Radial Diffusivity in Remote Optic Neuritis Discriminates Visual Outcomes

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Introduction Translating animal diffusion tensor imaging (DTI) studies of optic nerve injury with direct histopathologic correlation [1], we hypothesize that breakdown of myelin and axons would result in increased radial diffusivity (RD) that is proportional to loss of clinical function. This study expands upon our previous work [2] by enrolling a larger number of subjects, including optic nerve (ON) due to several etiologies rather than just multiple sclerosis (MS), assessing the relationship of DTI to different categories of vision loss, and providing a detailed analysis of the relationship between retinal nerve fiber layer (RNFL) and visual evoked potential (VEP) to visual function.

Methods Subjects: Baseline demographic information of 70 study subjects is listed in table 1.

Image Acquisition and Aalysis: DTI data were acquired by high resolution (1.3 mm isotropic) transaxial reduced field-of-view DTI protocol [3], processed with motion correction, and analyzed to avoid CSF contamination as previously described [2] (Fig. 1).

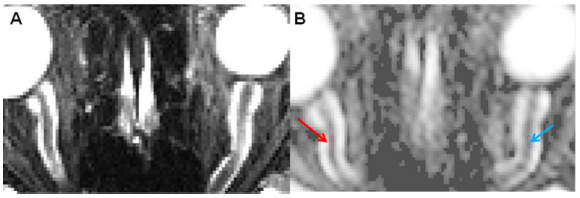

Figure 1. A representative T2W image (A) and RD map (B) with ROIs (arrows) mapped from b_0 image

Clinical Testing: Vision tests included Snellen 20, 5% contrast sensitivity (CS), and Pelli-Robson contrast sensitivity (PR). Best corrected vision was achieved with glasses or pinhole occluder. Visual-evoked potentials (VEP) P100 latency and N75:P100 were read in blinded fashion. Optical coherence tomography (OCT) fast RNFL thickness was obtained on a Zeiss StratusOCT III.

Statistics: Linear mixed modeling accounted for two eyes within a single individual. OCT was evaluated as the average overall RNFL for each individual eye. Visual acuity after ON was categorized based upon the Ranges of Vision Loss by the ICO.[4] The moderate (n = 6) and severe (n = 8) categories were combined and categorized as "severe". Rank correlation coefficients were obtained by randomly selecting a single nerve from each subject with 1000 repetitions.

N	70 subjects
Age, median (range)	42.5 y (21 - 65)
Gender	54 (77%) female 16 (23%) male
Diagnoses	7 CIS 48 MS 14 NMO 2 Other (1 Idiopathic, 1 ADEM)
Clinically Involved Eyes	102 of 140 eyes
Episodes of ON, per eye, median (range)	1.0 (0 - 5)
Years from 1st Episode of ON, median (range)	4.0 (1 - 41)
IV Glucocorticoids for Optic Neuritis	54% Yes
Acute Optic Neuritis Severity at Nadir	40% Mild to Moderate (≥20/200) 60% Severe (≤20/200)
Disease Duration, median (range)	7.0 (1 - 41)
EDSS, median (range)	2.0 (0 - 8)
MSSS, median (range)	3rd %tile (1st - 10th %tile)
Median Visual Acuity, median (range)	1.0 (1.54 - NLP)
Median Contrast Sensitivity, Pelli-Robson, median (range)	1.75 (0 - 1.90)
Median Contrast Sensitivity, 5%, median (range)	0.3 logMar (-0.10 - 1.0)
Median RNFL, median (range)	82.72 microns (35.30 - 119.40)
Median VEP P100 latency, median (range)	124 msec (92.8 - 170.0)
Median VEP N75:P100 amplitude, median (range)	5.39 mV (1.50 - 15.80)

Table 1. Baseline demographics.

Results and discussion *All Diffusion Parameters Correlated Strongly with Visual Outcomes* Of the DTI parameters, RD had high correlations with all visual outcomes, including VA (r= -0.61), PR (r= -0.60), and 5% CS (r = 0.61). MD values were similar to RD, as RD and MD were highly correlated (r = 0.98). Axial diffusivity (AD) and fractional anisotropy (FA) also displayed strong correlations with visual outcomes, but with correlations less than those found for RD and MD. The four DTI parameters revealed a similar hierarchy of abilities to discriminate among VEP measures and OCT, with RD and MD again having the highest overall correlations. In particular, RD displayed strong correlations with OCT (r = -0.75), VEP latency (r = 0.61), and VEP amplitude (r = -0.46).

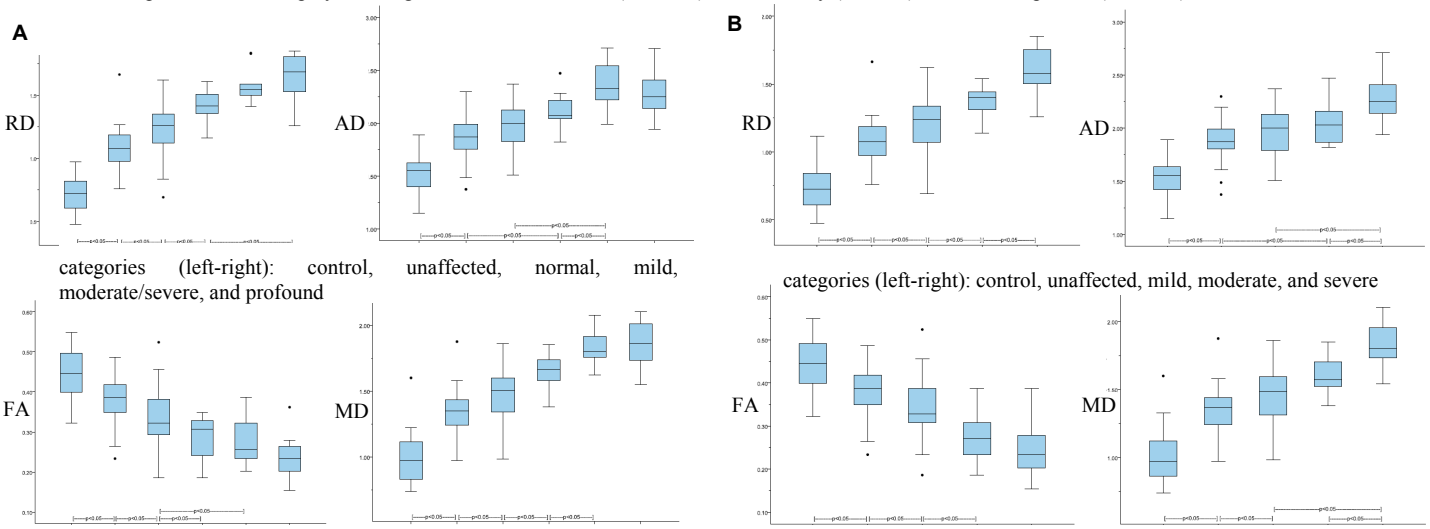

Figure 2. Boxplots of DTI parameters by visual acuity categories (A) and PR contrast sensitivity categories (B) recovery after optic neuritis

All Diffusion Parameters Discriminated Visual Recovery RD displayed a strong increasing trend after categorizing subjects into VA severity subgroups, as defined by the ICO of normal, mild, combined moderate/severe, and profound (Fig. 2A, mixed modeling p<0.0001). RD discriminated control nerves (adjusted mean and [CI] by mixed modeling: 0.72 [0.63, 0.80]) from unaffected fellow nerves (1.08 [1.02, 1.14]), unaffected from the affected nerves with normal recovery (1.23 [1.18, 1.27]), normal from mild impairment (1.42 [1.32, 1.52]), and mild from profound visual loss (1.65 [1.57, 1.75]). The mild from moderate/severe categories (1.61 [1.50, 1.71]), along with the moderate/severe from the profound categories were not distinguished by RD. DTI parameters were further evaluated with PR and 5% CS, subgrouped into clinically meaningful categories. RD displayed a strong linear trend with PR subgroups of unaffected, normal, mildly affected, moderately affected, and severely affected (Fig. 2B, mixed modeling p<0·0001). RD distinguished control (0·72 [0.63, 0.80]) from unaffected fellow nerves (1.07 [1.01, 1.13]), unaffected from affected nerves with normal recovery (1.22 [1.17, 1.27]), mild recovery (1.27 [1.20, 1.35]) from moderate impairment (1.46 [1.37, 1.56]), and moderate from severe (1.65 [1.57, 1.74]). RD did not discriminate normal recovery from mild visual loss by PR.

Reference [1] Song, et al. *Neuroimage.* **20**, 1714-22, 2003 [2] Naismith, et al. *Neurol.* **72**, 589-94, 2009 [3] Xu, et al. *NMR Biomed.* **21**: 928-40, 2008 [4] International Council of Ophthalmology (ICO) World Recommendation of Defining Visual Loss, 2002