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Diffusion Tensor Imaging of the Optic Tracts in Multiple Sclerosis: Association with Retinal Thinning and Visual Disability

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Abstract

Background and purpose—Visual disability is common in multiple sclerosis, but its relationship to abnormalities of the optic tracts remains unknown. Because they are only rarely affected by lesions, the optic tracts may represent a good model for assessing the imaging properties of normal-appearing white matter in multiple sclerosis.

Methods—Whole-brain diffusion tensor imaging was performed on 34 individuals with multiple sclerosis and 26 healthy volunteers. The optic tracts were reconstructed by tractography, and tract-specific diffusion indices were quantified. In the multiple-sclerosis group, peripapillary retinal nerve-fiber-layer thickness and total macular volume were measured by optical coherence tomography, and visual acuity at 100%, 2.5%, and 1.25% contrast was examined.

Results—After adjusting for age and sex, optic-tract mean and perpendicular diffusivity were higher ($p=0.002$) in multiple sclerosis. Lower optic-tract fractional anisotropy was correlated with retinal nerve-fiber-layer thinning ($r=0.51$, $p=0.003$) and total-macular-volume reduction ($r=0.59$, $p=0.002$). However, optic-tract diffusion indices were not specifically correlated with visual acuity or with their counterparts in the optic radiation.

Conclusions—Optic-tract diffusion abnormalities are associated with retinal damage, suggesting that both may be related to optic-nerve injury, but do not appear to contribute strongly to visual disability in multiple sclerosis.

Keywords

multiple sclerosis; optic neuritis; magnetic resonance imaging; diffusion tensor imaging; optic tract; optical coherence tomography

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Introduction

Visual dysfunction is common in multiple sclerosis (MS) and may relate to damage to either the anterior or posterior visual pathways [1]. Up to 80% of people with multiple sclerosis ultimately experience visual impairment as a consequence of their disease [2]. Despite a high degree of self-reported visual dysfunction and the importance of vision to quality of life [3], vision plays only a minor role in the two most commonly used disability scales in MS, the Expanded Disability Status Score (EDSS) and the MS Functional Composite (MSFC), so there is a need for quantitative measures of visual disturbance [4-6].

The anterior visual pathway is an important site of disease activity in MS: Optic neuritis is a common presenting syndrome, and approximately 50% of people with MS have an episode of optic neuritis in their lifetime [7]. Subclinical optic neuropathy in the absence of overt attacks is also well documented [8]. However, the extent of MS-related abnormalities in the optic tracts, which form the continuation of the optic nerves after the partial decussation at the optic chiasm, is less well understood. (This is not the case for the optic radiations, which comprise the posterior visual pathway and run within the periventricular white matter, making them highly susceptible to MS lesions.) Analyzing the optic tracts, which extend from the optic chiasm to the lateral geniculate nucleus, may provide further information about the role of the anterior visual pathway in visual dysfunction in MS, particularly since focal lesions of the optic tract are rare [9,10].

Correlation between disability and magnetic resonance imaging (MRI) in MS has generally been far from perfect, a phenomenon commonly referred to as the “clinical-radiologic paradox” [11], but the use of diffusion tensor imaging (DTI) to evaluate abnormalities within white-matter tracts has revealed some stronger associations between behavioral dysfunction and damage to the corticospinal tract, spinal cord, and corpus callosum [12-16]. Optic-nerve atrophy, as well as T2 lesion load in the optic radiations, primary visual cortex, and elsewhere, has been correlated with visual dysfunction in MS [17,18]. DTI has been used to study the optic nerves after acute optic neuritis and may be able to partially predict recovery [19-21]; it has also been used to examine both the optic chiasm and the optic radiations in MS [22,23]. To date, however, no dedicated DTI study has evaluated the role of the entire optic tract in MS, although DTI has been used to reconstruct the course of the optic tracts [24]. As the optic tracts are not classic sites of MS lesions, they are especially well-suited for evaluation by DTI, which may detect more subtle disease activity than conventional MRI – particularly acute axon damage [25,26].

Pronounced thinning of the retinal nerve-fiber layer (RNFL), detected at autopsy [27,28] and *in vivo* by optical-coherence tomography (OCT) [29-36], has been described in MS. The RNFL, which only consists of unmyelinated axons and glial cells [37], provides an excellent site to evaluate axon damage without the confounding effects of local demyelination. Axon loss may be responsible for much of the disability in MS [26,38-40]. RNFL thinning has been associated with both optic-nerve and global brain atrophy [17,32], as well as with low-contrast letter acuity [30], an established marker of visual dysfunction in MS [41,42], and cognitive dysfunction [43]. Compared to the more commonly tested high-contrast visual acuity, impairment in low-contrast acuity may be more indicative of the type of visual dysfunction that people with MS experience [44] and has been used as a tertiary endpoint in MS clinical trials [45].

In this study, we used tractography to reconstruct the optic tracts from whole-brain DTI data in individuals with MS and healthy volunteers in order to determine if there is detectable damage to the optic tracts even in the absence of focal lesions. We also evaluated the relationship of diffusion abnormalities in the optic tract to axon damage in the RNFL, the

integrity of the retinal-ganglion-cell bodies in the macula, and measures of visual dysfunction.

Methods

Participants

Individuals with MS were recruited from the Johns Hopkins MS Center after the treating neurologist confirmed the diagnosis of MS. Healthy volunteers were recruited from the Johns Hopkins community. We did not select study participants based on the presence or absence of a history of optic neuritis, though we excluded scans performed within 6 weeks of an episode of acute optic neuritis. Optical coherence tomography and visual acuity testing were performed on all participants with MS within 30 days of the MRI scan. The median time difference between MRI and OCT or acuity testing in the MS group was 5 days (range 0-30). All participants were free of known ophthalmologic or neurologic diseases other than MS. All participants gave their informed consent, and the study protocol was approved by the Institutional Review Boards at Johns Hopkins University and the Kennedy Krieger Institute.

MRI acquisition and post-processing

Details of our MRI acquisition protocol have been described elsewhere [46]. On a 3 Tesla Philips MRI scanner, we performed DTI with parameters as follows: spin-echo, echo-planar acquisition with parallel imaging (SENSE factor=2.5), 8-channel head coil (either stand-alone with 6 active channels or as part of a 16-channel neurovascular coil), 2.2 mm isotropic voxels, 32 non-collinear diffusion directions with $b=700 \text{ s/mm}^2$, 1 minimally diffusion-weighted scan with $b \approx 33 \text{ s/mm}^2$, 2 repeats. To process the raw diffusion images, we used CATNAP [47] to coregister all diffusion-weighted volumes to the first minimally diffusion-weighted volume, estimate the diffusion tensor, and create maps of fractional anisotropy (FA), mean diffusivity (MD), parallel diffusivity ($\lambda_{\parallel}$), and perpendicular diffusivity ($\lambda_{\perp}$). These four quantities are hereafter termed *diffusion indices*.

We used the following procedure to estimate whole-brain diffusion indices from the DTI data. We first used BET [48] to extract the brain parenchyma and cerebrospinal fluid (CSF) from the average of the diffusion-weighted scans. To ensure that a similar amount of brain tissue was analyzed for all participants, and to limit the effects of distortion near air-tissue interfaces, we registered the brain-extracted images from each participant to a version of the MNI-152 atlas, available for download at <http://www.mristudio.org>, using a 12-parameter affine transformation [49]. This version of the atlas has 1 mm isotropic resolution and a field-of-view of 181 (x) by 217 (y) by 181 (z) mm. For our global analysis, we only included voxels with $54 \leq z \leq 124$ and $37 \leq y$, which removes the anterior-most portion of the frontal lobe and brainstem (areas particularly susceptible to distortions in the DTI images) as well as the superior aspect of the brain (above the centrum semiovale). We then reverse-transformed the masks into the native space for each participant and segmented the data into brain and CSF compartments using a simple threshold of $\text{MD} \geq 1.7 \text{ } \mu\text{m}^2/\text{ms}$ to identify the CSF. We took the whole-brain diffusion indices to be the average values across all brain parenchymal voxels.

Tractography

The optic tracts were reconstructed using the fiber assignment by continuous tractography method implemented in DtiStudio [50,51], which is available for download at <http://www.mristudio.org>. In order to include damaged fibers (that may have low FA values) to the extent possible, we used permissive FA thresholds of 0.13 as starting and stopping criteria for tracking; the turning-angle cutoff was 30 degrees. This FA threshold is much

lower than typical optic-tract FA values (see Results), and our protocol allowed reconstruction of most of the optic tracts in all participants. Coronal reformations of the axially acquired DTI data were used for placement of regions of interest anteriorly around the optic chiasm and posteriorly at the level of, or just anterior to, the lateral geniculate nucleus; fibers that passed through both regions were selected for further analysis (Figure 1). Along the length of the reconstructed optic tract, we recorded the values of the four diffusion indices listed above.

We also created spatially normalized tract profiles to visualize the variation of the diffusion indices along the anatomic course of the optic tract and to compare that variation between the MS and healthy-volunteer groups [52]. To do so, we divided the anteroposterior distance between the optic chiasm and lateral geniculate nucleus into 40 segments of equal size and calculated the average diffusion index within each segment separately for the right and left sides. We then calculated the average values in each segment across groups (participants with MS and healthy volunteers), adjusting those values by the age-corrected mean for that participant (derived from the regression analysis described in the “Statistical analysis” section below).

Optical-coherence tomography and visual function testing

Details of our OCT protocol and visual function testing have been described elsewhere [23,31,32]. Briefly, retinal imaging was performed on an OCT-3 device (Stratus; Carl Zeiss Meditec, Dublin, CA) using the “Fast RNFL Thickness” protocol; macular scans used the “Fast Macular Thickness” protocol. Except for a specific analysis that examined RNFL thickness in individual retinal quadrants (described in further detail in Results), we averaged RNFL-thickness and total-macular-volume data across both eyes because the optic tracts receive projections from both eyes via the partial decussation at the optic chiasm. Best-corrected, binocular vision testing was measured with Sloan letter charts (Precision Vision, IL) at 100%, 2.5%, and 1.25% contrast. We recorded results as the percentage of letters correctly identified.

Statistical analysis

All statistical calculations were performed in Stata (version 9; Stata LP, College Station, TX). To assess the significance of differences in diffusion indices between the MS and healthy-volunteer groups, we used a mixed-effects regression model that accounts for age and sex and that allows for a different relationship between MRI index and age for the two groups. Specifically, we fit the following model:

$$y_{i,j} = \beta_0 + \beta_1 d_i + \beta_2 (a_i - \bar{a}) + \beta_3 d_i (a_i - \bar{a}) + \beta_4 x_i + u_i + w_{i,j} \quad (1)$$

where $y_{i,j}$ is the diffusion index for participant i and side j , the β_k 's are the regression coefficients, d_i is the diagnosis (1 for MS, 0 for healthy volunteers), a_i is the age of participant i , $\bar{a}$ is the average age across the entire cohort, x_i is sex (1 for men, 0 for women), u_i is a participant-specific random effect, and $w_{i,j}$ is the error term. The p -value associated with β_1 represents the statistical significance of the difference between the two groups' intercepts. The parameter β_3 represents group differences in the relationship between cross-sectional age and the diffusion index. We used the β_2 and β_3 coefficients from equation (1) to adjust the optic-tract profiles in Figure 2 to the average age in our cohort ($\bar{a}$).

To assess the association of optic-tract diffusion indices with mean OCT scores, we performed multiple linear regressions accounting for age, sex, and the corresponding whole-brain diffusion index (to account for global effects), from which we extracted the partial

correlation coefficients and associated p -values for each index. For this analysis, we used a fixed-effects regression model based on diffusion indices averaged across the right and left sides, because the optic tract receives fibers from both retinas. Similarly, to assess the association of optic-tract diffusion indices with visual acuity scores, we performed multiple linear regressions accounting for age, sex, the corresponding whole-brain diffusion index, and mean RNFL thickness (to account for the contribution of damage to the optic nerve, which often harbors focal lesions). Other regression models are described in the “Results” section.

For all comparisons (between the MS and healthy-volunteer groups and between diffusion indices and OCT or visual acuity scores), we analyzed 4 different diffusion indices (FA, MD, $\lambda_{\parallel}$, and $\lambda_{\perp}$). We therefore set our threshold significance level to a Bonferroni-corrected 0.0125.

Results

Demographics

We studied 34 participants with MS and 26 healthy volunteers (Table 1). Data regarding history of optic neuritis were available in 33 (97%) of the MS cases. In this group, 19 individuals (58%) reported no history of optic neuritis; 6 (18%) reported prior optic neuritis in the left eye; 5 (15%) reported prior optic neuritis in the right eye; 2 (6%) reported prior optic neuritis in both eyes; and 1 (3%) reported prior optic neuritis but could not remember which eye.

Optic-tract diffusion abnormalities in MS

We found no focal lesions of the optic tracts on accompanying whole-brain T2-weighted or FLAIR images. In order to characterize quantitative MRI abnormalities within the optic tract in MS, we created spatially normalized tract profiles to show average values of diffusion indices (FA, MD, $\lambda_{\parallel}$, and $\lambda_{\perp}$) along the anatomic course of the optic tract from the optic chiasm to the lateral geniculate nucleus (Figure 2). These profiles were adjusted for the average age of our participant cohort (39.6 years) using the β_2 and β_3 coefficients from equation (1). We found that diffusion indices generally followed a similar spatial pattern in participants with MS and healthy volunteers. In both groups, FA rose sharply directly posterior to the chiasm but then fell before rising again slightly anterior to the lateral geniculate nucleus. However, with the exception of brief sections near the chiasm, FA was lower throughout the optic tract in MS. The spatial variation in diffusivities was also similar across the two groups, but their values were higher along almost the entire tract in MS. The most prominent abnormalities, not surprisingly, were found in the secondary-progressive subgroup (data not shown).

Across the entire optic tract, FA was mildly but not significantly reduced in the MS group compared to healthy volunteers (respective mean values adjusted for age and sex: 0.373 vs. 0.401; $p=0.036$). There were significant elevations in MD (1.21 vs. 1.09 $\mu\text{m}^2/\text{ms}$, $p<0.001$), $\lambda_{\parallel}$ (1.80 vs. 1.69 $\mu\text{m}^2/\text{ms}$, $p=0.002$), and $\lambda_{\perp}$ (0.93 vs. 0.82 $\mu\text{m}^2/\text{ms}$, $p=0.001$). Perhaps because of the small number of participants in each of the MS subgroups, we could detect no significant differences between pairs of subgroups for any of the diffusion indices.

Correlation with baseline characteristics and overall disability

Although we included age and sex in the regression models used to determine differences in diffusion indices between the MS and healthy-volunteer groups, none of the associated regression coefficients was significantly different from 0. Similarly, there was no association between optic-tract diffusion indices and EDSS score after adjusting for age, sex, and the

corresponding whole-brain diffusion index. As seen in Table 2, however, low optic-tract FA was marginally associated with longer disease duration even after making these statistical adjustments.

Correlation with optic neuritis

As expected, optic-neuritis history was associated with thinning of the RNFL in the ipsilateral eye ($p=0.017$, mixed-effects model adjusting for age and sex and including data from both sides). However, optic-neuritis history had no effect on any optic-tract diffusion index ($p>0.05$ for each diffusion index after adjusting for age and sex). To test whether this lack of difference may be related to averaging of diffusion indices from optic nerves damaged by optic neuritis and those without such damage, we performed an additional regression that only included the 19 individuals with no history of optic neuritis and the 2 individuals with history of prior bilateral optic neuritis, again finding no effect of optic-neuritis history on optic-tract diffusion indices ($p>0.05$ for each diffusion index).

Correlation with retinal structure

We also evaluated the relationship of optic-tract diffusion indices to RNFL thickness and total macular volume in the MS group (Table 2). Low FA was found to be correlated with RNFL thinning ($r=0.51$, $p=0.003$ after adjusting for age, sex, and whole-brain FA) and reduced TMV ($r=0.59$, $p=0.002$). To assess the specificity of the correlation between RNFL thinning and optic-tract diffusion abnormalities, both of which might reflect damage to the optic nerve, we took advantage of the partial decussation at the optic chiasm. Specifically, we tested whether RNFL thickness in the temporal retinal quadrants is specifically associated with diffusion indices in the ipsilateral optic tracts that receive projections from those quadrants. We constructed separate mixed-effects regression models in which the ipsilateral optic-tract diffusion indices were the dependent variables and the independent variable of interest was the ipsilateral temporal-quadrant RNFL thickness. Covariates were age, sex, and ipsilateral nasal-quadrant RNFL thickness (fibers from this quadrant decussate at the optic chiasm and do not contribute to the ipsilateral optic tract); side was treated as a random effect. We found a specific association between temporal-quadrant RNFL thickness and ipsilateral optic-tract FA ($p<0.001$) and $\lambda_{\perp}$ ($p=0.004$). Note that these p -values are lower than the corresponding p -values in Table 2 (0.003 for FA and 0.04 for $\lambda_{\perp}$), highlighting the relevance of anatomic connectivity to the associations reported here.

Correlation with visual acuity scores

There were no specific associations between optic-tract diffusion indices and visual acuity scores at any contrast level. This differs from our prior findings in the optic radiations in a highly overlapping MS cohort, in which tract-specific diffusion indices were correlated with low-contrast visual acuity in cases with less severe retinal damage (i.e., RNFL thickness $> 80 \mu\text{m}$) [23]. For the optic tracts, restricting our attention to the same group ($n=21$) did not improve the correlations. For the group with more severe retinal damage (RNFL thickness $< 80 \mu\text{m}$; $n=13$), the correlation between optic-tract FA and 1.25% visual acuity improved but was not significant ($r=0.62$, $p=0.07$).

Correlation with optic-radiation diffusion indices

Finally, we tested whether optic-tract diffusion indices are specifically related to the corresponding indices in the connected optic radiation in participants with MS or healthy volunteers. We reconstructed the optic radiations as previously described [23]. In mixed-effects models treating side as a random effect, we found no association of optic-tract diffusion indices with optic-radiation diffusion indices ($p>0.05$ in all cases), or vice versa, after adjusting for age, sex, and the corresponding whole-brain diffusion index.

Discussion

Our data show that tractography of the optic tracts from whole-brain DTI is feasible in healthy volunteers and individuals with MS, and our reconstructed tracts conform well to the known anatomy. That the measurements derived from these reconstructions reflect optic-tract damage in MS is strongly suggested by the observation of significant correlations between optic-tract diffusion indices and a quantity derived from non-MRI visual testing, RNFL thickness.

Optic-tract diffusion indices

The tract profiles presented in Figure 2 provide information about the spatial variation in diffusion indices. The profiles followed a similar spatial pattern in both groups, but FA was lower and diffusivities higher virtually throughout the tract in the MS group. Lower FA and higher MD have been documented in many MS studies, in both lesions and extralesional normal-appearing white matter [12]. Given that the optic tract is a homogeneous and somewhat isolated structure, particularly within the suprasellar cistern, the spatial variation in diffusion indices, particularly FA, may reflect curving of the tract within individual voxels.

Several groups have demonstrated that acute damage to axons can result in decreased parallel diffusivity ($\lambda_{\parallel}$) without changes in perpendicular diffusivity ($\lambda_{\perp}$). We found no evidence for decreased $\lambda_{\parallel}$ in the optic tract, probably due to the fact that there was limited, if any, acute optic-tract damage in our cohort (we found no lesions in the optic tracts, and we included no cases with recent optic neuritis). In fact, $\lambda_{\parallel}$ was higher in the MS cohort than among healthy volunteers, though abnormalities in $\lambda_{\perp}$ and FA (essentially a measure of the contrast between $\lambda_{\parallel}$ and $\lambda_{\perp}$) were in general more striking. Based on results from animal studies [25,53], we believe that these findings, which are typical in MS [23,54], reflect chronic tissue injury (axon and myelin damage) rather than damage to a particular type of tissue.

A recent study raised important questions regarding interpretation of parallel and perpendicular diffusivity in the presence of pathology [55]. We share those concerns. Because we used tractography to reconstruct the optic tracts, however, and because such reconstruction was easily achieved even in the MS cases, any pathology-induced changes in the orientation of the diffusion-tensor eigenvectors must have been relatively small. Nevertheless, a re-analysis based on diffusion coefficients relative to estimates of the expected tract orientation at each point might yield additional insights. Such an analysis would require careful registration to an atlas derived from healthy individuals, which is technically challenging for a fiber bundle as small as the optic tract.

Optic tract and optic nerve

In contrast to the optic nerve, lesions in the optic tract are rare. While these lesions may be difficult to detect by imaging due to their relatively small size and location, the paucity of lesions in the optic tract has also been confirmed by *post-mortem* analysis [10]. However, autopsy studies of the optic tract have confirmed axon damage in the MS optic tract, demonstrating a reduction in axon density of approximately 30% without a frank difference in cross-sectional area of the optic tract [27]. Our images were not of sufficient spatial resolution to accurately assess optic-tract area or volume, and axon density is difficult to measure with current MRI techniques. Although the relatively subtle (5% to 15%) diffusion abnormalities that we detected may reflect this loss of axon density, we do not have evidence that any of the diffusion indices is a direct measure of axon density.

Optic tract and retinal structure

As retinal-ganglion-cell axons in the RNFL are unmyelinated, RNFL thickness has been proposed to be a relatively pure indicator of axon damage, although the RNFL does contain glial cells [37,56]. Axon loss is an important cause of disability in MS [26,38-40]. For example, optic-nerve atrophy, which presumably reflects axon loss to some extent, has been reported in the visual system even following a single attack of optic neuritis [16,56]. Thinning of the RNFL is well documented both after isolated optic neuritis and in MS, detected both at autopsy [27] and *in vivo* by OCT [28-36].

We demonstrated a significant association between optic-tract FA and RNFL thickness. This association appears to be especially strong in anatomically connected structures, in this case the ipsilateral temporal retinal quadrant and the optic tract. One plausible explanation for these findings is that abnormalities in both RNFL and optic tract reflect damage to the optic nerve, but other factors may play an important role. It is well known, for example that subclinical changes in the optic nerve can occur even in the absence of overt attacks of optic neuritis [7], and damage to the optic tract may occur on the same basis.

We also found a significant correlation between optic-tract FA and total macular volume, consistent with a common etiology for macular volume loss and RNFL thinning [30]. This highlights the links between abnormalities in white matter and the associated tissue of origin of the axons contained within that white matter (in this case, the macula).

Although correlations between OCT and diffusivity measurements (as opposed to FA) did not reach the Bonferroni-corrected threshold for significance, the direction of the associations (for example, higher diffusivity associated with thinner RNFL and reduced TMV) was appropriate in all cases. This suggests that the lack of significance may be related to our relatively small study cohort.

Optic tract and visual disability

The fact that correlations between disability and traditional MRI measures have generally been low (with correlation coefficients often less than 0.4) has been described as the “clinical-radiological paradox” and has led some to question the use of MRI as a surrogate marker of neurodegeneration in MS [8,57]. This is partly because conventional MRI measures are more sensitive to inflammation and demyelination than to axon damage, the presumed cause of disability. Recently, attention has been focused on the correlations between disability and both brain atrophy, often captured in the brain parenchymal fraction, and diffusion indices. The brain parenchymal fraction has been shown to be moderately correlated with MSFC scores [11], but no significant correlations between brain parenchymal fraction and high- or low-contrast visual acuity have been reported [17]. DTI studies of specific white-matter tracts have revealed some stronger associations with disability, and diffusion indices in the optic radiations in our cohort revealed significant correlations with low-contrast visual acuity [23].

In the present work, we found no specific associations between visual acuity, at either high or low contrast, and optic-tract diffusion indices after adjustment for RNFL thickness. Associations between low-contrast visual acuity and both RNFL thickness [30] and optic-nerve diffusion indices [20,21,58], which we did not specifically assess, have been well described. Given that we found moderate correlations between MRI abnormalities in the optic tract and thinning of the RNFL, which is itself associated with impaired low-contrast visual acuity, it may seem surprising that we found no correlations between optic-tract diffusion indices and low-contrast visual acuity. There are several possible explanations for this. First, and probably most important, we controlled for RNFL thickness, which may render difficult-to-detect any small residual associations between visual acuity and optic-

tract diffusion indices. Second, we did not evaluate large portions of the visual pathway, including the optic radiations, posterior cortical structures, and the oculomotor systems, that almost certainly affect acuity measures. Third, our study was relatively small; with a sample size of 34, we could only expect to detect a correlation coefficient of $|r|=0.42$ with 80% power at a significance level of 0.05, and thus our cohort may have been too small to detect weak residual correlations between optic-tract changes and visual disability [59]. Finally, detecting a link between the optic-tract abnormalities and visual function may require imaging with higher resolution and sensitivity.

Relationship of the anterior and posterior visual pathways

Diffusion indices in the optic radiation have been previously reported in an overlapping cohort [23], and the present study of the optic tract allowed us to investigate the relationship between diffusion indices in the anterior and posterior visual pathways. However, we found no such association, suggesting either that damage to the two structures is independent or that the effects on diffusion indices induced by such damage are relatively subtle.

Limitations

The key limitation of our study is the presence of partial volume averaging between the optic tract and adjacent CSF [60]. Partial volume averaging is present both on the surface of the optic tract in each slice and, because the optic tract runs oblique to our coronal slices, potentially within the substance of the tract as well. Although we do not expect abnormalities in CSF diffusion indices in MS, there may have been differences in the extent of partial volume averaging between the MS and healthy-volunteer groups. This may occur, for example, if a larger optic-tract circumference in healthy volunteers caused inclusion of more mixed voxels in that group, which would tend to diminish differences in diffusion indices between the two groups. However, the ramifications of partial volume averaging are no doubt more complicated than this scenario would imply. An additional limitation is that the average age of our healthy volunteers was more than ten years lower than the average age of our MS cohort, a difference that may not have been fully controlled in our regression models despite their complexity. Finally, we made no specific attempts to control for treatment type in our analysis, which may also have influenced the results.

Conclusions

Our results suggest that the role of the optic tracts in generating visual disability in MS is relatively limited and that diffusion abnormalities of the optic tracts may primarily reflect MS-related pathology in other areas, particularly the optic nerves. As such, diffusion imaging in the optic tract may be a good and relatively unadulterated marker for the extent of MS-related damage to otherwise normal-appearing tissue.

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Figure 1.

Regions of interest used for diffusion tensor imaging-based tractography of the optic tract and three-dimensional reconstruction of the optic tract. Regions of interest were drawn in the coronal plane (generated by reformatting the axially acquired data) anteriorly around the optic chiasm (panel A) and posteriorly at the level of, or just anterior to, the lateral geniculate nucleus (panel B). Fibers that ran through both regions of interest were selected for analysis. The reconstructed optic tracts conformed well to the known anatomy and are shown superimposed on axial (panel C) and coronal (panel D) diffusion-tensor-imaging color maps.

Figure 2.

Spatially normalized tract profiles of the optic tracts along the anatomic course from the optic chiasm to the lateral geniculate nucleus (LGN). Data are averaged across 34 participants with multiple sclerosis (solid lines) and 26 healthy volunteers (dashed lines) and are adjusted to the average age of our cohort (39.6 years). Error bars denote standard errors of the mean. (A) MD, mean diffusivity; (B) FA, fractional anisotropy; (C) $\lambda_{||}$, parallel diffusivity; (D) $\lambda_{\perp}$, perpendicular diffusivity.

Table 1

Demographic distribution of our study and cohort disease characteristics.

	AIIMS	RRMS	SPMS	PPMS	Healthy
participants, #	34	19	8	7	26
female, #	22 (65%)	14 (74%)	5 (62%)	3 (43%)	17 (65%)
mean age, years (range)	44 (29-67)	41 (30-54)	50 (40-60)	48 (29-67)	33 (22-63)
mean disease duration, years (range)	11 (1-32)	9 (1-21)	22 (9-32)	4 (2-7)	
prior optic neuritis, #	14 (42%)	9 (50%)	5 (63%)	0 (0%)	
median EDSS (range)	3.5 (0-7.5)	2.5 (0-6)	6.5 (3.5-7.5)	4 (2.5-6.5)	
mean RNFL thickness, mm (sd)	85.2 (15.0)	86.7 (12.6)	73.3 (14.8)	94.6 (14.5)	
mean total macular volume, mm ³ (sd)	6.44 (0.33)	6.42 (0.34)	6.31 (0.36)	6.64 (0.20)	
mean 1.25% contrast visual acuity, # of letters correct, max =70 (sd)	18 (12)	24 (9)	6 (8)	14 (13)	
mean 2.5% contrast visual acuity, # of letters correct, max =70 (sd)	33 (13)	38 (6)	24 (17)	29 (16)	
mean 100% contrast visual acuity, # of letters correct, max =70 (sd)	62 (13)	64 (6)	55 (22)	59 (13)	

Abbreviations: MS, multiple sclerosis; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS; EDSS, expanded disability status scale.

Table 2

Partial correlation coefficients between diffusion indices and outcome measures in multiple sclerosis. Correlation coefficients for disease duration, EDSS, RNFL thickness and TMV are adjusted for age, sex, and the corresponding whole-brain diffusion index (to account for global disease effects), whereas coefficients for visual acuity are adjusted for age, sex, the corresponding whole-brain diffusion index, and mean RNFL thickness (to account for the contribution of optic-nerve damage to visual disability). Significance levels (*p*-values) are given in parentheses, and values meeting the Bonferroni-adjusted significance threshold of 0.0125 are shown in bold face.

outcome variable	fractional anisotropy	mean diffusivity	parallel diffusivity	perpendicular diffusivity
disease duration	-0.45 (0.011)	0.34 (0.07)	0.16 (0.40)	0.39 (0.03)
EDSS	-0.30 (0.10)	0.14 (0.46)	0.12 (0.53)	0.14 (0.45)
RNFL thickness	0.51 (0.003)	-0.33 (0.07)	-0.05 (0.79)	-0.37 (0.04)
TMV	0.59 (0.002)	-0.40 (0.04)	-0.13 (0.54)	-0.47 (0.016)
visual acuity, 1.25% contrast	0.32 (0.08)	-0.26 (0.16)	-0.17 (0.38)	-0.31 (0.09)
visual acuity, 2.5% contrast	0.18 (0.34)	-0.14 (0.45)	-0.16 (0.39)	-0.15 (0.42)
visual acuity, 100% contrast	0.09 (0.62)	-0.12 (0.53)	-0.18 (0.35)	-0.11 (0.58)

Abbreviations: EDSS, expanded disability status scale. RNFL, retinal nerve fiber layer. TMV, total macular volume.