Hybrid Diffusion Imaging in a Spinal Cord Model of Dysmyelination

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Introduction: Diffusion tensor imaging (DTI) is widely used for the study of white matter (WM) diseases and fractional anisotropy (FA) is commonly used as a measure of WM integrity. However, FA is also highly sensitive to such factors as non-Gaussian diffusion, crossing fibers and imaging noise, which may impair its specificity. Other DT measures, such as axial diffusivity (*Da*) and radial diffusivity (*Dr*), are similarly limited. It has been suggested that the former is related to axonal integrity while the latter is related to myelination [1]. In addition to DTI, q-space imaging and diffusion spectrum imaging (DSI) have also been utilized to extract additional information about WM microstructure [2, 3].

The shaking (*sh*) pup is a canine mutant model of dysmyelination analogous to Pelizaeus-Merzbacher disease in humans. The *sh* pup suffers from severe and widespread myelin deficiency, without the confounding effects of inflammation or edema, and is therefore an excellent model for studying the sensitivity and specificity of imaging methods with regard to myelin content. In a previous study of *sh* pup brain, the zero displacement probability (Po), a measure of water diffusion restriction, was shown to differentiate between a control and diseased pup with respect to myelin content [3]. In this study, white matter integrity is examined in the spinal cord of *sh* pup using both DTI and DSI measurements acquired from a hybrid diffusion imaging (HYDI) approach [5]. Standard DTI measures (FA and *Dr*) and Po are compared to see if one or both are sensitive to changes in myelin content between *sh* pup and control, as well as to more subtle differences between two diseased *sh* pups.

Materials and Methods: In-vivo DTI and HYDI experiments were performed on 2 anesthetized, 2 year-old shaking pups as well as an age-matched control at a 3.0T GE SIGNA scanner using a SS-SE-EPI pulse sequence and HD knee coil. Specific imaging parameters were TR/TE=5000/84.6 ms, matrix=256x256, FOV=12 cm, and 23 axial 4 mm slices for DTI and TR/TE=3500/105 ms, matrix=256x256, FOV=12 cm, and 18 axial 5 mm slices for HYDI. The HYDI diffusion sampling scheme consisted of 6 icosahedral shells with a total of 132 encoding directions, with b_{max}=4000 s/mm^2. Due to the small size of the cord and the inherent partial voluming, the entire cord (WM + GM) was segmented out from the surrounding cerebrospinal fluid (CSF), from which Po, FA, MD, *Da*, and *Dr* maps were drawn. A volume normalized histogram of each diffusion measure was produced for each pup. In addition, mean and standard deviation were calculated for each diffusion measure along the entire volume of the cord (Table 1). Qualitative histopathology was performed on cord sections using toluidine blue.

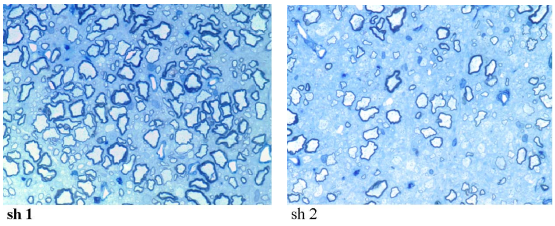

Figure 1: C1 cervical spinal cord, ventral column of *sh* pups.

Table 1: Cord Measurements (mean ± standard deviation)

	Po	FA	*Da* (10^{-6} mm^2/s)	*Dr* (10^{-6} mm^2/s)
Control	.91 ± .18	.67 ± .17	1900 ± 388	506 ± 210
Sh 1	.72 ± .12	.65 ± .10	2100 ± 285	623 ± 196
Sh 2	.69 + .11	.63 + .10	2000 ± 297	629 ± 182

Results and Discussion: While both *sh* pups displayed substantially less myelin than control (as expected in this model), shaking pup 1 (*sh* 1) was less severely affected (Fig. 1) than shaking pup 2 (*sh* 2), indicating for the first time distinct phenotypic differences between animals with this mutation. The volume-normalized FA histograms show *sh* pups shifted to the left with respect to control, and *sh* 1 shifted to the right with respect to *sh* 2 (Fig. 2a). The *Da* histograms of *sh* pups are highly overlapped (Fig. 2c). The *Dr* histograms show *sh* pups shifted furthest to the right with respect to the control, while there is essentially no separability between *sh* 1 and *sh* 2 (Fig. 2d), making it difficult to conclude that higher *Dr* is an indicator of reduced myelin content, as has been suggested by previous studies [6]. Of all the diffusion measures, Po had the most separable histograms between control and *sh* pups and, more importantly, between the *sh* pups themselves (Fig. 2b). The *sh* pups were shifted furthest to the left with respect to control, while *sh* 2 was shifted to the left with respect to *sh* 1.

Conclusions: In the *sh* pup model, Po not only shows greater sensitivity to profound dysmyelination than tensor-based parameters, but is also better able to differentiate more subtle differences in myelination between two *sh* pups themselves, implying that Po might be a better indicator of myelination than *Dr*. Comparison with quantitative histopathology (pending) will ultimately be required to fully elucidate the relationships between diffusion measures and tissue microstructures.

References: [1] Song et al. Neuroimage (2002). [2] Assaf et al. MRM (2002). [3] Wu et al. Proc ISMRM (2007). [4] Duncan et al. Neuropathol Appl Neurobiol (1983). [5] Wu & Alexander Neuroimage (2007). [6] Song et al. Neuroimage (2003).

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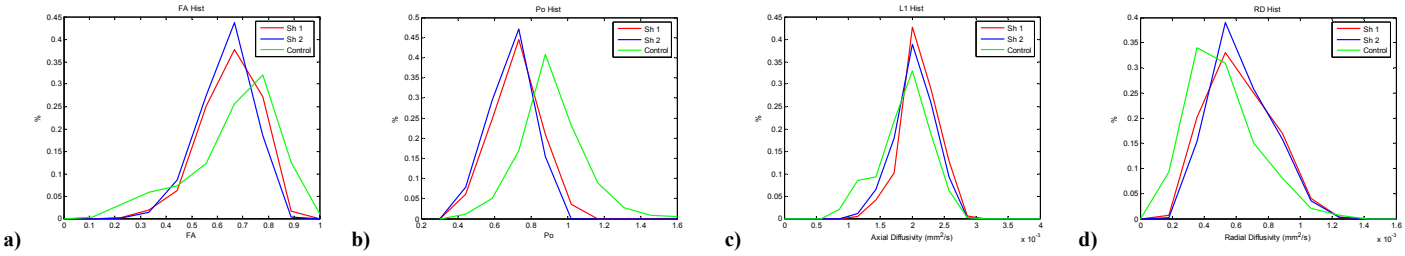

Figure 2: Compact spinal cord (WM + GM) histograms for control (green), *sh* 1 (red), and *sh* 2 (blue). (a) FA, (b) Po, (c) *Da* and (d) *Dr*.