Hybrid Diffusion Imaging in a Brain Model of Dysmyelination

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Background

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 DT 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 WM disease and relate them to changes in diffusion properties observable with MR.

Materials and Methods

HYDI experiments were performed on an anesthetized, 3-month-old *sh* pup and an age-matched control dog at a 3T GE SIGNA scanner using a SS-SE-EPI pulse sequence and quadrature extremity coil. The HYDI diffusion sampling scheme (Table 1) consisted of four icosahedral shells with a total of 129 encoding directions. The second shell was used for DTI processing, the whole dataset was used for DSI processing, and the outter shell was used for q-ball imaging (QBI) processing [3]. Other MR parameters were: TR/TE = 7500/140 ms, matrix = 80x80, FOV = 14 cm and 26 axial 3mm slices. The total scan time was roughly 20 min. DTI and DSI measures including FA, mean diffusivity (MD), major eigenvector colormap, $D_{//}$ (i.e. the major eigenvalue of DT), $D_{\perp}$ (i.e. the average of medium and minor eigenvalues of DT), Po, mean squared displacement (MSD) and the orientation distribution function (ODF) were post-processed. Highly compact WM tissues were selected by intersecting the segmentation outputs of the FAST [5] algorithm on Po, $D_{//}$ and $D_{\perp}$ maps. Histograms of diffusion measures for WM were compared between control and *sh* pups. In addition, mean and standard deviation were calculated for 3-D ROIs in the internal capsules.

Table 1. HYDI scheme

HYDI Shell	Ne	G (mT/m)	b value (s/mm^2)
	1	0	0
1	6	8	320
2	21	16	1280
3	45	24	2880
4	56	40	8000
total	129		

Results and Discussion

Aside from the decreased WM volume evident in the *sh* pup, FA maps (Figure 1a) were similar between control and *sh* pups; this was confirmed with the volume-normalized FA histograms (Figure 2b), which were highly overlapped. This confirms previous observations that ordered axonal structures yield anisotropic diffusion even in the absence of myelin. The contrast between WM and GM was decreased in the Po map of the *sh* pup (Figure 1b), reflecting less restriction of water diffusion in WM. This can also be seen in Figure 2b, where the Po histogram of the *sh* pup was shifted to the left relative to the control. Interestingly, of all the diffusion measures, Po had the most separable histograms between the control and *sh* pup. WM appeared hyperintense on the $D_{//}$ maps and hypointense on the $D_{\perp}$ maps (Figure 1c,d). Note that the differences in $D_{//}$ and $D_{\perp}$ between the control and *sh* pups were hard to observe from the maps alone, but can be seen in the histograms (Figure 2c,d). Given the intact axonal fibers of this young *sh* pup and the hypothesis that reduced axial diffusivity is an indicator of axonal degeneration [1], it is reassuring that WM $D_{//}$ was increased in the *sh* pup (right-shifted histogram in Figure 2c). Absence of myelin sheaths was reflected by increased radial diffusivities in the *sh* pup WM (Figure 2d). Results of ROI measurements in Table 2 are consistent with the histograms.

Table 2. ROI measurements (mean ± standard deviation)

	Po (x10)	MSD (10^{-6}mm^2/s)	FA	MD (10^{-6}mm^2/s)	Da (10^{-6}mm^2/s)	Dr (10^{-6}mm^2/s)
control	0.42 ± 0.02	560 ± 20	0.56 ± 0.11	525 ± 77	887 ± 99	344 ± 91
sh	0.35 ± 0.03	619 ± 19	0.50 ± 0.06	680 ± 63	1096 ± 105	472 ± 63

Conclusion

This study demonstrates that HYDI is an efficient imaging approach to acquire all diffusion measures (both DTI and DSI) in a single scan. In the young *sh* pup model, characterized by intact axonal fibers with congenital absence of myelin sheaths and without other confounding pathologies such as inflammation, edema or gliosis, Po shows greater sensitivity to dysmyelination than tensor-based parameters. FA has been shown to be sensitive to pathology in many other WM diseases; it showed only nominal myelin-related changes in the setting of axonal preservation in this study. The increased radial diffusivity ($D_{\perp}$) is consistent with observations in another dysmyelination model (*shiverer* mouse [1]); similarly, the increased (rather than decreased) axial diffusivity ($D_{//}$) presumably reflects the axonal preservation for which the young *sh* pup is known [1,4]. Comparison with histopathology (pending) will ultimately be required to fully elucidate the relationships between diffusion measures and tissue microstructure.

References 1. Song S-K et al. NeuroImage 2002;17:1429-1436. 2. Assaf Y et al. MRM 2002;47:115-126. 3. Wu Y-C & Alexander AL Proc. ISMRM 2005:578. 4. Duncan ID at al. Neuropathol Appl Neuobiol 1983;9:355-368. 5. Zhang Y et al. IEEE Trans. Med. 2001;1:45-57.

Fig. 1 (bottom) DTI and DSI parameter maps for the control and *sh* pup. (a) FA, (b) Po, (c) $D_{//}$ and (d) $D_{\perp}$.

Fig. 2 (right) Compact WM histograms for the control (black lines) and *sh* (blue lines) pup. (a) Po, (b) FA, (c) $D_{//}$ and (d) $D_{\perp}$.