

DIFFUSION TENSOR IMAGING DETECTS AXONAL DEGENERATION AND ITS EXTENT IS ASSOCIATED WITH DISABILITY IN CHRONIC SPINAL CORD INJURY

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Introduction:

Spinal cord injury (SCI) produces degenerative changes in descending and ascending pathways that manifest in morphometric changes in spinal and rostral white and grey matter [1,2]. Thus, flow of axonal information is impeded and motoneurons below the site of injury are often deprived from supraspinal input [3] resulting in clinical disability. Following traumatic SCI, diffusion tensor metrics are altered both in the spinal cord [1,4] and in the brain [5]. However, little is known about whether in the chronic phase of injury microanatomical spinal changes (i.e. axonal degeneration and progressive demyelination) are reflected in DTI parameters and can provide information on the pathological processes rostral to the site of injury. In this study we hypothesize that in chronic SCI, DTI metrics still provide insight into the degenerative mechanisms and relate to clinically relevant measurements of motor function impairment.

Methods

Study design and clinical assessment:

We recruited nine male SCI subjects (mean age 46±10 yrs) with bilateral upper and lower limb impairment, who presented no head or brain lesion associated with the trauma leading to the cord injury and showed no seizures or medical or mental illness. We also recruited nine age- and gender-matched right-handed healthy subjects (mean age 38±16 yrs) without any history of neurological or psychiatric illness. Upper extremity function was bilaterally assessed on the 9-Hole Peg Test (9HPT) and the reciprocal of the average of two trials for each hand of the 9HPT were calculated. Three SCI subjects were unable to perform the 9HPT with their non-dominant hand and were scored with the maximum time allowed for the 9HPT (300 sec).

DTI data acquisition: Cardiac gated DTI was performed on a 1.5T scanner (Sonata, Siemens healthcare, Erlangen, Germany) using a twice refocused spin-echo EPI sequence [6] with the following parameters: image matrix=96x96, sinc interpolated in image space to 192x192, FOV=144x144mm², slice thickness=5mm, 20 slices, TE=90ms, TR≈180ms. Two data sets were acquired with alternating phase encoding blip directions and then combined into a single dataset to remove susceptibility induced geometric distortions [7]. Each data set consisted of 68 images with a low b-value of 100 s/mm² for the first 7 images and a high b-value of 1000 s/mm² for the remaining 61 diffusion directions. The diffusion tensor model was fitted to the interpolated data on a voxel-by-voxel basis using Camino (www.camino.org.uk)[8]. From the estimated tensor, fractional anisotropy (FA), as well as radial (RD), axial (AD) and mean (MD) diffusivity maps were calculated for each subject.

Region of interest analysis: In each participant, four regions of interest (ROI) were manually drawn on the average low-diffusion weighted image between C1 and C3 similar to those used in [9]. The four ROIs comprised the left and right CST running in the lateral columns and sensory tracts in the anterior and posterior columns (see Figure 1). The mean value of each diffusion parameter within each ROI was calculated. In addition, a ROI over the cross section of the cervical cord was determined using a semi-automatic region growing segmentation applied to the FA map with a threshold of FA=0.15. Average whole cord DTI parameters were corrected for partial volume contribution from surrounding CSF using in-house software. A two-sample t-test (confidence interval 95%) was used to investigate differences in DTI metrics between SCI subjects and controls. Linear regression was performed to identify independent associations between DTI parameters and clinical measures in SCI subjects.

Results: Compared to controls, SCI subjects show significantly lower FA in all ROIs and higher MD in the anterior column of the spinal cord (see Figure 2). Moreover, we find higher RD in the left CST-ROI, anterior columns and cross-section of the cervical cord and a lower AD in the right CST-ROI. FA in the CST in the cervical cord rostral to the site of initial trauma is associated with motor impairment, i.e. FA of the right CST-ROI correlated with dominant hand 9HPT score (coefficient 0.16, p=0.005) and non-dominant hand 9HPT score (coef. 0.18, p=0.007) (see Figure 3). No significant correlation is detected with MD, RD and AD.

Discussion: Consistent with recent studies investigating DTI metrics in the injured spinal cord [1,4] we report decrease in FA in all ROIs and increased MD in the anterior column. The directional diffusivities provide evidence that RD and AD also change following SCI. RD and AD have the potential to provide information on the pathological processes in addition to that derived from the standard diffusion metrics in animal models of spinal involvement [10]. Alterations of the axonal architecture suggest both axonal degeneration and progressive demyelination occur at sites rostral to trauma of the cervical cord. Crucially, we also find independent associations between lower FA measured in ROIs that correspond to the lateral CST and impaired motor function in SCI subjects. These clinically relevant relationships suggest that the integrity of the motor and sensory function is related to microanatomical changes and that these may be a significant factor in chronic SCI disability.

Conclusion: This study establishes an independent relationship between disability and disruption of the tissue architecture rostral to the site in subjects with chronic cervical injury. Besides these correlations, we observed trauma induced quantitative changes of the standard diffusion metrics reflected by reduced FA and increased MD. Importantly, we complement these findings as we demonstrate for the first time alterations of the directional diffusivities (AD/RD). These findings are in agreement with studies in animal models [10] and suggest that both axonal degeneration and demyelination in the chronically injured cervical cord persist. Alterations in the microstructure of the axonal architecture of the injured spinal cord in descending and ascending pathways are clinical eloquent and deserve further assessment in longitudinal studies. In view of the clinical correlations we suggest that pathological damage detected by DTI contributes to disability in chronic SCI subjects.

References: [1] Ellingson et al, AJNR 29 (2008) [2] Freund et al, SFN #542.22/T1 (2009) [3] Dietz, Nat Rev Neurol 6 (2010) [4] Shanmuganathan et al, AJNR 29 (2008) [5] Wrigley et al, Cereb Cortex 19 (2009) [6] Reese et al, MRM 49 (2003) [7] Andersson et al, Neuroimage 20 (2003) [8] Cook et al, ISMRM, 2006 [9] Freund et al Mult Scler 16. 2010 [10] Budde et al. J Neuroscience 29 (2009)

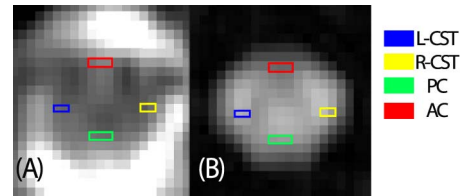


Figure 1: Axial images of mean $b=100$ s/mm² (A) and FA (B) in the cervical cord in one control subject showing the locations of the four ROIs placed in the anterior (AC), lateral (L&R-CST) and posterior columns (PC).

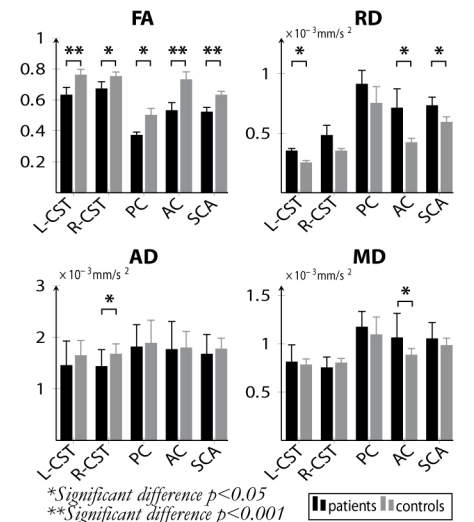


Figure 2: Mean and standard deviation of diffusion metrics obtained in the cervical spinal cord ROIs in the left and right lateral CST, anterior (AC) and posterior columns (PC) and cross sectional cord area (SCA), in SCI subjects and controls.

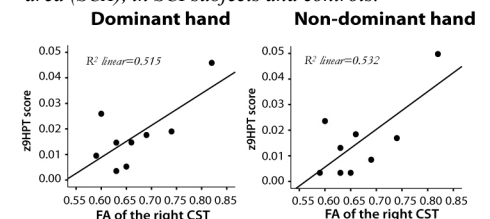


Figure 3: Associations of FA in the right lateral CST with dominant and non-dominant hand 9HPT scores.