Increasing diffusion time improves in vivo DTI sensitivity to white matter degeneration

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Introduction: Diffusion tensor imaging (DTI) has emerged as a sensitive noninvasive diagnostic tool to examine the white matter integrity *in vivo*[1, 2]. It has been reported that the diffusion time (t_D) has significant influence on the diffusion parameters[3,4]. It is not clear whether the different diffusion times would show the different sensitivities in detecting the white matter injury. In the present study, we investigate the effect of two diffusion times (t_D=Δ-δ/3, 6 and 38 ms) in detecting white matter injury at 4 weeks of cuprizone treatment.

Materials and Method: Five eight-week-old female C57BL/6J mice were placed on 0.2 % (w/w) cuprizone diet (Harlan Teklad, Madison, WI) for 4 weeks after baseline DTI measurements. After 4 weeks of cuprizone feeding, in vivo DTI was performed using a diffusion weighted spin-echo sequence with icosa-6 diffusion sensitizing gradients of b-value = 750 s/mm^2. The other acquisition parameters were: TR 1500 ms; TE 55 ms; Δ 7 and 39 ms; δ 3 ms; FOV 2 cm × 2 cm, data matrix 192 × 192 (zero-filled to 384 × 384); number of average 4.

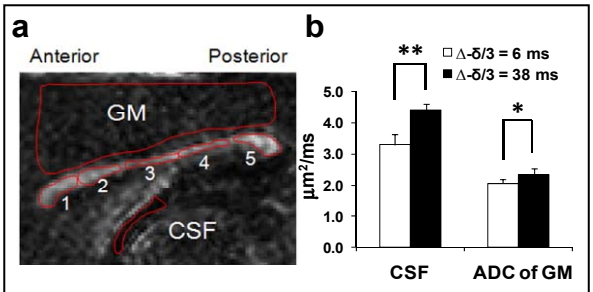

Figure 1 Relative anisotropy map (a) of corpus callosum (CC) is shown with ROIs of corpus callosum (CC), gray matter (GM) and CSF. The anterior (CC1), middle (CC2~CC4) and posterior (CC5) were identified based on the RA maps. The ADC of CSF and GM of two diffusion times: 6 and 38 is shown (b). The increase of ADC is 25 % for CSF and 5 % for GM. *P<0.05, **P<0.01

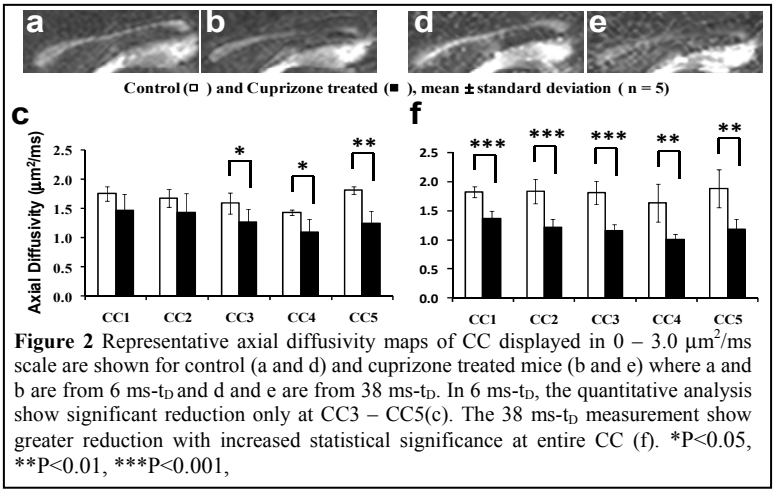

Figure 2 Representative axial diffusivity maps of CC displayed in 0 – 3.0 μm^2/ms scale are shown for control (a and d) and cuprizone treated mice (b and e) where a and b are from 6 ms-t_D and d and e are from 38 ms-t_D. In 6 ms-t_D, the quantitative analysis show significant reduction only at CC3 – CC5(c). The 38 ms-t_D measurement show greater reduction with increased statistical significance at entire CC (f). *P<0.05, **P<0.01, ***P<0.001,

Results and Discussion: Corpus callosum is readily seen in the RA map at diffusion time of 6 and 38 ms enabling detail ROI analysis (Fig. 1). In control mice, the ADC of cerebral spinal fluid (CSF) increased 25% with longer diffusion time, possibly induced by CSF pulsation, while only subtle change was seen in ADC of gray matter with no change was seen in CC (data not shown). The sensitivity of axial diffusivity to cuprizone treatment is shown in Fig. 2. After 4-week cuprizone treatment, the significantly decreased axial diffusivity was only seen in CC3-CC5 (Fig. 2a-c) at 6 ms-t_D. However, statistically significant axial diffusivity reduction was seen from the entire CC including at 38 ms-t_D (Fig. 2d-f). The profound axial diffusivity reduction and enhanced statistical significance with diffusion time increase may suggest the improved sensitivity for detecting axon injury. Abnormal white matter is clearly seen in the T2W images with hyper-intensity at posterior CC (Fig. 3a and b) consistent with the previous report[3,4]. The radial diffusivity maps show increased radial diffusivity in the CC as well as the thickening of CC (Fig. 3c and d). However, the heterogeneous demyelination of CC in cuprizone fed mice[3] rendered ROI analysis less sensitive to the actual pathology. Further work including histology is being pursued for correct ROI localization of demyelination on radial diffusivity map.

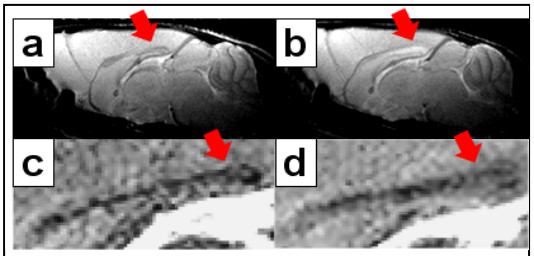

Figure 3 T2W of brain (a and b) and radial diffusivity map of CC with 38 ms-t_D (c and d) are shown for control (a and c) and cuprizone treated mouse (b and d). Radial diffusivity map is displayed in 0 – 1.0 μm^2/ms scale. Compared to the control, hyper-intensity in caudal CC of cuprizone fed mouse is clearly seen in b. In radial diffusivity map, cuprizone fed CC thickened, possibly due to cell infiltration, and bright, possibly reflects demyelination (d).

Conclusions: The effect of diffusion time to probe the white matter injury caused by cuprizone toxicity on *in vivo* DTI parameters was examined in this study. The decrease of axial diffusivity at 4 weeks was substantially lower at diffusion time of 38 ms in CC, supporting our previous speculation that increased diffusion time will improve the sensitivity of axial diffusivity in detecting axonal injury. The enhanced visualization of possible demyelination was also seen qualitatively with increased diffusion time. Our findings strongly support that intra-axonal water diffusion decreases after axonal injury. To improve the sensitivity of DTI to detect demyelination in the presence of axonal injury, increased diffusion time allowing the water molecule to sufficiently sample its environment is necessary.

References: 1. Song, et al., Neuroimage 2002, 17: 1429-1436. 2. Kim, et al., MRM 2007, 58: 253-260. 3. Wu, et al., JMRI 2008, 27: 446-453. 4. G. Nair et al., Neuroimage 2005, 28: 165-174.

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