DTI at Long Diffusion Time Reveals Increased Sensitivity to Diffusion Anisotropy

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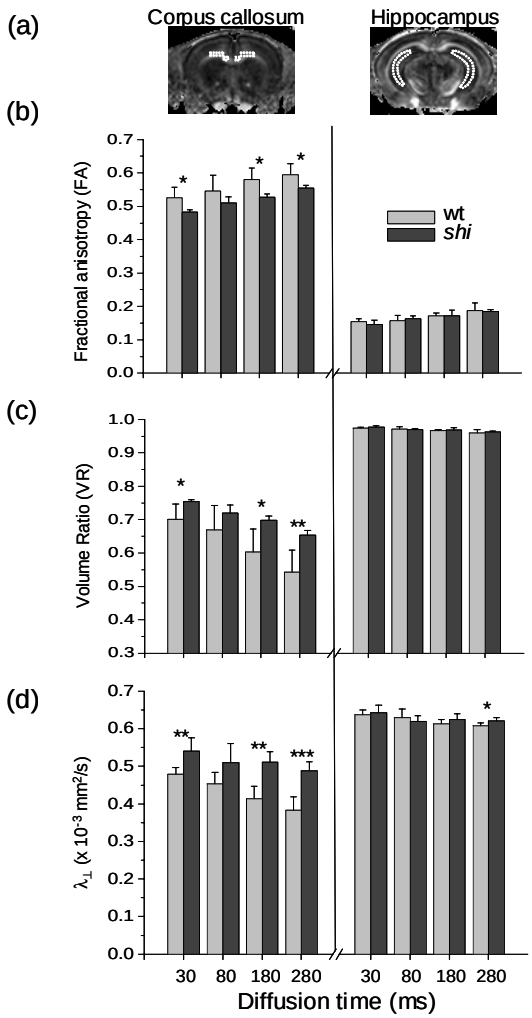
Introduction Anisotropic diffusion in central nervous system (CNS) white matter is thought to arise from barriers (e.g., cell membranes of axons and oligodendrocytes) that hinder water diffusion in some orientations more than others, giving rise to DTI contrast in the brain. Most DTI studies use relatively short diffusion times (t_{diff}) because of signal loss due to T_2 decay at long t_{diff}. Since diffusion displacement parallel to the CNS white matter fiber tracts, in principle, is less restricted relative to that perpendicular to the fibers, we predicted that DTI contrast should improve at longer t_{diff}. We based this prediction on previously reported measurements[1-3] of ADC on axons, which showed that, at very short t_{diff} of ~ 2 ms, the ADC perpendicular to the axonal fibers ($\lambda_\perp$) was high and close to the ADC parallel to the axonal fibers ($\lambda_{//}$). When t_{diff} was lengthened to 28 ms, the ADC perpendicular to the axonal fibers was reduced by half, whereas ADC parallel to the axonal fibers was largely unchanged. Knowledge of the t_{diff} dependent effects on DTI contrast is important for future experiments aimed at improving sensitivity of DTI technique to detect changes in myelination.

In this study, we investigated the sensitivity of DTI contrast as a function of t_{diff} ranging from 30 to 280 ms in wild type (wt) and s*hriverer* (*shi*) mice. *Shi* mouse is a mutant, deficient in myelin basic protein, and shows extensive dysmyelination in the CNS white matter. *Shi* mouse is a good model to compare DTI contrasts at variable t_{diff}. Stimulated-Echo-Acquisition-Mode (STEAM) sequence, modified to include diffusion gradients, was used for diffusion weighted imaging making it possible to use long t_{diff} without substantial signal loss due to T_2 decay by increasing the mixing time (TM).

Methods Five wild type (wt) and five s*hi* mice were studied at different t_{diff}. Mice were anesthetized with 1% isoflurane. Rectal temperature and respiration rate were monitored and maintained. MRI was performed on a 9.4 T, 89 mm vertical bore magnet with a 100 G/cm gradient insert and a small surface coil. Diffusion weighted images were acquired at high b-value (b=1200 s/mm^2) in 6 different directions[4] and with low b-value (b = 5 s/mm^2, one direction), TR =2.5 s, TE = 14 ms, imaging matrix of 64x64 zero filled to 128x128, FOV = 1.28x1.28cm, 7 slices of 0.9-mm thickness with interslice gap of 0.1 mm, and t_{diff} ranging from 30 to 280 ms. Matlab® programs were used for eigen decomposition and calculation of fractional anisotropy (FA) and volume ratio (VR) maps. ROI's of the corpus callosum (representative white matter) and hippocampus (gray matter) were analyzed.



RESULTS Sensitivity of DTI parameters to different t_{diff} was evaluated for the corpus callosum and the hippocampus in wt and *shi* mice (ROI shown in **Panel a**). There were strong trends of increasing diffusion anisotropy with increasing t_{diff} for the corpus callosum but were significantly weaker for the hippocampus in both wt and *shi* mice. In the corpus callosum, group-average FA (**Panel b**), VR (**Panel c**), and $\lambda_\perp$ (**Panel d**) were statistically different in wt and *shi* mice at all t_{diff}. The differences between wt and *shi* mice in $\lambda_\perp$ and VR become significantly larger at longer t_{diff} (*=P < 0.05, **=P < 0.01, ***=P < 0.001). $\lambda_{//}$ was, however, not statistically different between wt and *shi* mice. In contrast, group-average FA, VR, $\lambda_\perp$, and $\lambda_{//}$ *in the hippocampus* were not statistically different between wt and *shi* mice at any t_{diff} except $\lambda_\perp$ at 280 ms t_{diff}.

DISCUSSION & CONCLUSION Varying t_{diff} by changing TM in the STEAM sequence could result in reduced SNR at longer t_{diff} and preferential weighting toward water molecules with long T_1, which could confound the interpretation of the t_{diff}-dependent effect. Although not negligible, SNR reduction with increasing t_{diff} was small due to the long T_1 and high SNR at high field. Reduced SNR could be compensated by increasing signal averaging at long t_{diff}. Increased anisotropy observed with increasing t_{diff} could be due to T_1 weighting of white matter at the expense of gray matter within a voxel, thus giving rise to artificial increase in anisotropy. However, white matter, which has shorter T_1 than gray matter, is expected to be weighted less in the STEAM sequence. Thus the T_1 effect could not explain the observed t_{diff}-dependent effects and the reported t_{diff} dependence is likely a conservative estimate. The long T_1 at high field is expected to minimize the T_1 effect associated with the use of diffusion-weighted STEAM sequence.

In the presence of restricted and anisotropic diffusion, a longer t_{diff} could improve DTI contrast. However, this effect on DTI contrast has not been systemically investigated. Significant reduction in $\lambda_\perp$ for t_{diff} ranging from 5 to 50 ms had been reported using multiple quantum experiments[5]. White-matter ADC (not DTI) in the human brain had been reported[6] to show a t_{diff} dependence for t_{diff} ranging from 40 to 800 ms. These data were obtained with variable b-values which yielded differential weighting to different spin populations and confounded interpretation of the t_{diff} dependent effects. On the contrary, another study[7] had shown no significant changes in ADC perpendicular or parallel to the fiber tracts in humans with t_{diff} ranging from 16 to 79 ms. A potential explanation could be the small range of t_{diff} applied. Indeed our data showed small differences in DTI parameters at t_{diff} of 30 ms and 80 ms for both wt and *shi* mice. However, a strong trend in the corpus callosum was observed across t_{diff} = 30 to 280 ms.

CONCLUSION *Shi* mutant offers a unique model to study the effect of DTI contrast as a function of t_{diff}. Our results showed that most anisotropy indices (except $\lambda_{//}$) were modulated by t_{diff}. In contrast to those in the hippocampus, DTI parameters in the corpus callosum showed markedly stronger t_{diff} dependence, and the differences in these parameters between wt and *shi* mice grew larger at longer t_{diff}, suggesting that DTI contrast could be improved by using long t_{diff}.

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