DTI and Visually Evoked Potential Changes in Mice with Optic Neuritis

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Introduction

Optic neuritis is usually the first symptom of Multiple Sclerosis (MS). It manifests as recurrent inflammation of the optic nerve, leading to demyelination and axonal disruption, causing neuronal loss (1). In vivo imaging using Diffusion Tensor Imaging (DTI) can detect the degeneration (2-4), but its relation to neuro-functional decline is not clear. The initial damage may start as a result of focal inflammation, but it is not known whether this focal damage can propagate to distal sites, and directly lead to neuronal loss. The aim of this study is to use an animal model to better understand axonal degeneration in MS. Given that degeneration along optic nerves and tracts can proceed rapidly in wild type mice (3, 4), mutant Slow Wallerian Degeneration Mice (WldS), which decelerate the degeneration process, were used to allow temporal evaluation. In this study, we examined the relationship between structural change within the visual pathway (as measured by DTI) and correlated it to changes in visually evoked potentials across a time-course in a MOG-induced experimental autoimmune encephalomyelitis (EAE) model of MS.

Materials and Methods

Eight week old female WldS mice were used in this study. At 2,4,8 and 12 weeks-post EAE induction (n=5 at each time point), mice had DTI collected using a Bruker 11.7T BioSpec small animal MRI with slice thickness 0.5 mm, FOV of 1.5 cm x 1.5 cm and matrix 128 x 128 (zero filling to 256 x 256), TR 2.5 s, TE 29 ms, Δ 20 ms, δ 3 ms, and 21-direction diffusion scheme with b-values of 0 and 0.85 ms/μm2. Using software written in Matlab, the λ||, λ⊥ and RA maps were generated. For VEP recording, animals were anesthetized with a mixture of oxygen and isoflurane. VEPs were recorded using a small loop of silver wire overlaid on the visual cortex following light stimulation.

Results

Significant changes in λ||, λ⊥ and RA were observed during the duration of disease (Fig 1.), suggesting ongoing axon and myelin damage. Significant reductions in VEP latency were also seen, with significant increases in latency observed after 12 weeks (Fig 2). VEP amplitude showed a trend toward reduction, though differences in amplitude between timepoints did not reach significance at any time point (Fig 2). Both VEP latency and amplitude significantly correlated to changes in optic nerve and tract RA and λ⊥ but not with λII (Fig 3).

Discussion

This study is the first to compare DTI and VEP measures across time points in an animal model of optic neuritis. This study shows that both DTI metrics (RA, λ⊥ and λII) and VEP metrics (N1 latency and amplitude) change progressively with longer durations of optic neuritis. The study also demonstrates that optic nerve and tract DTI measures (λ⊥ and RA) significantly correlate with both VEP latency and amplitude measures across the time-course of disease activity.

Reference **1.**Shindler K et al, Experimental Eye Research 87 (2008) 208-213. **2.** Sun SW et al, Neurobiology of Disease 2007; 28: 30-38. **3.** Xie M et al, Neuroscience 197 (2011) 339–347. **4.** Sun SW et al, Neuroimage 2008; 40: 1-10. **Acknowledgement** NIH R01 NS062830.

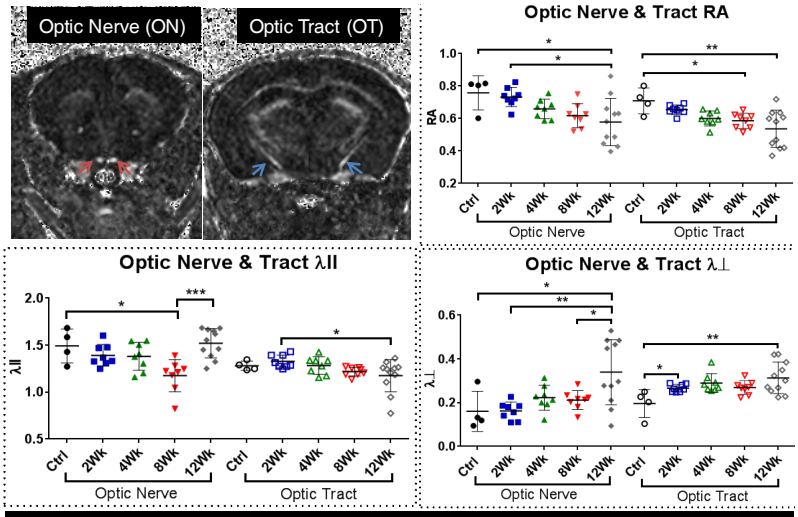

Figure 1. DTI change within ON and OT during EAE

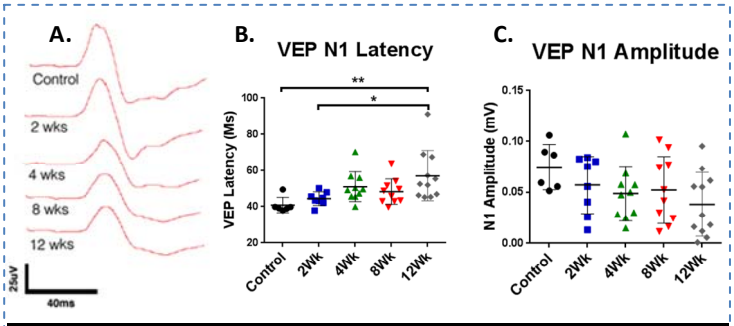

Figure 2. Averaged VEP waveforms (A) with quantified VEP latency (B) and amplitude (C)

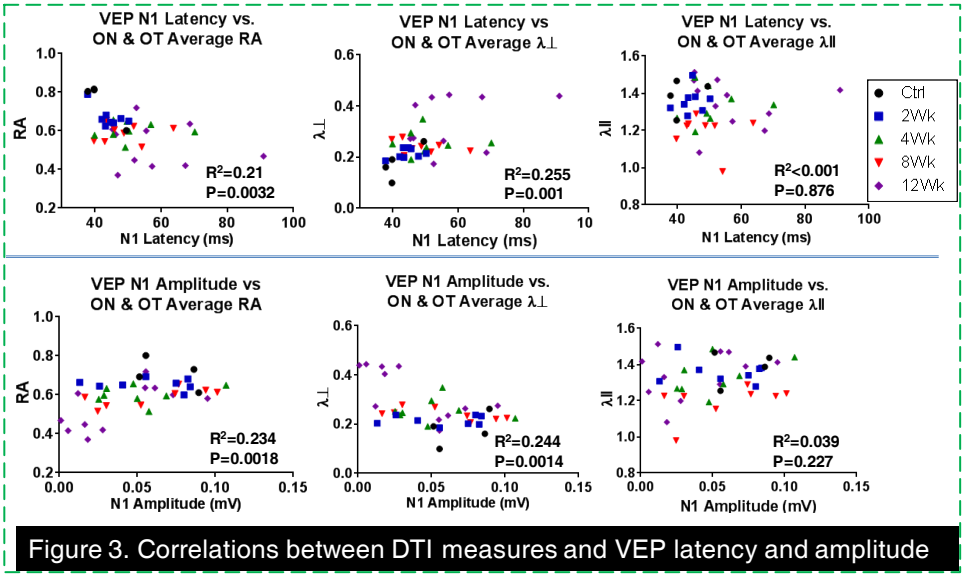

Figure 3. Correlations between DTI measures and VEP latency and amplitude