Hybrid Diffusion Imaging (HYDI) in a Brain 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 degrade its specificity. It has recently been proposed that the axial diffusivity ($D_{//}$) of the diffusion tensor is specifically related to axonal integrity while the radial diffusivity ($D_{\perp}$) is related to myelination [1]. Alternatively, q-space imaging and diffusion spectrum imaging (DSI) may provide additional information about WM microstructure. The zero displacement probability (Po) is a measure of water diffusion restriction [2,3] that has been found to have significant diagnostic value in multiple sclerosis (MS) [2]. In this study, the dysmyelinating *shaking* (*sh*) pup model was studied using both the DTI and DSI measurements acquired from a hybrid diffusion imaging (HYDI) approach [3]. The *sh* pup is a canine mutant with a profound paucity of myelin, without the confounding effects of axonal loss, inflammation or edema [4]. This reductionist disease model may help to disentangle the many confounding pathological changes that occur in MS and other WM diseases and relate them to changes in diffusion properties observable with MR.

Materials and Methods

Six *sh* pups and four age-matched control dogs were scanned (once or twice) at ages ranging between 4 and 46 months. HYDI experiments were performed on anesthetized pups with a 3T GE SIGNA scanner with SS-SE-EPI and a quadrature extremity coil. The HYDI sampling scheme (Table 1) consisted of four icosahedral shells. The second shell was used for DTI processing, the whole dataset was used for DSI processing [3]. Other MR parameters were: TR/TE=7500/140ms, matrix= 96x96, FOV=15 cm and 26 axial 3mm slices. DTI and DSI measures including FA, MD, $D_{//}$, $D_{\perp}$, Po and mean squared displacement (MSD) were post-processed. WM tissues were segmented by two-stage segmentation using the FAST algorithm [5]. The first 2-class segmentation was done on MD to eliminate CSF from parenchyma; the second 2-class segmentation was done on FA to separate WM and GM. Diffusion measures of WM were compared between controls and *sh* pups and observed across the age range. In addition to whole brain WM, ROI analysis of the bilateral internal capsules was performed to specifically assess the most compact white matter.

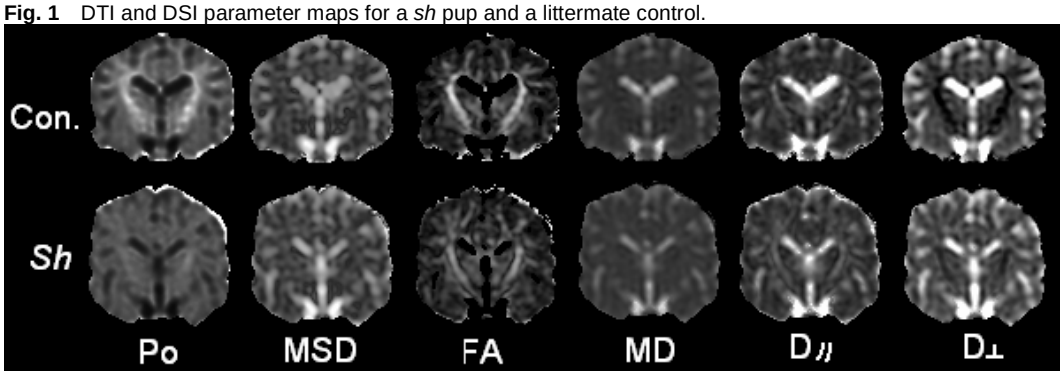
Table 1. HYDI scheme

HYDI Shell	Ne	b value (s/mm^2)
	1	0
1st	6	320
2nd	21	1280
3rd	45	2880
4th	56	6500
total	129	

Results and Discussion

The WM/GM contrast is decreased most visibly in the Po map of the *sh* pup (Fig. 1), reflecting less restriction of water diffusion in WM. Decreased WM Po is also shown in the plot across ages (Fig. 2(a)). Although WM FA is decreased in the sh pup (Fig. 2(c)), the FA map (Fig. 1) still has substantial GM/WM contrast. This supports previous observations that ordered axonal structures yield anisotropic diffusion even in the absence of myelin. One advantage of the preserved tissue contrast in FA is to help with segmenting WM tissues in brains of *sh* pups in this study. WM appears hyperintense on the $D_{//}$ maps and hypointense on the $D_{\perp}$ maps (Fig. 1). Note that the differences in $D_{//}$ and $D_{\perp}$ between the control and *sh* pups are hard to observe from the maps alone, but can be seen in the bar plots in Fig. 2(e) and (f). The WM $D_{//}$ of the *sh* pups is less affected than other DTI measures, which may reflect what we know to be preserved axons in this model [1] but the fact that $D_{//}$ does differ between *sh* pups and controls suggests at least some sensitivity to factors other than axonal integrity. The absence of myelin sheaths is apparently reflected by increased radial diffusivities ($D_{\perp}$) in the *sh* pup WM. It is noteworthy that DSI (specifically Po) reveals more substantial differences between *sh* pups and controls than does DTI, relative to the regional variance in these parameters (compare Figs. 2a and 2c); also note that expected age-related changes in putative myelin-related parameters (Po, FA, $D_{\perp}$) are seen not only in controls but also in *sh* pups, despite the fact that these animals are known to synthesize virtually no myelin. Insight into the pathophysiological substrates of these observations awaits forthcoming analysis of tissue from sacrificed animals.

Fig. 1 DTI and DSI parameter maps for a *sh* pup and a littermate control.



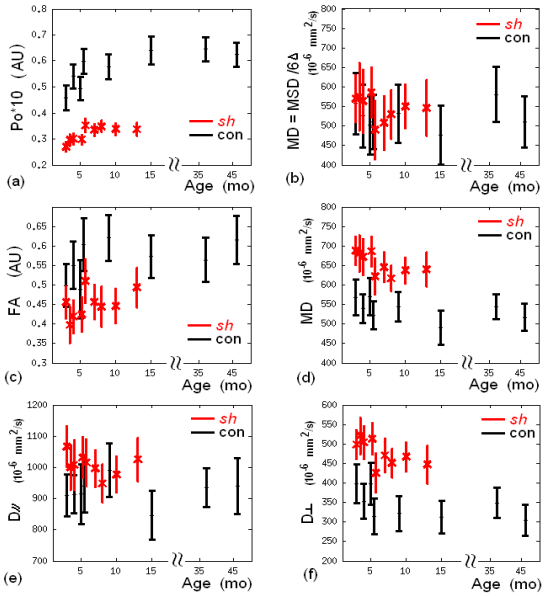


Fig. 2 Bar figures of WM diffusion measures across ages and between controls and *sh* pups. The errorbar denotes one standard deviation across three dimensional ROI at the bilateral internal capsules.

Acknowledgements

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References

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