Diffusion Tensor Imaging Correlates of Visual Impairment in Multiple Sclerosis and Chronic Optic Neuritis

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PURPOSE. To compare white matter (WM) injuries associated with vision loss in multiple sclerosis (MS) and optic neuritis (ON).

METHODS. Twenty-three patients with clinically definite relapsing–remitting MS and chronic unilateral ON and 14 neurologically healthy volunteers were monocularly tested with Sloan 100%, 2.5%, and 1.25% contrast visual acuity charts. Primary visual pathway and whole-brain WM injury were assessed with optical coherence tomography (OCT) and diffusion tensor imaging (DTI). OCT and DTI correlates of high- and low-contrast visual impairment were identified using correlation analyses.

RESULTS. The MS patients displayed significantly reduced retinal nerve fiber layer (RNFL) thickness and altered optic nerve and radiation DTI measures compared with the controls. In the patients, 2.5% and 1.25% contrast letter acuity in the unaffected eye correlated significantly and independently with optic nerve and optic radiation DTI measures. Visual acuity in affected eyes did not correlate with optic nerve or optic radiation DTI measures, but did correlate with DTI measures in prefrontal and temporal brain regions that were shown to connect structurally to visual cortices.

Conclusions. In unaffected eyes, visual impairment was associated with WM injury in the visual pathway. In contrast, irrecoverable visual impairment after ON was associated with injury to frontal WM, which potentially impairs the capacity for remapping visual processing. (Invest Ophthalmol Vis Sci. 2012;53:825–832) DOI:10.1167/iovs.11-8864

Optic neuritis (ON) is common in patients with multiple sclerosis (MS) and can lead to persistent visual dysfunction experienced as a loss of visual acuity, contrast sensitivity, and color vision.1 High-contrast letter acuity is commonly used to track recovery after ON, but is insensitive to subtle extant optic nerve demyelination after ON, which is evident as prolongation of visual evoked potentials (VEPs). In contrast, Sloan low-contrast letter acuity (LCLA) can reveal subtle persistent visual dysfunction after ON.2 As such, adoption of LCLA could improve the clinical characterization of visual function, and LCLA has thus been posited as the visual function score to be included in the proposed MS functional composite (MSFC).5 However, the neural injuries that underlie LCLA dysfunction have not been clearly elucidated.

Studies have demonstrated associations between LCLA dysfunction and injury to the anterior visual pathway (optic nerve, chiasm, and tracts).2,5,9 The optic radiations, and brain injury more generally5,9,10 in MS patients, with and without ON. However, most studies have not clearly differentiated patients with optic nerve involvement from those without, and visual pathway injury is likely to differ in the two conditions.

Several imaging tools have been used to study white matter (WM) injury in the primary visual pathway. Optical coherence tomography (OCT) can reveal thinning of the unmyelinated retinal nerve fiber layer (RNFL), regarded as a marker of optic nerve axonal degeneration.8–10 Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that is sensitive to WM injury in MS lesions and T2 normal-appearing WM (NAWM).11,12 Studies by our group and others have demonstrated that DTI is sensitive to optic nerve and postgeniculate WM injury in patients with ON and MS.1,6,13–16

This study was conducted to investigate the loss of high- and low-contrast visual acuity in patients with MS and unilateral ON in the context of (1) primary visual pathway injury and (2) injury to WM outside the primary visual pathway, given recent evidence suggesting a role for functional plasticity within extrastriate visual cortices in mediating vision loss after ON.17–19

METHODS

Participants

Twenty-three patients (7 men and 16 women; mean ± SD age, 46.4 ± 11.4 years) with clinically definite relapsing–remitting MS...
and a single presentation of unilateral ON more than 1 year previously were recruited (Table 1). ON was diagnosed at the time of clinical presentation as demyelinating inflammation of the optic nerve based on standard clinical diagnostic procedures: temporal profile of vision loss evolving over days, ocular pain aggravated by eye movement, loss of color vision and contrast sensitivity, the presence of visual field loss consistent with an optic nerve lesion, and the presence of afferent papillary defect. Only patients with no recurrence of ON were included in the study. All patients had Snellen visual acuity of 6/7.5 or worse in the clinically affected side and 6/7.5 or better in the unaffected side. Patients underwent neurological examinations, and the Multiple Sclerosis Severity Score (MSSS) was calculated from each patient’s Expanded Disability Status Scale (EDSS) and disease duration, by using freely available software (www.gene.cimr.cam.ac.uk/MSgenetics/GAMES/MSSS) and a population distribution.

All patients were imaged with three-dimensional (3D) T1-weighted and 3D T2-weighted FLAIR sequences. Brain parenchymal volume (BPV) was calculated using the T1 images and SIENAX. Lesions were delineated on the FLAIR images by a semi-automated thresholding technique. For each patient, lesion volume was calculated as a percentage of BPV.

Fourteen neurologically healthy volunteers, actively recruited in an attempt to closely match the age and sex distribution of the patients (2 men and 12 women; mean ± SD age, = 40.4 ± 8.2 years), were recruited for comparative MRI data. A separate group of 25 healthy volunteers (6 men and 19 women; mean ± SD age, 35.9 ± 11.2 years) were used for OCT comparisons. Control data were collected on the same MRI and OCT scanners, with the same scanning protocols as used for OCT comparisons. Control data were used in obtaining the patient data.

All MRI sequence parameters are included in the Supplementary Material (http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-8864/-/DCSupplemental). All MR imaging was performed with a 3-Tesla MRI system (Trio TIM; Siemens, Erlangen, Germany) with a 12-channel head coil. The research complied with the Declaration of Helsinki. All study participants provided written, voluntary consent and the study was approved by the Royal Melbourne Hospital human research ethics committee.

### TABLE 1. Patient Demographic and Disease Data

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### Visual Function Tests

On the same day as they underwent MRI, the patients and controls underwent monocular visual acuity assessments at a 2-m distance in a well-lit room, with Sloan letter charts of 100%, 2.5%, and 1.25% contrast (Precision Vision, La Salle, IL). Visual acuity was the number of correctly reported letters of the total 60 letters viewed. Patients’ affected and unaffected Sloan data were compared by using Wilcoxon signed rank-sum tests.

### Primary Visual Pathway Imaging and Analysis

OCT was performed using the fast RNFL protocol (Stratus OCT-3 scanner, ver. 3.0 software; Carl Zeiss Meditec, Dublin, CA). Only scans with a minimum signal strength of seven were accepted. Three circular scans with diameters of 3.4 mm centered on the optic disc were acquired. Average RNFL thickness was calculated for each eye in all subjects, according to previously described procedures. Three patients were unable to present at the OCT study site, leaving data from 20 patients for analysis. No subjects needed pupil dilation before scanning. In almost all cases DTI and OCT were tested on the same day except in a small number of cases where patients were unable to present at both testing sites on the same day. In those cases, DTI and OCT were collected within 1 month of each other.

Patients and controls underwent optic nerve DTI according to a previously described procedure. Each optic nerve was scanned individually with a FLAIR DTI sequence. Average axial, radial, and mean diffusivities and fractional anisotropy (FA) were calculated from the intraorbital optic nerves in manually delineated regions of interest (ROIs) with high reproducibility, as previously described.

Patients and controls underwent whole-brain DTI for calculation of optic radiation and whole-brain measures. Raw diffusion-weighted images were eddy-current corrected and spatially aligned by using an affine registration algorithm. Weighted averages for axial, radial, and mean diffusivities (MDs) and FA were calculated for the whole optic radiations bilaterally by using a previously described protocol.
Primary Visual Pathway Statistical Analyses

All DTI and OCT measures were tested for normality with Kolmogorov-Smirnov tests. Distributions for DTI or OCT measures did not differ significantly from normal; therefore, parametric statistical analyses were performed. Unpaired *t*-tests were used to compare affected and unaffected optic nerve DTI measures and RNFL thickness with the control data and to compare affected nerve DTI measures and RNFL thickness with unaffected data. Pearson correlation analyses were performed between DTI measures and RNFL thickness for affected and unaffected nerves. Patient and control optic radiation DTI measures were compared by using unpaired *t*-tests. Pearson correlations were performed between optic radiation DTI measures and optic radiation lesion volume, optic nerve DTI measures, and RNFL thickness.

Because visual acuity measures are not continuous variables, Spearman rank correlation analyses were performed between affected and unaffected Sloan visual acuities and optic nerve DTI, RNFL thickness, and optic radiation DTI.

Voxelwise DTI Regression and Tractography

Voxelwise regression was used to assess covariance between high-contrast visual acuity loss in the affected eyes of patients and FA or MD in the brain. Diffusion tensor images were spatially normalized to a template space (MNI-152) using a DTI nonlinear registration toolkit (DTI-TK). After normalization, FA and MD maps were smoothed by using a 5-mm Gaussian filter, and voxelwise statistics were computed with SPM8 (www.fil.ion.ucl.ac.uk/spm; University College, London, UK). Two voxelwise linear regression analyses were performed. The first tested for significant covariance between FA or MD and affected-side, high-contrast visual acuity, when adjusted for age. The second design controlled for age and mean affected optic nerve and optic radiation FA, to investigate whether DTI alterations in regions outside the primary visual pathway were independently associated with reduced visual acuity. A conservative *P* value threshold (*P* < 0.005) and a cluster extent threshold (>100 voxels) were used to correct for multiple statistical tests. Only FA and MD maps were included in this analysis, because axial and radial diffusivities are poorly defined in most cerebral WM voxels, which are believed to contain crossing and/or merging fibers.

Diffusion tractography was used to reveal anatomic connectivity from brain regions elucidated by the voxelwise regression analysis. Detailed tractography methods are included in the Supplementary Material (http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-8864/i/DCSupplemental). Connectivity was assessed in healthy subjects rather than patients, because WM injury can alter tractography results that depend on robust estimates of the principal direction of diffusion.

RESULTS

Patient Disease Severity

Disease and demographic data are shown in Table 1. The patients had a median MSSS of 3 (range, 0.9–7.7). All except one patient (lesion volume, 13.8% of BVV) exhibited relatively small brain lesion volumes (range, 0%–3% of BVV). Although the patients displayed considerable variation in disease duration and time since the onset of ON, all exhibited chronic unilateral optic nerve injury evidenced by unilateral visual disability (median affected VA = 6/9 vs. median unaffected VA = 6/6). There was no left/right bias in the side of ON in the patient cohort (12 right vs. 11 left).

Sloan high- and low contrast letter acuities revealed significant visual dysfunction in the patients’ affected eyes (in all cases, *P* < 0.0001 compared with unaffected eyes; Table 1). With the affected eye, a patient could read an average of 40 (mean unaffected, 56) 100% contrast letters, 14 (mean unaffected, 31) 2.5% contrast letters, and 10 (mean unaffected, 23)
In both affected and unaffected optic nerves, DTI measures and RNFL thickness differed significantly from control values (Table 2). RNFL thickness correlated significantly with DTI measures in both unaffected (radial diffusivity: \( R = -0.64, P = 0.003 \); MD: \( R = -0.59, P = 0.008 \); and FA: \( R = 0.64, P = 0.003 \)) and affected optic nerves (radial diffusivity: \( R = -0.56, P = 0.01 \); MD: \( R = -0.54, P = 0.01 \); and FA: \( R = 0.54, P = 0.01 \)). In the patients, optic radiation DTI measures obtained from lesions correlated significantly with those from NAWM (radial: \( R = -0.78, P = 0.0001 \); MD: \( R = -0.70, P = 0.0001 \); FA: \( R = 0.87, P = 0.0001 \)), and DTI measures are therefore reported for the radiations as a whole. The patients’ optic radiation DTI measures differed significantly from control values (Table 2) and correlated with optic radiation lesion volume (radial diffusivity: \( R = 0.67, P = 0.001 \); radial diffusivity: \( R = 0.72, P = 0.0001 \); MD: \( R = 0.73, P = 0.0001 \); and FA: \( R = -0.61, P = 0.003 \)). Optic radiation lesions had an average (%SD) volume of 19% ± 14% of the total optic radiation volume. Whole optic radiation DTI measures did not correlate with optic nerve DTI measures or RNFL thickness in either the affected or unaffected sides.

### Primary Visual Pathway Injury in the Patients

In both affected and unaffected optic nerves, DTI measures and RNFL thickness differed significantly from control values (Table 2). RNFL thickness correlated significantly with DTI measures in both unaffected (radial diffusivity: \( R = -0.64, P = 0.003 \); MD: \( R = -0.59, P = 0.008 \); and FA: \( R = 0.64, P = 0.003 \)) and affected optic nerves (radial diffusivity: \( R = -0.56, P = 0.01 \); MD: \( R = -0.54, P = 0.01 \); and FA: \( R = 0.54, P = 0.01 \)).

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### Visual Disability and WM Injury in the Patients

We observed significant correlations between LCLA in the unaffected eyes and FA (2.5% contrast: \( \rho = 0.37, P = 0.04 \); 1.25% contrast: \( \rho = 0.37, P = 0.04 \)) in the unaffected optic nerves and radial diffusivity (2.5% and 1.25% contrast: \( \rho = -0.42, P = 0.02 \); \( \rho = -0.42, P = 0.02 \)) in the affected optic nerve and \( (\rho = -0.39, P = 0.05) \) in the unaffected optic radiation and \( (\rho = -0.40, P = 0.05) \) in the affected optic radiation. Whole optic radiation DTI measures did not correlate with optic nerve DTI measures or RNFL thickness in either the affected or unaffected sides.

No significant correlations were observed between affected-eye visual acuity and optic nerve or radiation DTI measures or RNFL thickness (Table 3; Figs. 1C, 1D). Voxelwise linear regression analyses identified voxel clusters where FA or MD correlated significantly with high-contrast visual acuity in a dis-
tributed network of frontal and temporal WM regions (Fig. 2, Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-8864/-/DCSupplemental). After statistical adjustment for optic nerve and radiation FA, a cluster of voxels remained significant in the left frontal WM for FA only (cluster peak MNI coordinate: $x = -33$ mm; $y = 44$ mm; $z = 6$ mm; Fig. 3). The WM connections from the left frontal WM region extended to the contralateral orbitofrontal cortex via the genu of the corpus callosum, to the thalamus via the internal capsule, to the temporal lobe via the arcuate fasciculus, and to the occipital lobe via the inferior longitudinal fasciculus (Fig. 4).

**DISCUSSION**

Recent interest in LCLA as a marker for visual dysfunction in MS necessitates investigations of the mechanisms underlying such dysfunction. In this study, we assessed correlations between Sloan high- and low-contrast letter acuities, and imaging markers for WM injury in the optic nerves and radiations and brain. Our principal results were: (1) variation in LCLA in the clinically unaffected eyes was explained by primary visual pathway injury evidenced by DTI changes in optic nerves and radiations; (2) variation in high- and low-contrast visual acuities in the clinically affected eyes did not correlate with injury to either the primary visual pathway or extrastriate visual areas; and (3) loss of high-contrast visual acuity in the affected eyes was associated with reduced FA in prefrontal and temporal WM regions, most notably in the left frontal lobe, a region displaying anatomic WM connections to visual processing areas.

**Substrates of Visual Impairment in Clinically Unaffected Eyes**

The DTI abnormalities and concomitant RNFL thinning observed in the unaffected nerves suggested subclinical axonal degeneration in the absence of acute inflammatory demyelination. One previous study has reported DTI changes in optic nerves previously unaffected by ON but several studies of patients with recent ON reported no differences from healthy nerves.10,14,16,27,28 One study revealed RNFL thinning in patients with primary progressive MS in the absence of optic nerve inflammation.29 Together, these data suggest that in MS the optic nerve is affected by slow-burning axonal degeneration in the absence of overt inflammation, which could reflect processes such as subclinical inflammation, chronic neuronal dysfunction, and transsynaptic degeneration.6,13 The patients also displayed optic radiation injury evidenced by inflammatory lesions and associated DTI abnormalities in surrounding NAWM. Optic radiation DTI abnormalities have been demonstrated in the context of MS and ON, specifically.6,13,31

LCLA in the clinically unaffected eyes significantly correlated with DTI measures in the patients’ unaffected optic nerves and optic radiations. Other studies have demonstrated significant correlations between LCLA and visual pathway injury in MS patients.4–6 In particular, significant correlations
have been observed between LCLA and DTI measures in the optic nerves and radiation, and T2 lesion volume in the primary visual cortex, the optic radiations, and the optic tracts. Recent studies have argued for the use of LCLA as a visual function measure to be incorporated into the MSFC. Our results demonstrate that variability in LCLA in MS is relevant to visual pathway injury and as such, LCLA is a useful measure of visual function.

Substrates of Visual Impairment in Clinically Affected Eyes

Compared with the unaffected optic nerves, the affected nerves displayed larger DTI abnormalities and concomitant RNFL thinning. Significant correlations between optic nerve DTI parameters and RNFL thickness indicate that axonal loss is the most likely pathologic contributor to DTI abnormalities after ON. We and others have reported correlations between optic nerve DTI and OCT or electrophysiological markers of optic nerve axonal degeneration in patients with ON. However, despite good agreement between OCT and DTI measures, neither was found to correlate with visual acuity in the affected eyes suggesting that persistent visual impairment may result from alternative pathophysiological mechanisms.

In two studies, Naismith et al. have reported significant correlations between DTI parameters or RNFL thinning and visual acuity. However, in both studies, affected and unaffected optic nerves were pooled in correlation analyses. We chose to analyze affected and unaffected nerves separately for two reasons: because we hypothesized that the pathophysiology leading to visual impairment in affected and unaffected eyes would be different, the visual impairment in affected eyes being a case of poor recovery and that in unaffected eyes resulting from long-term neurodegeneration.

Recent studies using functional MRI to map the functional anatomy of the visual responses of patients with ON have argued that extrastriate visual areas may be involved in compensatory visual processing. We therefore hypothesized that failure to recover visual function after ON may also relate to failure to invoke compensatory visual processing, potentially due to injury to connections to extrastriate cortices. To test this hypothesis we performed a voxelwise correlation between visual acuity and FA or MD in the whole brain. We observed no correlation between loss of acuity and FA or MD abnormality in occipital regions, but did observe correlations with FA and MD in prefrontal and temporal brain regions. This result suggests that prefrontal and temporal cortices may be involved in compensatory visual processing, and injury to these compensatory pathways leads to permanent loss of vision.

In two studies, functional MRI demonstrated functional activation of frontal and temporal regions in patients after ON. Both studies showed widespread blood-oxygen-level-dependent (BOLD) activation of prefrontal and temporal regions during photic stimulation of the affected eyes of patients with improved visual acuity but extant prolongation of VEPs after ON. Werring et al. observed a strong correlation between extraoccipital BOLD activity and VEP latency, indicating that alternative cortical areas could provide functional compensation. Consistent with our findings, patients in those previous studies exhibited long disease durations and conse-
quently, any dynamic changes associated with acute ON would have resolved.

Levin et al. reported compensatory BOLD activity in patients who recovered to normal visual acuity after ON while viewing complex images. Reduced BOLD activity in primary visual cortex was observed during stimulation of affected eyes with simple visual stimuli, and enhanced BOLD activity was observed in lateral and inferior occipital gyri with complex object stimuli. The authors suggested that lateral and inferior occipital gyri may be involved in compensatory visual processing. However, a whole-brain analysis was not performed, and so the anatomic distribution of such compensatory activations in other regions of the cortex was not elucidated.

Diffusion tractography is a method for estimating the structural connectivity of brain regions based on the directionality of WM fibers estimated from diffusion MRI data. We used diffusion tractography to estimate connectivity from the left frontal WM implicated by the voxelwise regression analysis. Tractography results demonstrated connections to visual processing regions in the occipital cortex and thalamus, most notably the inferior longitudinal fasciculus (or fronto-occipital fasciculus). The inferior longitudinal fasciculus is believed to connect visual attention regions in dorso- and ventrolateral prefrontal cortices (areas 46, 12, and 45) to visual cortices. The role of this region in mediating letter acuity is unclear but could involve loss of recruitment of prefrontal neurons for compensatory visual processing. The observed asymmetry preferencing the left frontal WM could relate to lateralization of processing of alphabetical symbols in left occipitotemporal areas. Neither Werring et al. nor Toosy et al. observed significant laterality of prefrontal BOLD activity when using simple photic stimulation.

Several limitations restrict the conclusions that can be drawn from this study. First, the cross-sectional design prevents investigation into the evolution of the relationship between frontal and temporal WM injury and visual disability. Therefore, future longitudinal studies are needed to assess the determinants of visual recovery after ON. Such studies would benefit from comprehensive structural and functional assessments of ON patients as undertaken recently. Second, we did not perform functional MRI analysis on the patients. Follow-up experiments should be conducted to determine whether patients with poor visual recovery exhibit reduced compensatory activity compared with that of patients with complete visual recovery.

**CONCLUSIONS**

Recovery from ON is common despite extant electrophysiological deficits in most patients, and functional compensation is therefore likely to play a role in mediating visual disability after ON. In patients with greater visual disability after ON, we observed greater injury to frontal and temporal lobe WM, rather than abnormalities associated with WM injury within the primary or extrastriate visual pathways. We conclude that frontal WM injury and associated loss of functional compensation could be a significant determinant of chronic visual disability after ON.
Acknowledgments

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References