AN EFFICIENT PROTOCOL FOR COMPREHENSIVE ASSESSMENT OF WHITE MATTER MICROSTRUCTURE BY COMBINING RELAXATION AND DIFFUSION IN ONE MODEL

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Introduction: Fractional Anisotropy (FA) is modulated by multiple factors in white matter (WM). Axonal membranes play the primary role but myelination modulates the degree of anisotropy [1]. Moreover, the fibre *architectural paradigm* has a huge impact where the presence of differently oriented fibre populations within a voxel leads to a reduction in the measured FA. Lastly, water diffusivity parallel to the axon will also modulate FA. This notorious lack of specificity of DTI measures to different sub-components of WM microstructure has prompted increased interest in different MRI techniques that provide complementary tissue-specific information (e.g. axon density, axon diameter, myelination, fibre ODFs). However, the acquisition time to collect all these data with existing approaches precludes their combination into a single practical protocol. In this work, we develop an efficient and clinically-applicable protocol that provides comprehensive assessment of WM microstructure, providing not only estimates of FA, but also of the attributes of WM that drive differences in FA. The approach assumes a simple cylindrical geometry and uses only a few parameters derived from: CHARMED analysis [2] - namely the restricted fraction (RF), the intra-axonal longitudinal diffusivity (D_{ax}) and the number/orientation of axonal compartments; and from McDESPOT [3] – namely the myelin water fraction (MWF). Combining these metrics, and assuming: (a) that the ratio of inner to outer diameter of the axon conforms to published 'g-ratio' curves [4]; and (b) a Poisson distribution for the axonal diameter (AD), we show that the mean AD can be recovered. Thus, we have a protocol to comprehensively characterize WM features allowing specific conclusions to be drawn when looking at group differences. Specifically, we demonstrate that: 1) we are able to recover axon diameter maps combining CHARMED and McDESPOT; and 2) using a multivariate linear regression (MLR) analysis, we can determine the relative contributions of WM substructure attributes (AD, myelination, axon density) to the observed FA values in different regions of interests (ROI). Moreover, we show that the limited set of parameters harvested from the combined CHARMED/McDESPOT protocol is sufficient to explain variations in FA - which we verify by successfully *predicting* FA values for each subject based on the MLR parameters calculated on the remaining *N*-1 subjects. Thus, we have devised a highly efficient strategy that yields not only metrics such as FA – but allows us to probe deeper into the separate WM substructures that the tensor model can only condense into a single substrate of 'microstructure'.

Methods: *N*=17 healthy volunteers, (mean age/std.dev.=24/3y), underwent an MRI protocol at 3T comprising: cardiac-gated DTI (TE=93ms, 45 directions, max b-value=1200s/mm^2), CHARMED protocol (TE/TR=114/17000ms, 130 directions, max b-value=7500s/mm^2), mcDESPOT (SPGRs: TE/TR=2.1/4.7ms, flip angle(a)=[3,4,5,6,7,9,13,18]; bSSFPs: TE/TR=1.6/3.2ms, a=[10.6,14.1,18.5,23.8,29.1,35.3,45,60]). DTI analysis was performed with *ExploreDTI* [5] to obtain FA maps for later comparison. CHARMED and McDESPOT analyses were performed according to [2] and [3], respectively. To recover AD maps, a routine was implemented (Matlab 2010) to find the best RF, D_{ax} and AD to fit the diffusion data, given the value of MWF. The CHARMED RF, calculated assuming a mean AD from histology, was used as the initial guess to find AD according to the g-ratio curve of [4] (assuming the myelin to be a perfect annulus allows us to relate MWF to axon diameter via the g-ratio). RF was then re-calculated using the new AD and the procedure was iterated until negligible changes in the residuals were observed. The statistical analysis was performed within 39 ROIs obtained by combining the TBSS skeleton [6] with an automatic ROI selection using WM labelling in standard space [7]. A MLR within ROIs and across subjects of $FA=\alpha*RF+\beta*D_{ax}+\gamma*AD+\delta$ was performed removing one subject per time and considering only those voxels characterized by one fibre population (i.e. those voxels where the Bayesian Information Criterion dictates that a single fibre model is the most parsimonious); the MLR parameters were then used to predict FA on the skeleton of the eliminated subject. The null hypothesis that the regression slope is 1, and thus the predicted FA trend is not statistically different from the actual FA, was tested using the t-statistic at p=0.05 confidence level (CL). α, β, γ, and δ for each subject were stored and used to predict FA on the entire image. In voxels characterized by 1 predominant fibre population, we simply applied the regression $FA=\alpha*RF+\beta*D_{ax}+\gamma*AD+\delta$. In voxels where model parsimony on the CHARMED indicated > 1 fibre population, the regression was applied separately for each compartment and the resulting tensors combined, weighted by the respective volume fractions, according to the angle that the fibre populations define.

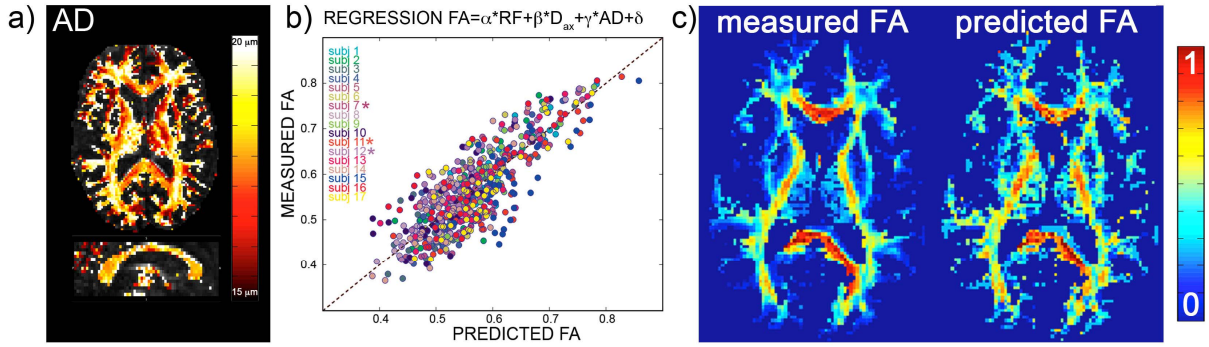

Fig1a. A typical map of mean axon diameter. **Fig1b.** MLR for each subject calculated across ROIs. Asterisks indicate significant differences between predicted and measured FA. Dashed red line is line of identify. **Fig1c**. Maps of FA measured from the DTI protocol and FA predicted by our model (thresholded at FA>0.2)

Results and Discussion: Figure 1 shows example results and confirm that AD maps can be obtained by combining relaxometry and diffusion information. Compared to [8], the method proposed here: a) does not need high gradient performance; and b) is able to account for a *distribution* of axons diameters, rather than a single diameter. The trend in AD across the corpus callosum shown in Fig.1a is similar to published histological results [9], albeit with a positive bias in the absolute value, as found also in [8]. When only voxels containing one predominant fibre population are considered, the regression $FA=\alpha*RF+\beta*D_{ax}+\gamma*AD+\delta$ is always statistically significant (at p =0.05), and in the leave-one-out analysis, the modelled FA accurately predicts (p = 0.05) the actual FA in 14 of the 17 participants. The regression weights and the information on fibre architecture are used to reconstruct FA maps from scratch, as shown in Fig.1c. In 16 of the 17 subjects, the predicted FA maps are not statistically different from those derived from the DTI protocol. This indicates that our model comprehensively captures all the relevant contributions to FA, revealing finer details of the white matter structure than afforded by DTI. We are currently investigating whether a larger training set will enable us to gain even greater predictive power. Importantly, the combined CHARMED / McDESPOT whole brain protocol only takes 37 minutes (which could readily be accelerated through emerging techniques such as multiplexing [10] and compressed sensing).

Conclusion: This work demonstrates that: a) maps of AD can be obtained easily with a clinical setup, combining relaxometric and diffusion acquisition; and b) RF, D_{ax} and AD, plus the CHARMED information on the number and orientation of the different compartments, can be comprehensively used to model WM geometry.

References: [1] Beaulieu C NMR Biomed. 15:435 (2002) [2] Assaf and Basser MRM 52:965 (2004); De Santis et al. Proc. ISMRM (2011) [3] Deoni et al. MRM 60:1372 (2008) [4] Paus and Toro Front. Neuroanat. 3:14 (2009) [5] Leemans et al. Proc. ISMRM (2009) [6] Smith SM et al NI 31:1487 (2006) [7] De Santis et al. MAGMA (2011, in press) [8] Alexander et al. NI 52:1374 (2010) [9] Aboitiz et al. Brain Res. 598:143 (1992); [10] Feinberg DA et al. PLoS One. 5:e15710 (2010).