

Optic Nerve Dedicated Magnetization Transfer and Diffusion Tensor Imaging Shows Correlation with Thickness of Retinal Nerve Fiber Layer Detected by Optical Coherence Tomography

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Introduction: The human optic nerves (ON) are small, dense, white matter fiber bundle that exit the eyes, course postero-medially and superiorly in the orbit, pass through the optic canal, and converge in the optic chiasm. The ON is responsible for communicating all visual sensory information from each eye to the brain and is affected by a number of CNS diseases (1), including multiple sclerosis (MS) (2,3). Approximately 40-60% of MS patients have visual deficits localized to the ON, and ON inflammation (optic neuritis) is the initial presenting symptom in 17-25% of all MS cases (2,3). Studies of low contrast visual acuity and optical coherence tomography (OCT) demonstrate that standard ophthalmoscopic exam may underestimate the degree of optic nerve damage in MS. Thus, it is important to develop non-invasive MRI technologies that can assess ON morphology and improve the understanding of the relationship between optic neuritis and MS. Magnetization transfer (MT) and diffusion tensor imaging (DTI) show relationships between signal abnormalities and axonal and myelin pathology (4,5) but have been limited to study of the brain and spinal cord. Smaller structures such as the ON present technical hindrances because the ON is, at most, 3-4 mm in diameter, is highly mobile, sits superior to the large maxillary sinuses (causing image distortions at the air-tissue interface), and is surrounded by cerebrospinal fluid and meningeal layers. Conventional MRI (pre-, post-contrast T₁w and T₂w) have revealed cross-sectional ON swelling and lesions in optic neuritis, but it has been difficult to quantitatively assess the diffusion and magnetization transfer properties of the ON *in vivo*. Our hypothesis is that assessment of the ON using MRI methods sensitive to axonal and myelin integrity can provide quantitative information about microscopic tissue damage in MS that relates to thickness of the retinal nerve fiber layer (RNFL) as determined by OCT.

Methods: MRI Acquisition: Thirty-one MS patients were studied after signed, informed consent, and all studies were approved by the local institutional review board. Scans were performed on a Philips 3T MRI system (body coil excitation, 16-channel neurovascular coil reception), and all imaging was performed in the coronal plane with the 1st slice placed anterior to the optic nerve head. DTI of the ONs was performed using a multi-slice spin echo with single-shot EPI. Five minimally weighted (b₀) and 15 diffusion-weighted volumes (b-value = 400 s/mm², non-collinear directions) were acquired. Other parameters were: TR/TE = 5.3s/53 ms, nom. resolution = 1.2x1.2x2.5mm³ (FOV = 80x80x62.5mm³), 25 slices, 2 averages, and 4 min scan time per acquisition. MT weighted imaging was performed using a 3D GRE sequence, (TR/TE/α = 86ms/9.5ms/9°) with a 24ms, 5-lobed sinc-gauss MT prepulse (10.5 μT, 1.5 kHz off-resonance). A reference scan was acquired without MT preparation. MT sequences were obtained with the same FOV as DTI, but with a nominal resolution of 0.67x0.88x2.5mm³, 25 slices, and total scan time = 7 min. **Data Analysis:** All images were coregistered to the initial b₀ using a 3D rigid body alignment (AIR). After coregistration, the diffusion tensor was estimated and the fractional anisotropy (FA), mean diffusivity (MD), perpendicular diffusivity (λ_⊥), parallel diffusivity (λ_∥) and magnetization transfer ratio (MTR) were calculated from the DTI and MT data, respectively. From the MD images (Fig 1, 2nd row), ROIs were placed bilaterally in the central voxels of the ON slice-by-slice from the orbit to the optic chiasm, and the median of each metric was calculated. The retinal nerve fiber layer (RNFL) thickness was calculated from OCT data (6) for each eye and was correlated with the median MR metrics from that eye.

Results and Discussion: Fig 1 shows DTI and MTR maps for right (OD) and left (OS) ONs in one MS patient with a history of optic neuritis in the left eye. The ON (as seen on the FA map) is the small, bright region surrounded by an annulus of CSF, but note that all DTI-derived indices discriminate the ON (arrow) from surrounding CSF. The median DTI and MTR values across all MS patients are given in the Table. Fig. 2 shows the correlation between median DTI metrics and RNFL thickness (μm), each showing a significant (p < 0.05) correlation except for λ_∥ (r = 0.35, p = 0.06). There was no significant correlation with MTR (r = 0.25, p = 0.18). It is interesting to examine the strong correlation between RNFL and FA (r = 0.59, p < 0.001) and λ_⊥ (r = 0.60, p < 0.001) as each of these metrics measures a different phenomenon in the tissue. FA reports on the degree of anisotropy of water diffusion in the ON, which, in MS patients may be lowered due to myelin and/or axonal damage. λ_⊥ reports on the diffusion of water perpendicular to the long axis of the ON and decreases with increasing RNFL thickness. In fact, data from animal models suggests that λ_⊥ is informative about axonal damage and, one possible hypothesis is that if ON axons are lost, the RNFL thickness may decrease causing the extracellular space in the ON to increase, and the perpendicular diffusion of water could therefore be less hindered and increase. The lack of correlation between MTR and RNFL may stem from: 1) imprecise coregistration between the two scans and the b₀ would increase partial volume effects from the surrounding CSF,

which could reduce the correlation, 2) RNFL is not affected by myelination, and thus a direct comparison with the MTR which is hypothesized to be myelin sensitive is not transparent. Future correlations with visual acuity and assessment of healthy controls will be necessary for a better understanding of how these metrics relate to visual function/loss in patients with and without history of optic neuritis.

Conclusion: Combined DTI/MT MRI of the optic nerve may allow a quantitative assessment of the structural integrity of the ON and its relationship to a sensitive metric of anterior visual pathway health. Thus, DTI and MTR imaging may be useful in evaluating damage to the ON in a variety of diseases and follow tissue evolution over time.

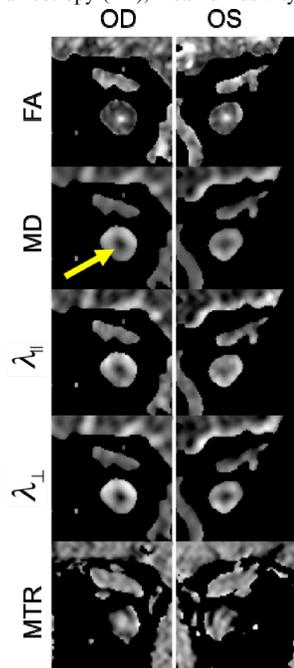


Fig 1: MT/DTI-derived metrics for the ON in one patient with history of optic neuritis (OS)

	mean ± SD
FA	0.62±0.12
MD (μm ² /ms)	0.89±0.26
λ _∥ (μm ² /ms)	1.50±0.31
λ _⊥ (μm ² /ms)	0.58±0.25
MTR	0.28±0.05

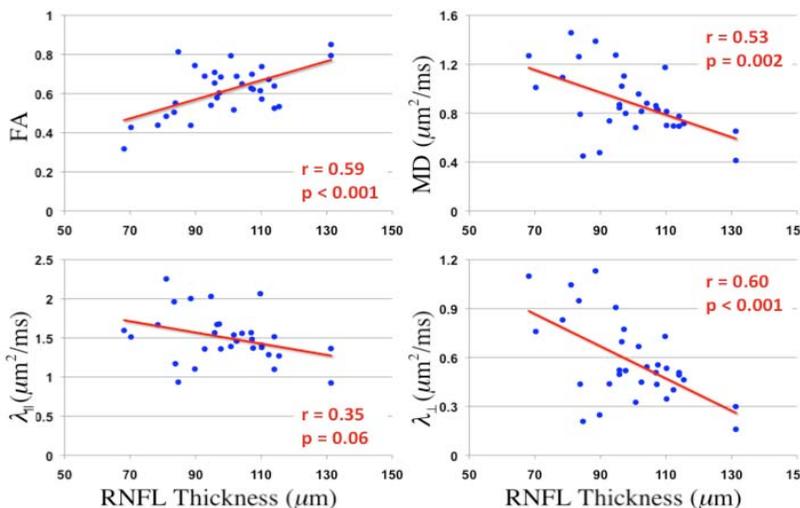


Fig 2: Correlation between median DTI-derived metrics and RNFL over all MS patients studied. All correlations were significant except λ_∥ (p = 0.06) and MTR (p = 0.2)

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