Full tensor is not required to quantify the white matter damage in contusive spinal cord injury

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Introduction

It has been reported that axial ($\lambda_{\parallel}$) and radial diffusivities ($\lambda_{\perp}$) derived from the diffusion tensor imaging (DTI) could be used to assess the axonal and myelin damage in SCI (1). In order to accurately derive the diffusivity in the central nervous system (CNS) white matter, multiple directions of diffusion weighting gradients are needed. In principle, at least six-directions are required to calculate the diffusion tensor (2). However, the six-direction DTI gradient-encoding scheme is time consuming for its application to the mouse spinal cord measurements. In this study, a two-direction DWI gradient-encoding scheme is proposed to estimate the directional diffusivities of mouse spinal cords *in vivo*. It is hypothesized that the alignment of mouse spinal cord white matter tracts of interest, 3 segments in our setup, is parallel to the magnet axes allowing the parallel diffusivity ($D_{\parallel}$) and perpendicular diffusivity ($D_{\perp}$) to be derived with diffusion weighting gradients at parallel and perpendicular directions. These single axis gradient derived diffusivities would match $\lambda_{\parallel}$ and $\lambda_{\perp}$ derived with the full tensor analysis. Thus, the two-direction diffusion weighting may be used to derive directional diffusivities for the spinal cord white matter injury assessment with significantly reduced experiment time.

Materials and Methods

Spinal Cord Injury

Ten 10-12 week-old female C57BL/6 mice, weighing 18-22 g, were anesthetized with isoflurane/oxygen mixture. After dorsal laminectomy at the T9 vertebral level, five mice received mild contusive SCIs utilizing a modified OSU impactor. The rest five mice underwent laminectomy without contusion served as the control. All mice were evaluated with Basso Mouse Scale (BMS) with the 14-day averaged score of 7.6 ± 1.

Diffusion Tensor Imaging

Data were acquired at the sub-chronic phase (14 days) using spin-echo sequence modified by adding *Stejskal-Tanner* diffusion-weighting gradient. The spin echo time (TE) = 38 msec, time between application of gradient pulses (Δ) = 21 msec, and diffusion gradient on time (δ) = 7 msec for all measurements. The repetition time (TR~1.5 sec) was varied according to the period of respiratory cycle (~270 msec). Three different image slices were collected during every breath period. Images were obtained with diffusion sensitizing gradients combining both six and two directions at the same time: (Gx,Gy,Gz) = (1,1,0), (1,0,1), (0,1,1), (-1,1,0), (0,-1,1), (1,0,-1), (0,1,1), (1,0,0). Diffusion gradient = 12.5 G/cm. Two diffusion-sensitizing b values of 0 and 1.02 ms/μm^2 were used. Eight scans were averaged per k-space line with field of view (FOV) = 1 × 1 cm^2 and data matrix = 128 × 256 (zero-filled to 256×256). Three eigenvalues (λ_1, λ_2, λ_3) were calculated from the diffusion tensor matrix obtained from the six-direction DTI scheme. In the CNS white matter, λ_1, represents the water diffusivity parallel to the axonal fibers and is defined as $\lambda_{\parallel}$ (3). The water diffusivity perpendicular to the axonal fibers λ_2, and λ_3, are averaged to be $\lambda_{\perp} \equiv (\lambda_2+\lambda_3)/2$. (3). Relative anisotropy, RA, map was determined according to Eq. (1)

$$RA = \frac{\sqrt{(\lambda_1 - < D >)^2 + (\lambda_2 - < D >)^2 + (\lambda_3 - < D >)^2}}{\sqrt{3} < D >} \quad (1)$$

From two-direction DWI, $D_{\parallel}$, $D_{\perp}$, and anisotropy index (AI) were directly obtained from the relation of signal intensity (*SI*), *b* value and the diffusion gradients *G(t)*, regardless of tensor analysis. $D_{\parallel}$ represents the water diffusivity along the axonal fiber and $D_{\perp}$ represents the water diffusivity perpendicular to the axonal fiber. The anisotropy index, AI, was derived according to Eq. (2)

$$AI = \frac{D_{\parallel} - D_{\perp}}{D_{\parallel} + D_{\perp}} \quad (2)$$

Histological analysis

Following *in vivo* DTI measurements, all mice were perfusion fixed and undergoing histological analysis to validate the DTI findings. Fixed spinal cords were embedded and sectioned on a sliding microtome at a thickness of 5 μm. Axon integrity was evaluated using antibody against phosphorylated neurofilament (SMI-31).

Results

On the control cord, both RA and AI show the high anisotropy in the white matter, appearing bright in the anisotropy maps, with isotropic gray matter appearing dark in the anisotropy index maps (Fig. 1). On the injured cords, RA, $\lambda_{\perp}$, AI, and $D_{\perp}$ all provide excellent contrasts between gray and white matter tissues (Fig. 2). The maps of AI, $D_{\perp}$, and $D_{\parallel}$ are highly comparable with the maps of RA, $\lambda_{\perp}$ and $\lambda_{\parallel}$ respectively. The region of residual white matter determined from both six-direction DTI and two-direction DWI show good agreement with the SMI-31 immunostaining, suggestive of the validity in detecting residual white matter using both six-direction DTI and two-direction DWI (Fig. 3).

Discussions and conclusions

Axonal injury is observed both by $\lambda_{\parallel}$ and $D_{\parallel}$. At the chronic phase, compared to the controls, $\lambda_{\parallel}$ and $D_{\parallel}$ has a ~ 18 % decrease; both $\lambda_{\perp}$ and $D_{\perp}$ have a two-fold increase suggesting the myelin degeneration (Fig. 4). Both measurements have consistent decreases in anisotropy thus show the identical regions of residual white matters. Our current findings suggest that two-direction DWI derived indices are potential biomarkers of axonal injury in the mouse model of contusive SCI.

References

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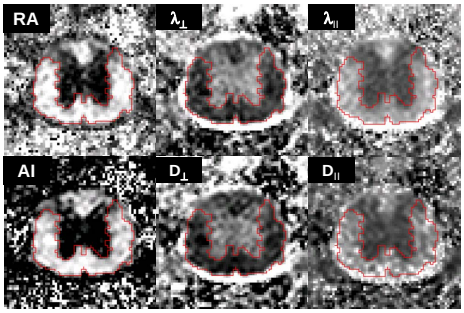

Fig. 1 six-direction DTI vs. two-direction DWI of control cord. ROIs are based on the six-direction DTI maps.

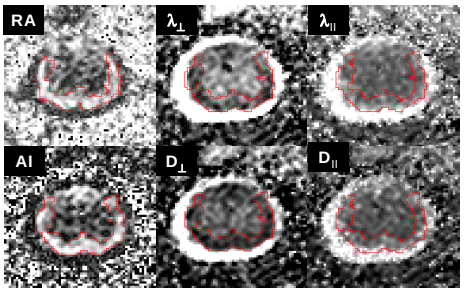

Fig. 2 Images of mildly injured cord. Top row: six-direction DTI maps. Bottom row: two-direction DWI maps. ROIs indicate the region of residual white matter.

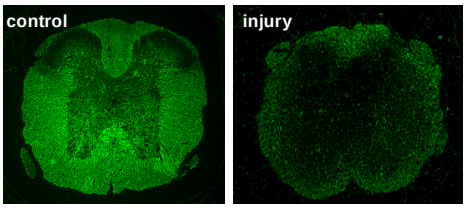

Fig. 3 SMI-31 immunostaining of the control and the injured spinal cords.

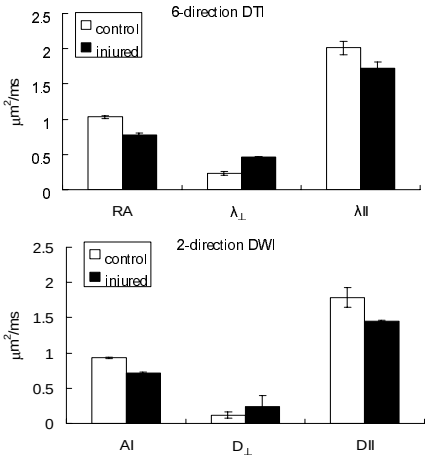

Fig.4 Quantification data of anisotropy indices of six-Direction DTI and two-Direction DWI from the control and injured ventrolateral white matter. *(RA and AI are dimensionless indices)*