Focal lesions do not cause neurological impairment in EAE: Correlating histology with in vivo DTI

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Introduction

The directional diffusivities derived from diffusion tensor imaging (DTI) have shown promise as specific biomarkers of white matter pathology. It has previously been shown that a decrease in axial diffusivity in the spinal cord white matter of mice with experimental autoimmune encephalomyelitis (EAE), a mouse model of Multiple Sclerosis, correlates with both axonal damage and hindlimb motor function. However, mice with EAE have varying degrees of long-term impairment as well as heterogeneous distributions of lesions. The purpose of the current study is to use *in vivo* DTI of the spinal cord of mice with EAE to address the relationship between localized axonal damage and neurological impairment.

Materials and Methods

Thirty-three mice were immunized with MOG_{35-55} to induce EAE, and eight mice served as controls. Mice were evaluated using a 0-5 scoring system. Mice underwent respiratory-gated *in vivo* DTI in the chronic phase of the disease (>day 25), using diffusion sensitizing gradients applied in six orientations (b = 0 and 0.785 ms/μm^2). DTI parameter maps were registered to a common space using an affine transformation. Parameter maps were correlated, on a pixel-by-pixel basis, with the EAE score on the day of imaging. Maps were thresholded at $p < 0.01$, corrected for multiple comparisons (Figure 1). Histological sections stained for intact axons using SMI31 were registered to match the *in vivo* images (Figure 2).

Results and Discussion

A decrease in axial diffusivity was correlated with EAE severity throughout almost the entire white matter (Figure 1). Furthermore, the decrease in axial diffusivity is associated with a decrease in SMI31 staining, with the patterns of injury strikingly similar between the two disparate modalities (Figure 3). In conclusion, axonal damage is widespread in MOG_{35-55} induced EAE, and this can be detected noninvasively using axial diffusivity derived from DTI. This has important implications in the use of mice in preclinical studies as well as in the diagnosis and management of MS.

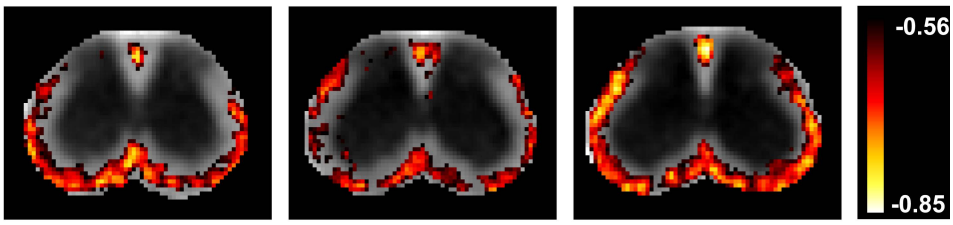

Figure 1. Pixel-by-pixel correlations between axial diffusivity and EAE score for three adjacent lumbar cord slices from thirty-three EAE mice and eight control mice. Scale bar displays the R-value of the correlation, thresholded at $p < 0.01$, corrected for multiple comparisons.

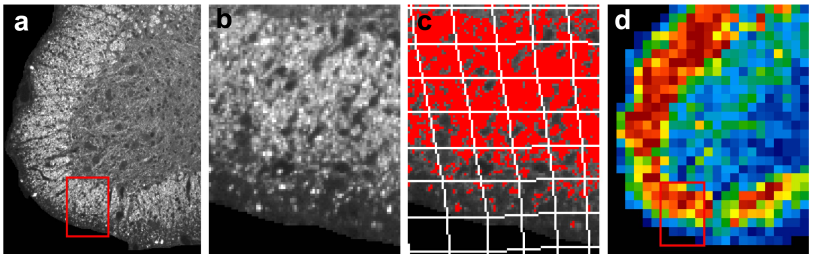

Figure 2. Histological sections acquired at 10× magnification (a & b) were registered to the DTI resolution by identifying corresponding landmarks (not shown), thresholding the image to designate foreground and background staining (c), and overlaying the computed deformation grid. Each pixel in the resulting image (d) represents the fraction of a grid square staining above the background intensity.

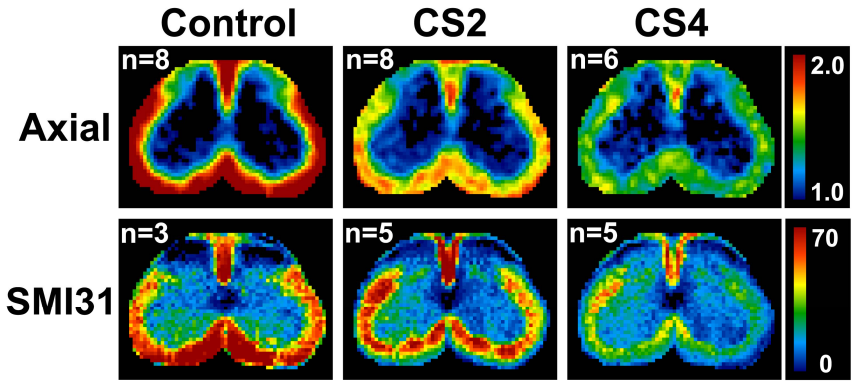

Figure 3. Registered axial diffusivity maps (top) from chronic EAE mice averaged according to clinical score on the day of imaging show the decrease in axial diffusivity that accompanies increased EAE score. Registered histological sections stained for intact axons (SMI31, bottom) confirm the presence of axonal damage throughout the white matter.