# Sub-acute DTI predicts long-term behavioral outcome in the mouse models of spinal cord injury

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## Introduction

The extent of residual ventrolateral white matter (VLWM) is crucial to evaluate the secondary injury and to predict the functional outcome in the rodent model of spinal cord injury (SCI) (1, 2). However, few methods have been reported to non-invasively assess the content of residual VLWM. Axonal injury and myelin damage are the two key components of the injured VLWM. Axial ($\lambda_{\parallel}$) and radial ($\lambda_{\perp}$) diffusivity derived from diffusion tensor imaging (DTI) have been demonstrated as a biomarker of axonal and myelin damage in the central nervous system (3) providing a method to assess the integrity of the VLWM (4). In this study, DTI derived relative anisotropy (RA) was evaluated in the SCI mouse model to assess the extent of residual VLWM. Our result demonstrates close correlations between the extent of residual white matter at sub-acute phase and the chronic neurological outcomes assessed by the hindlimb function.

## 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 (impact distance = 0.8 mm, impact speed = 0.2 m/s). The rest five mice underwent laminectomy without contusion served as the control. All mice were evaluated with Basso Mouse Scale (BMS) for 21 days.

### *Diffusion Tensor Imaging*

Data were acquired at acute (~3 hrs) and sub-acute phase (7 days) using a spin-echo sequence modified by adding *Stejskal-Tanner* diffusion-weighting gradients. The spin echo time (TE) = 38 ms, time between application of gradient pulses ($\Delta$) = 21 msec, and diffusion gradient on time ($\delta$) = 7 ms for all measurements. The repetition time (TR ~1.5 sec) was varied according to the period of respiratory cycle (~270 ms). Three image slices were collected during every breath. Images were obtained with diffusion sensitizing gradients: (Gx,Gy,Gz) = (1,1,0), (1,0,1), (0,1,1), (-1,1,0), (0,-1,1), (1,0,-1). Diffusion gradient = 12.5 G/cm. Two diffusion-sensitizing b values, 0 and 1.02 ms/$\mu m^2$ 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).

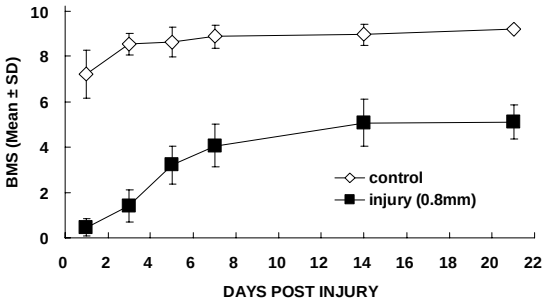


Fig. 1. Mean Basso Mouse Scale for hindlimb locomotion scores from the SCI and control mice. .

## Results

### *Behavioral Assessment*

BMS scores for locomotion over the 21-day period showed a complete recovery in the control group while the SCI mice only partially recovered (Fig. 1). Both groups reached plateaus of locomotion recovery around 7 days post injury (DPI). The current impact distance at 0.8 mm induced a moderate SCI which have significantly lower BMS scores (BMS ~ 5) than the controls (BMS ~ 9).

### *DTI of SCIs*

RA maps at acute and sub-acute phases show the clear evolution of these parameters after SCI (Fig. 2). Consistent with our previous reports (2, 4), RA provides clear contrast between gray and white matter in the control and SCI mice. The residual VLWM was determined by applying threshold of mean ± 2 × SD of RA from control VLWM. After the segmentation of the residual white matter, spatial volumes of residual white matter for acute, sub-acute injury cord and control cord were calculated and normalized by control cord (Fig. 3)

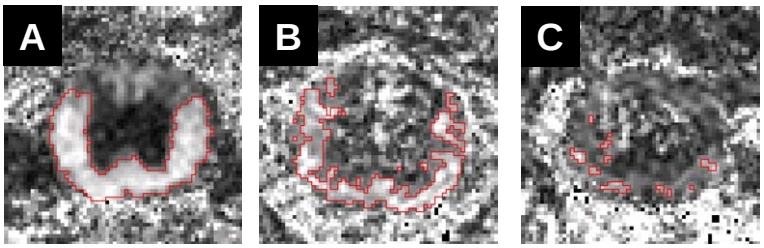


Fig. 2. The RA maps of control (A), injured at acute phase (~3 hrs) (B), and injured at sub-acute phase (7-days) (C) are shown with delineated ROI of residual VLWM. Residual VLWM was determined by threshold with mean ± 2 × SD of RA from control VLWM

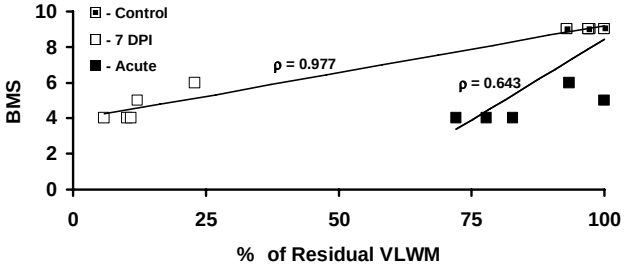


Fig. 3. The normalized residual VLWM of acute (~3 hrs) and sub-acute (7 DPI) injury cord, including control, are shown with chronic phase (21 DPI) BMS. The correlation of residual ventrolateral white matter (VLWM) to BMS is shown for between acute and control and between sub-acute (7 DPI) and control.

## Discussions and conclusions

We further examined the acute and sub-acute residual white matter extent for the prediction of animal's long-term behavioral outcomes (Fig. 3). At the acute phase, anisotropy is largely preserved in the white matter resulting in overestimating residual white matter volume for accurate assessment of its correlation with animal's long term behavior. However, at the sub-acute phase (7 DPI), we observed an excellent correlation between residual white matter and the chronic (21 DPI) BMS score. Our results suggest that the anisotropy map derived from DTI measurements has potential to predict the long-term behavioral outcomes by accurately estimating the extent of the residual VLWM sub-acutely (7-DPI) but not at the hyper-acute phase (less than a few hours).

## References

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