

Measurement of the myelin-to-axon diameter g-ratio in very-preterm infants using multi-modal MRI

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Introduction: Infants born prematurely are at increased risk of adverse neurodevelopmental outcome [1]. The measurement of white matter tissue composition and structure can help predict functional performance. This work develops a novel combined biomarker from diffusion MRI and multi-component T_2 relaxation measurements in a group of infants born very preterm and scanned between 30 and 40 weeks equivalent gestational age (EGA). This biomarker was not measurable prior to the combination of these acquisitions. The proposed biomarker, which can be measured independently from histology, is related to axonal energetic efficiency and conduction velocity (in terms of axonal membrane charge storage) and is thus linked to the tissue electrical properties [2,3], giving it a good theoretical justification as a predictive measurement of functional outcome.

Method: Imaging data were acquired for 11 preterm infants (one with longitudinal data at 30 and 40 weeks EGA) (Mean birth gestation=25.1±0.7wks) on a 3T Phillips Achieva. Diffusion weighted imaging was acquired over 16 directions at a b-value of 750s.mm⁻² and 32 directions at b=2000s.mm⁻² at resolution 1.75x1.75x2mm³. A multi-component diffusion model was used to fit an intra-axonal volume fraction v_{in} [5]. Fractional Anisotropy (FA) maps were obtained by linear fitting of the tensor model to the imaging data. 32-echo multi-component quantitative T_2 imaging was acquired at 0.4x0.4x3mm³ resolution using a GraSE acquisition at 12ms TE. T_2 component fitting was carried out using the extended phase graph algorithm (EPG) [4] to extract a short component from 20 log-spaced components used to infer tissue myelin-water fraction, v_{mwf} (where v_{mwf} is the proportion of signal estimated to have $T_2 < 60$ ms). We define the geometrical g-ratio (assuming cylindrical axons) as the ratio of myelinated to non-myelinated axon diameters $g=r_{in}/r_{out}=(1+v_{mwf})/((1-v_{mwf})v_{in})^{-0.5}$ [3], where the additional v_{mwf} term in the denominator adjusts for the absence of myelin signal in the DWI. The g-ratio combines the structural sensitivity (but non-specificity) of DWI with the myelin specificity (but structural insensitivity) of multi-component T_2 relaxometry and is theoretically related to the electrical properties of the tissue.

Results: We obtained maps of FA, v_{in} , v_{mwf} and g-ratio as defined above in 11 infants. Figure 1 illustrates changes in myelin content detected between infants at 30 and 40 weeks EGA overlaid on directional colour-coded FA images. Figure 2 plots the change in these parameters in the ascending cortico-spinal tract (manually defined on the FA map) with EGA between 30 and 40 weeks EGA. Both FA and v_{in} increase significantly with gestational age ($r=0.83$ $p<0.001$ and $r=0.94$ $p<0.001$ respectively). The g-ratio is obtained on a per-voxel basis using the expression above and we find that the mean value decreases with gestational age from an average value close to 1 at 30 weeks EGA toward a value of 0.9 at 40 weeks EGA (Spearman's $p=0.79$, $p=0.002$).

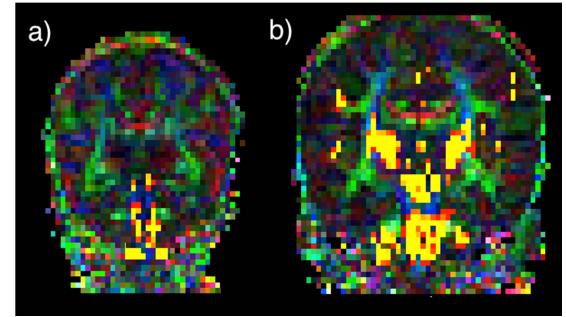


Figure 1: Changes in MWF between 30 and 40 week EGA for one infant overlaid on colour FA maps.

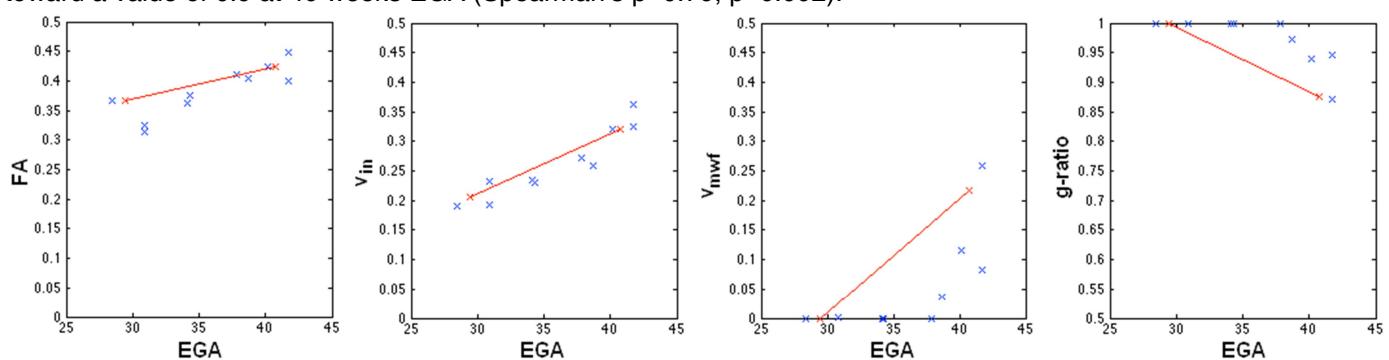


Figure 2: Changes in corticospinal DWI and MWF imaging parameters between 30-40wks EGA for a) FA b) v_{in} c) v_{mwf} and d) g-ratio. Red lines indicate parameter values for the infant with two imaging timepoints.

Conclusion: The multi-modal data presented in this work has allowed a potential biomarker of electrical efficiency to be derived and we obtain plausible cerebrum values for this biomarker *in vivo*. DWI alone is not specific to myelin content, neither is T_2 sensitive to local structural orientation, but the combination of these features allows new information to be obtained. Importantly, measurement of the g-ratio can be linked with a relatively simple physical model to predict the effect of change in myelin thickness on conduction velocity and energetic efficiency [3]. Future work will use this model to make predictions about functional development in preterm children. This is plausible since there is a well-defined sequence of myelination from the PLIC outward [6], and delays to this might be expected to predict corresponding delays in functional progression of motor, language and executive function as the brain increases functional electrical energetic efficiency. Irrespective of the combination of measurements in this work, the acquisition of widely available multi-shell DWI and multi-echo T_2 imaging within clinically feasible time frames (23mins total time) is important and will stimulate the generation of novel predictive structural biomarkers with a tangible physical link to neuronal function.

[1] Moore et al 2012 BMJ 345 e7961 [2] Stikov et al 2011 NeuroImage 54 1112-1121 [3] Chomiak 2009 PLoS ONE 4:11 e7754 [4] Prasloski et al 2012 MRM 67 1803-1814 [5] Zhang et al 2012 NeuroImage 61 1000-1016 [6] Brody et al 1987 J Neuropathol Exp Neurol 46 283-301