

## **“Tractometry” – Comprehensive Multi-modal Quantitative Assessment of White Matter Along Specific Tracts**

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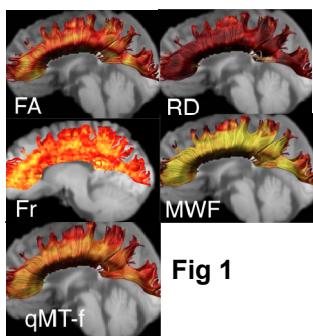
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**INTRODUCTION:** A comprehensive assessment of tract-specific microstructural measurements is introduced. This method, called tractometry, combines macromolecular measurements from optimized magnetization transfer imaging<sup>1</sup>, multicomponent T<sub>2</sub> species from relaxometry<sup>2,3</sup>, and ‘axon density’ measurements from CHARMED<sup>4</sup> along specific white matter pathways reconstructed from diffusion MRI. Quantitative magnetization transfer (qMT) imaging<sup>1</sup> provides information on the relative density of macromolecules (including myelin), known as the f map. Multi-component driven-equilibrium single-pulse observation (mcDESPOT)<sup>2,3</sup> of fast- and slow-T<sub>1</sub> and T<sub>2</sub> quantifies tissue microstructure, notably the myelin water fraction (MWF). CHARMED<sup>4</sup> characterizes hindered and restricted water diffusion within white matter – with the restricted compartment (Fr) taken as a proxy estimate of ‘axon density’. Diffusion MRI at b-values of around 1000 s/mm<sup>2</sup> is sensitive to the hindrance of water. Radial diffusivity of the diffusion tensor is often (and often incorrectly!) assumed to reflect myelination. This study provides insights into the relationships between these quantitative metrics in different metrics, including – for example – the relationship between radial diffusivity and other metrics of axon / myelin morphology.

**METHODS:** Healthy volunteers (N=28, age=31.1±6.7y) were studied using a 3T MRI scanner (HDx system GE Medical Systems, Milwaukee, WI). Cardiac-gated diffusion-weighted data were acquired with a single-shot spin-echo EPI sequence with the following parameters: b-value = 1200 s/mm<sup>2</sup>; 60 gradient directions; six non-DW images; 60 axial slices; TR = 20 R-R intervals<sup>5</sup>. Sequence specific parameters for mcDESPOT-SPGRs were: TE/TR = 2.1/4.7 ms, flip angle ( $\alpha$ ) = [3,4,5,6,7,9,13,18]; mcDESPOT-bSSFPs were: TE/TR = 1.6/3.2 ms,  $\alpha$  = [10.6,14.1,18.5,23.8,29.1,35.3,45,60]<sup>6</sup>. The qMT protocol<sup>1</sup> consisted of a 3D MT-weighted spoiled gradient recalled-echo sequence with the following parameters: TR/TE = 26.65/1.86 ms, Gaussian-MT pulses, duration  $\tau$  = 14.6 ms, with collection of additional B<sub>1</sub> and B<sub>0</sub> mapping. CHARMED sequence specific parameters were as described elsewhere<sup>4</sup>. All participants gave written informed consent to participate in this study under a protocol approved by the local Ethics Committee /IRB.

Fibre tracking based on fibre orientational density (FOD) peaks from CSD<sup>7</sup> was used to reconstruct different white matter fasciculi (corpus callosum and uncinate), using *ExploreDTI*<sup>8</sup>. Diffusion images were then corrected for CSF-partial volume contamination using the approach detailed in<sup>9</sup>, giving a free water correction (FWC), which was subsequently used to correct all other indices where appropriate. After optimized non-linear registration of each quantitative metric map to the fractional anisotropy map, samples of each metric were taken at each vertex of the reconstructed tracts - and tract-specific means derived for FA, MD, RD, Fr, MWF and qMT-f.

**RESULTS:** Results in the corpus callosum clearly demonstrate differences in the spatial distribution of the microstructural indices (Fig 1). Both MWF and qMT-f are lower as the tracts reach the grey matter and homogenous throughout the rest of the pathway. FA and RD appear to be more sensitive to areas of intra-voxel heterogeneity (tract curvature / dispersion - as expected!), and are thus more heterogeneous throughout the whole tract. We have also conducted a comprehensive comparison of the inter-correlations between the different metrics in specific pathways (See Table 1 for Summary of correlations). Space prohibits us from showing all results here – so we focus on FA vs MWF and RD vs. MWF in the uncinate fasciculus. In any given participant: (a) MWF and FA; and (b) MWF and RD are un-correlated.

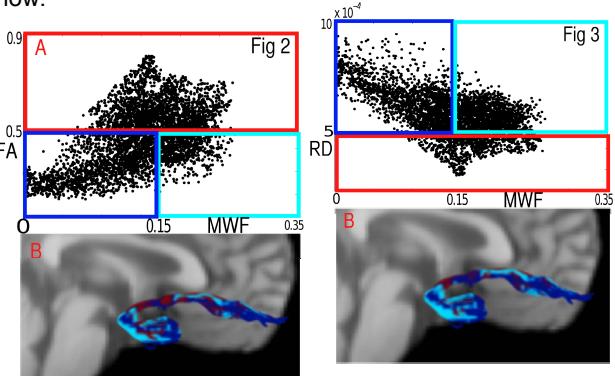


**Fig 1**

To explore this relationship further, we subdivided scatter plots of MWF vs FA and MWF vs RD into 3 separate domains and the data points lying within these domains back-projected onto the tracts for visualization and interpretation (Fig 2 [low MWF/low FA (dark blue), high MWF/low FA (light blue), high FA (red)] and Fig 3 [low RD (red), low MWF/high RD (light blue), high MWF/high RD (red)]). As expected low-MWF / low-FA is found in areas close to the cortex (grey matter). As expected, disparity between FA and MWF (i.e. low FA /high MWF) occurs in areas of tract dispersion/curvature where the intra-voxel orientational heterogeneity will be low.

	FA	RD	MWF	qMT-f	Fr
FA		$R^2=0.9$			$R^2=0.7$
RD					$R^2=0.7$
MWF					
qMT-f					

**Table 1**



**DISCUSSION: Tractometry** provides a comprehensive assessment of multiple

microstructure metrics in a unique way – along *specific* white matter tracts. Importantly, we find little correlation between proxy indices of myelination and axonal morphology, suggesting that additional *complementary* WM microstructural information is obtained with our approach

### **REFERENCES**

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