Comparison of white matter damage progression in dislocation versus contusion injury in rat spinal cord using longitudinal diffusivity measurements

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TARGET AUDIENCE: Spinal cord injury (SCI) researchers who will find this work relevant include those who are interested in MRI characterization of damage patterns as a function of injury mechanism (dislocation vs. contusion).

PURPOSE: The type of initial mechanical injury to the cord has been shown to influence the degree of neurological dysfunction throughout the primary and secondary phases of SCI[1], and is therefore important to identify and track in order to guide treatment. Imaging techniques that are sensitive to damage in the white matter microstructure are attractive in characterizing the injury mechanism, especially since different injury models have produced different histological patterns in white matter tracts that are critical to function. Diffusion tensor imaging (DTI) can potentially provide information on this scale; the literature suggests that longitudinal diffusivity (D_{long}) has been associated with axonal integrity in white matter in the acute phase, whereas transverse diffusivity and fractional anisotropy (i.e. other DTI indices) were shown to have a poorer correlation to axonal health[2,3]. Here, we assess the ability of ex vivo D_{long} measurements to differentiate between two rat models of SCI (dislocation vs. contusion) at various time points after injury (3 hours, 24 hours, 7 days).

METHODS: Sprague-Dawley rats (male, 300g) were injured at the C5/C6 level with an electromagnetic linear actuator (Test Bench ELF LM-1) integrated with a novel spinal cord injury system[4]. For contusion, a 1.3 mm injury was produced with C5 and C6 held in a stationary position. Fracture-dislocation at C5/6 was produced by holding C4 and C5 stationary while dislocating C6 and C7 dorsally over a 1.75mm displacement. These displacement magnitudes correspond to a moderate severity based on previous experience and the literature[4]. Cords were perfusion-fixed and extracted at 3 hours, 24 hours and 7 days post-injury (N=5 for a particular time point and injury model). DTI-EPI was acquired with a Bruker 7T preclinical scanner at 11 axial slices centered around the lesion epicentre at 50 µm in-plane resolution and 1mm slice thickness (TE/TR =38.61/2750 ms, 8 shots, 6 directions, b=1000 s/mm2, NA=18, 128x128, FOV=6.4mm, 11 slices). The white matter was segmented into ventral, lateral and dorsal ROIs from which average Dl_{ong} values were calculated for each slice. Significant difference between the ROIs for a particular slice position was assessed by Kruskal-Wallis comparison of medians at a significance level of $p<0.05$.

RESULTS: Figure 1 shows D_{long} averages for each white matter sector ROI across slice position for a particular injury model and time point post-injury. Variability in the data precluded definitive comparison between sector ROIs within a given group and slice, as seen by the relatively few instances of statistically significant differences. However, a description of trends may be attempted to compare the injury patterns between dislocation and contusion, as outlined in Table 1.

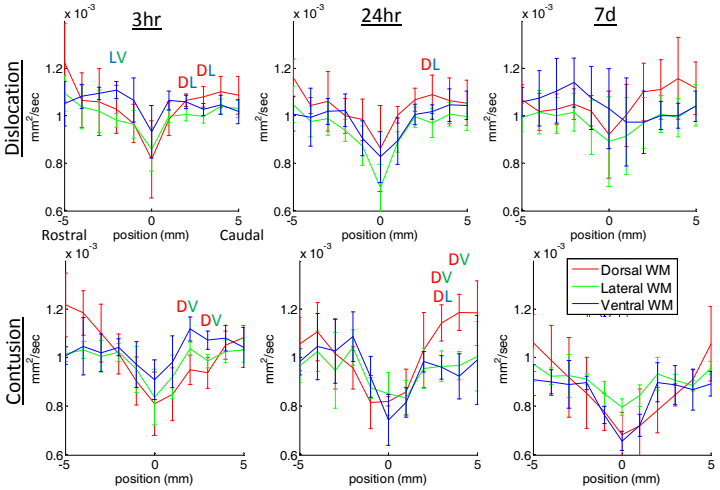

Figure 1. WM ROI averages of D_{long}. Error bars show standard deviation. Text annotations show significantly different pairs of ROIs (DV= dorsal vs. ventral; DL = dorsal vs. lateral, LV = lateral vs. ventral).

	Dislocation	Contusion
3hr	Dorsal & lateral D_{long} show most reduction, with the low lateral D_{long} extending further from epicentre.	Dorsal D_{long} shows most reduction followed by lateral D_{long}.
24hr	All sectors show further reduction in D_{long}. Lateral WM shows lowest D_{long}, followed by ventral WM.	Near epicentre, dorsal D_{long} remains about the same as 3hr, while lateral and ventral D_{long} decrease to dorsal levels. Large increase in dorsal D_{long} detected on distal caudal side.
7d	General recovery towards higher D_{long} values is seen. Near epicentre, lateral D_{long} experiences the most recovery but is still the lowest. Largest caudal increase in D_{long} detected in dorsal WM.	All sector D_{long} are lower than hyperacute values, with ventral and dorsal D_{long} experiencing the largest decrease

Table 1. Description of trends seen in D_{long} across time point and injury model

DISCUSSION: The lack of statistical significance between sector ROIs as well as the lack of control subjects limit the predictive value of these results; however, this will be ameliorated with inclusion of more subjects as the study progresses, and the use of specific white matter tracts for use in ROI comparisons. However, the fact that D_{long} decreases is consistent with several other reports in rodent contusion models at 3 hours[3], 24 hours and 7day[2] post-injury. These literature reports show a high correlation between histologically-confirmed area measurements of damaged ventrolateral white matter and area measurements of low D_{long} regions, and suggest that the reduction in D_{long} seen during the hyperacute to acute phase is suggestive of the interrupted and offset axons as a result of primary stretch and tensile injury[2,3,5]. The current data did not show the same recovery towards higher D_{long} at 7 days that was previously shown by Kim et al.[2] in ventrolateral white matter in a mouse model of contusion. In terms of characterizing a dislocation injury model with D_{long} (which is entirely novel), the observed patterns seem distinctly different as compared to contusion data. In particular, there seems to be a greater D_{long} reduction in the lateral WM than the dorsal WM, which matches with previous histological studies of dislocation injury models[4]. A comparison of absolute D_{long} values between injury models is difficult, since even an identical displacement of the injury actuator in both models may lead to a completely different energy distribution and thus different injury severities. A comparison of spatial patterns to the injury is more feasible, and will be confirmed by histology as the study continues.

CONCLUSION: The current data suggests that D_{long} elucidates differences in white matter injury patterns in the early phases of SCI, as a result of a difference in injury mechanism. Inclusion of more subjects and histological analysis will hopefully strengthen these conclusions. If successful, clinical DTI may potentially provide an in vivo biomarker for injury mechanism, which may lead to improved patient outcomes. **Acknowledgments**: This work is supported by the Wings for Life Spinal Cord Research Foundation. **References**: 1. Tator et al., Clin Neurosurg 1983: 479-94. 2. Kim et al., MRM 2007:253-60. 3. Loy et al., J Neurotrauma 2007:979-90. 4. Choo et al., Exp Neurology 2008:490-506. 5. Budde et al., MRM 2007:688-95.