlate with any cognitive measures. Since this voxel based analysis excludes voxels with low MWF, the HMV measure is independent of the size of the structure.

The subtests which comprise the VIQ score are generally associated with higher functions, requiring skills in language vocabulary and comprehension, arithmetic and general knowledge. The results presented here support the hypothesis that the development of myelin within the CC is related to cognitive ability since the CC is required for interhemispheric communication.

The SFR filter successfully isolated the voxels which exhibited true MWF and excluded falsely high MWF due to CSF 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: The strong and significant correlation between the number of $HMV_{0.12}$ and VIQ provides compelling support for a larger study investigating the relationship between myelination and cognitive ability. The results endorse the novel, voxel based analysis and use of an SFR filter to remove poorly fitting data. This technique provides a non-invasive, *in vivo* method of quantifying myelin development which will allow the myelination process to be better understood than was possible with previous methods.

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REFERENCES: [1]Laule, C *et al*. Multiple Sclerosis *In Press* 2006. [2]MacKay, A *et al*. Magn. Reson. Med. 1994:31;673-7. [3]Whittall, KP *et al*. Magn. Reson. Med. 1997;37:34-43.[4]Kaplan & Saccuzzo. *Psychological testing: Principles, applications, and issues* 2005. [5]Yakovlev & Lecours. *The Myelogenetic Cycles of Regional Maturation of the Brain* 1967. [6]Schmithorst *et al*. Hum Brain Mapp 2005:26(2):139-47. [7]Juraska & Kopcik Brain Res 1988:450:1-8. [8]Whittall, KP *et al.* J Mag Res 1989:84;64-71