PINNING DOWN SPECIFICITY OF BIOMARKERS TO AXON AND MYELIN DAMAGE: PRELIMINARY RESULTS

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Target audience: Researchers interested in developing and using mathematical models of the diffusion MR signal in the presence of demyelination and axon loss in order to study pathologies such as multiple sclerosis (MS) and spinal cord injury (SCI).

Purpose: To test the feasibility of parameters such as exchange time τ_i and axon density f estimated from diffusion MRI as biomarkers for axon and myelin loss. Axon loss and demyelination are important factors in white matter (WM) pathologies such as MS and SCI. MS is characterised primarily by demyelinating lesions in brain and spinal cord (SC) WM followed by axonal loss, whereas SCI is characterised primarily by axonal damage and subsequent breakdown of myelin. Differentiating between these pathologies is important in order to monitor disease progression and develop/assess treatments for both MS and SCI patients. Although both types of damage are detected in structural MRI, they cannot currently be differentiated. Diffusion-weighted (DW) MRI, which is sensitive to the motion of water molecules, can provide more detailed information about tissue structure; however commonly used indices such as fractional anisotropy (FA) and mean diffusivity (MD) are also non-specific to this type of tissue damage, e.g. axon loss and demyelination both lead to reduced FA and thus cannot be distinguished. Measures such as axial and radial diffusivities are hypothesised to be more discriminating[1], but they still do not distinguish the biophysical mechanisms underlying the tissue changes. Potentially more specific diffusion MR biomarkers include water exchange time, which we hypothesise correlates with demyelination and myelin loss, and axon density, which we hypothesise correlates with axonal loss. In this study, we investigate the applicability of these biomarkers using an animal model of axonal loss.

Methods *Animal model:* Lipopolysaccharide (LPS) was injected into the dorsal column (DC) in the lumbar SC of three adult rats to induce demyelinating lesions in the dorsal funiculus with subsequent axonal degeneration rostral to the lesion site[2]. 14 days after injection, the rats were perfusion fixed and the SCs excised for scanning. *Data acquisition:* DW images of the SCs were acquired on a 9.4T small bore scanner (Agilent Inc) using a stimulated echo (STE) imaging sequence. The imaging parameters were: NEX=4, TE/TR=12/2000ms, δ=2ms, Δ=15,50,100,200,500,650ms. For each combination of δ/Δ, DW gradients of strength G=60-600mT/m (in steps of 60mT/m) were set along 3 orthogonal directions (2 perpendicular, 1 parallel to fibre direction) along with 2 unweighted images, giving a total of 192 images. Field of view=11.5×11.5mm^2 and matrix size=128×128, with a resulting in-plane resolution equal to 90×90µm^2. We acquired 3 slices of thickness 2mm. *Model fitting:* We model the DW signal using two compartments[3]. Intra-axonal signal, which is a fraction f of the total signal, is modelled as the signal due to water with diffusivity d inside a cylinder with axon radius R. Extra-axonal signal is modelled using a cylindrically symmetric tensor with parallel diffusivity d and perpendicular diffusivity $d^*(1-f)$[3]. Water exchange between the compartments is included using the Karger formalism[4], which incorporates the intracellular exchange time τ_i between the intra- and extra-axonal compartments, into the model. As we use a STE sequence, we account for signal differences due to T1 decay (due to variable Δ) and correct the effective diffusion weighting for the effects of the crusher/slice select gradients[5]. The model is fit to the data using Markov chain Monte Carlo[6], with a burn-in of 10,000 after which 1000 samples are collected at an interval of 20 iterations. We fix d=70µm^2/s to improve the stability of the fit[3]. *Region of interest (ROI) selection:* Regions of axonal loss are apparent as hyperintensities in the left side of DC on T2-weighted images in two of the three SCs (top row, Figure 1). In these samples, we select two ROIs in the DC: the damaged WM (DWM) in the ipso-lateral side of the lesion and normal appearing WM (NAWM) on the contra-lateral side of the DC. We fit the model within these ROIs and use t-tests to detect significant differences between DWM and NAWM voxels in each sample. We also create parameter maps over the whole of the SC by fitting the model to all WM voxels (FA>0.35) individually.

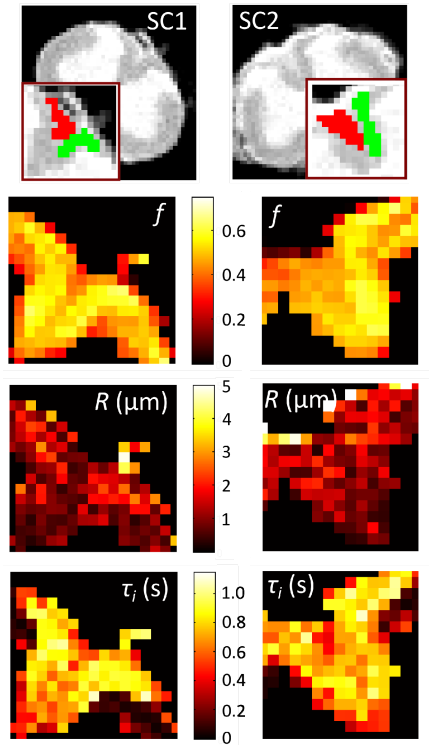

Figure 1: DWM (red) and NAWM (green)ROIs and maps of f, R and τ_i in the DC for both SCs.

Results Table 1 shows the means and standard deviations of the fitted model parameters in DWM and NAWM ROIs in two SC samples. In both samples, f is significantly lower in the DWM than NAWM. We find both R and τ_i increased in the region of axonal loss; however the changes are only significant in SC1. Figure 1 shows maps for f, τ_i and R in both samples. The damaged region is visible in the maps for f and τ_i, as shown in the zoomed region. The damage cannot be seen clearly in maps for R, although these estimates are noisy, most likely due to the low SNR of the data at long Δ and high gradient strengths.

Discussion These preliminary results suggest that f, which shows the most significant change, can be used as a marker of axon loss in regions of degenerating WM. Lower values of f suggest a reduction in axon density, which is the primary damage we would expect in these samples. We find τ_i reduced at the site of axonal loss in both samples, suggesting that axons become more permeable as the myelin sheaths break down or secondary demyelination. Future work will address the specificity of these indices in different animal models where only demyelination, only axonal loss and both pathologies are present.

	SC1		SC2	
	DWM	NAWM	DWM	NAWM
f	0.36(0.15)**	0.54(0.04)**	0.45(0.11)**	0.57(0.05)**
R(µm)	1.71(1.00)*	0.98(0.32)*	1.33(0.81)	1.05(0.56)
τ_i (ms)	688(188)*	801(116)*	708(138)	766(132)

Table 1: Fitted parameters in ROIs in both samples. * indicates p value<0.05, ** indicates p value<0.0005

References 1. Song, *NeuroImage* 2003 2. Felts, *Brain* 2005 3. Alexander, *MRM* 2008 4. Karger, *Adv in MR* 1988 5. Alexander, *ISMRM* 2012 6. Gamerman, *Markov Chain Monte Carlo*, 1997