Retinothalamic White Matter Abnormalities in Amblyopia

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PURPOSE. Amblyopia is associated with a broad array of perceptual and neural abnormalities in the visual system, particularly in untreated or unsuccessfully treated populations. Traditionally, it has been believed that the neural abnormalities are confined to the visual cortex and subcortex (e.g., lateral geniculate nucleus). Here, we investigate the presence of neuroanatomical abnormalities earlier in the visual stream, in the optic nerves and tracts, of participants with two predominant forms of amblyopia.

METHODS. We used diffusion magnetic resonance imaging and probabilistic tractography to compare the microstructural properties of five white matter visual pathways between 15 participants with amblyopia (eight anisometropic, five strabismic, and two exhibiting both etiologies), and 13 age-matched controls.

RESULTS. Participants with amblyopia exhibited significantly smaller mean fractional anisotropy in the optic nerve and optic tract (0.26 and 0.31 vs. 0.31 and 0.36 in controls, respectively). We also found greater mean diffusivity in the optic radiation compared to controls (0.72 µm2/s vs. 0.68 µm2/s, respectively). Comparing etiologies, the abnormalities in the precortical pathways tended to be more severe in participants with anisometropic compared to strabismic amblyopia, and anisometropic participants’ optic nerves, optic tracts, and optic radiations significantly differed from control participants’ (all, P < 0.05).

CONCLUSIONS. The results indicate that amblyopia may be associated with microstructural abnormalities in neural networks as early as the retina, and these abnormalities may differ between amblyopic etiologies.

Keywords: diffusion MRI, amblyopia, white matter, optic nerve

Although amblyopia arises due to poor or poorly coordinated visual input to the two eyes, it is typically characterized as a cortical visual disorder because the anatomical and physiological consequences are largely restricted to visual cortex. The current model of amblyopia posits that the chronic, irresolvable mismatches between the two retinal images leads to binocular competition in early visual cortex, creating lasting structural abnormalities at the level of binocular integration and ocular dominance.1–3 Indeed, the structure and function of early visual cortex (and subcortical areas) is often abnormal in people with amblyopia, particularly in individuals who are untreated, unsuccessfully treated, or treated later in life.4–6 Visual white matter is also abnormal in amblyopia, particularly in fascicles connecting the thalamus to the visual (striate and extrastriate) cortex, such as the optic radiation.7,8 These structural abnormalities appear to have downstream consequences, affecting not only the way visual information is processed in the cortex but also how that information is integrated in thalamocortical feedback networks. These abnormalities can vary by etiology and sometimes scale with the degree of perceptual loss, although these relationships are not always clear.7 Nevertheless, congenital chronically mismatched visual input, as seen in amblyopia, is associated with a range of cortical, subcortical, and white matter abnormalities.

A more controversial aspect of this model, however, is whether the eyes and/or prethalamic pathways (i.e., optic nerve and optic tracts) are abnormal in amblyopia as well. With respect to visual disorders, one of the unique etiologic aspects of amblyopia is a lack of ocular malformations. In fact, a defining characteristic of amblyopia is misalignment and/or a mismatch between otherwise healthy eyes. Despite this classification, some human10–13 and animal14 studies of amblyopia have reported structural abnormalities at the level of the eye and/or optic nerve. Of note, one large-scale study reviewing photographs of optic nerves of human patients found evidence of optic nerve head dysversion or segmental hypoplasia in 45% of the patients, primarily affecting anisometropic amblyopes.15 Additionally, some studies report that the optic nerve of the amblyopic eye contains significantly fewer axons compared to the fellow eye.14–17 At least one study reported equally severe reductions in the number of affected eye optic nerves in deprivation, strabismic, and anisometropic amblyopia animal models.14 However, few studies have been conducted in humans, and interpretation of the existing literature is difficult as methodology impacts the accuracy of postmortem gross fiber counts.16,19

Overall, evidence for retinal and/or optic nerve anomalies remains mixed in the literature, and questions remain about whether anisometropia is associated with a different pattern of structural abnormalities more akin to deprivation- than strabismus-induced amblyopia. Resolving these discrepancies is critical because identification of the site of the deficit has implications for treatment options and prognosis. Unfortunate-
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Our statistical analysis focuses on the two most common dMRI measurements of microstructural properties, fractional anisotropy (FA) and mean diffusivity (MD). FA provides a normalized measure of the uniformity of diffusion of water molecules in each voxel (larger values indicating greater anisotropy, presumably due to greater fiber density and/or white matter integrity). MD provides a measure of the inter- and intra-axonal molecular diffusion rate (square micrometer per second) in each voxel (larger values indicating greater diffusivity, presumably due to less impedance and/or lower tissue density). Generally speaking, larger FA values and smaller MD values are associated with compact, uniformly oriented bundles of axons, well as thalamocortical (optic radiation) and corticocortical structural abnormalities in amblyopia exist at the level of the optic nerve (and presumably the retina) as well as thalamocortical pathways. This result challenges the model of amblyopia as a purely cortex-based disorder.

METHODS

Participants

Participants With Amblyopia. Fifteen individuals (six females) with amblyopia, aged between 13 and 47 years (mean = 21.8, SD = 10.1), participated in the study. Eight had anisometropic amblyopia, five had strabismic amblyopia, and two exhibited a mixture of anisometropia and strabismus. Amblyopia was defined as having a fellow eye distance Snellen visual acuity of 20/25 or better and an affected eye best-corrected visual acuity of 20/40 or worse, as measured during a clinical eye exam at the pediatric eye clinic of the Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison. This included the absence of clinically apparent optic nerve hypoplasia per the examination of an experienced pediatric ophthalmologist. All participants received treatment for their amblyopia early in life (between 4 and 8 years old), but none have fully recovered vision. See Table 1 for patient details.

Control Participants. Thirteen normally sighted individuals (seven females), aged between 14 and 34 years (mean = 21.0, SD = 5.5), participated in the study. All control participants reported normal or corrected-to-normal vision (a best-corrected acuity of 20/25) and reported no history of visual disorders. All work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Acquisition of Magnetic Resonance Imaging Data

Scans were collected with a 3T GE Discovery magnetic resonance scanner equipped with a 32-channel head coil at the Waisman Center in Madison, Wisconsin. The scanning
session included a T1-weighted anatomical scan (2.95 ms echo time; 6.70 ms repetition time; 1 mm³ voxel size), followed by four diffusion-weighted scans (48 direction +6 b0; 76.7 ms TE; 8.1 s TR; 2 mm³; b = 2000 mm²/s; two scans anterior-posterior [AP] phase-encoded; two posterior-anterior [PA] phase-encoded; reconstruction matrix field of view: left-right [LR] 212 mm × anterior-posterior [AP] 212 mm × foothead [FH] 144 mm).

Data Preprocessing

Artifact Compensation and Diffusion Tensor Fitting. Data were collected with pairs of reversed phase-encoded blips, resulting in two pairs of images with distortions in opposite directions. From these pairs, the susceptibility-induced off-resonance field and subject head motion was estimated using a method similar to that described in Andersson et al.²⁰ as implemented in the FMRIB Software Library (FSL). Four blips were acquired, and the four diffusion images were combined into a single, error-compensated volume.

Mean $b = 0$ was computed for the compensated volume and residual motion, and eddy currents were compensated and aligned to the anterior/posterior cingulate (AC-PC) aligned T1 image. Tensors were then fit using the least-squares tensor estimation (bootstrapped 500 times).²² Aside from the initial off-resonance field compensation step, diffusion imaging preprocessing was performed using Vistasoft (available from Stanford University, Stanford, CA, USA; https://github.com/vistaslab/vistasoft). Processing was done for each participant’s data independently.

Regions of Interest (ROIs). To identify the starting point for the optic nerve we placed a 3-mm radius sphere just proximal to the globe of each eye, centered on the emerging optic nerve (as identified using gross anatomical landmarks in the T1 image). A 4-mm radius sphere was placed in the center of the optic chiasm (also identified using gross anatomical landmarks in the T1 image). The diameter of these ROIs was chosen to be larger than any of the participants’ optic nerves or optic tracts to prevent undersampling at the tractography stage. Indeed, all the optic nerve and optic tract tractographical estimates were oversampled, with many false-positive fiber estimates spilling into the surrounding nasal cavity. We manually pruned these false-positive fibers to ensure all optic nerve and optic tract fiber estimates were within the confines of the ground-truth anatomy, using the T1 volume for reference (see: Fiber Tracking and Cleaning).

Using the chiasm ROI as a seed region, we used a tensor-based streamlined tracing technique (STT) (2-mm step size, 60° angle threshold, 0.2 FA threshold, linear interpolation) to estimate the location and termination points of the optic tract (a reliable marker of lateral geniculate nucleus [LGN] location).²¹ Forty-millimeter radius spheres were placed around the nasal cavity. Where the optic tract tractography fibers terminated in lateral thalamus as estimates of LGN location. A 6-mm radius sphere was also placed in the medial-posterior-most aspect of the corpus callosum for seeding interhemispheric pathways. V1 and hMT+ were identified using the automatic cortical segmentation toolbox in the open source FreeSurfer software package.²⁴-²⁶

Fiber Tracking and Cleaning

Fiber tracking and cleaning was conducted in a protocol identical to that described by Allen et al.⁷ To summarize, tissue orientation was estimated in each voxel using constrained spherical deconvolution (CSD; Imax = 6), and the white matter connections between specified ROI pairs were estimated using probabilistic tractography. In addition to the automatic cleaning step, each participant’s optic nerve and optic tract estimates were overlaid on an anatomical T1 and manually pruned by an experienced neuroanatomist to ensure the fiber estimates were contained within the ground-truth anatomy. See Figure 1 (top row) for renderings of the exemplar anatomy.

Tract-Based Analysis of Diffusion Measures

Since the tractography estimates are generated in the same space and at the same scale as the tensor fits (but using separate diffusion models), we treated the tracts as white matter ROIs and extracted the properties of the tensors fit to the voxels contained in the ROI. Since the length and overall volume of pathways differ between participants, we normalized pathway measurements by sampling at 100 evenly spaced slices through each pathway and calculating a Gaussian-weighted average (centered at the anatomical core of the pathway) of the MD/FA values of each slice. When averaging across these samples to generate single-value summaries of pathway properties, we excluded the 20 samples nearest to each white/gray matter interface to ensure we are taking average measurements of unambiguous white matter. For the initial group comparisons, left and right hemisphere values were averaged to provide a single-value estimate of the average properties of a given pathway for each participant.

RESULTS

Methodological Advances in Retinothalamic Visual Pathway Tractography

The scanning and preprocessing protocol used in the current study expands on the methodology we used in our previous dMRI study of amblyopic populations⁴ by allowing us to correct for the off-resonance field distortions that previously prevented us from identifying and quantifying the properties of the optic nerves. Aside from visually confirming that the correction step recovered significant amounts of signal in our dMRI data, we also tested the improvement by attempting to track optic nerves in a subsample of three control non-correction cases. We were unable to identify any optic nerve fibers that survived cleaning and ground-truth pruning in our three uncorrected test cases. Taken together, the success of the tractography protocol in the current study demonstrates the efficacy of multiscan-based off-resonance distortion correction approaches in improving the signal-to-noise ratio in and around the nasal cavity.

Comparisons of White Matter Microstructure Between Controls and Participants With Amblyopia

For the initial comparisons of pathway-specific white matter microstructural properties between control and amblyopic participants, the left and right pathway values were averaged for each participant, and an average of these means was calculated for the two groups. All pairwise tests were conducted using independent samples t-tests. See Figure 2 for plots comparing average diffusion measures across the five pathways of interest in all amblyopic and control participants and Table 2 for a list of the statistical results of the pairwise comparisons.

Independent samples t-tests indicate significantly smaller mean FA in the optic nerves (M = 0.26, SD = 0.05) and optic tracts (M = 0.31, SD = 0.05) of amblyopic participants,
compared to controls ($M = 0.31$, $SD = 0.06$ and $M = 0.36$, $SD = 0.03$, respectively; see Table 2 for test statistics) (Figs. 2A, 2B, respectively). Amblyopic participants also exhibited significantly increased mean MD in the optic radiations ($M = 0.72$, $SD = 0.05$) compared to controls ($M = 0.68$, $SD = 0.02$; see Table 2 for test statistics) (Fig. 2H). No other pairwise comparisons indicated statistically significant differences between control and amblyopic white matter.

Comparisons Between Fellow and Affected Eye Optic Nerves in Amblyopic Participants

Since the previous analysis averages left and right pathway measurements, the observed reduction in optic nerve FA can be attributed to either an overall reduction in the fractional anisotropy of both optic nerves or to an averaging artifact, where (presumably) the affected eye’s optic nerve is abnormal...
relative to the fellow eye’s optic nerve and this monocular deficit drives the effect. Differentiating these possibilities has implications for the interpretation of this reduction in FA, since the former would suggest amblyopia is a more generalized optic disorder, while the latter suggests a more deficit-driven model.

Accordingly, in our second analysis, we compared the microstructural properties of the affected and fellow eye optic nerves in our sample of participants with amblyopia. As a reference, we also compared the microstructural properties of the dominant and nondominant eye optic nerves in our control participants. See Figure 3 for tract profile plots of average optic nerve properties in affected/fellow and dominant/nondominant eyes.

A paired-samples t-test did not reveal a significant difference in MD or FA of the optic nerve between the affected and fellow eye (both, t(14) < 0.5, P > 0.6). Furthermore, among controls, no significant differences were observed between dominant and nondominant eye optic nerve FA or MD (both, t(14) < 0.4, P > 0.7). We were therefore not able to determine that the abnormalities observed in the optic nerves in participants with amblyopia were specific to the amblyopic eye.

Comparisons of White Matter Microstructure Between Types of Amblyopia

Our analyses so far consider only whether participants have amblyopia or not. Since our amblyopic sample is heterogeneous with respect to etiology, we also wished to compare white matter properties across etiologies. However, it is worth highlighting that over half (eight) of our sample of 15 amblyopic participants exhibited anisometropia, while only a third (five) exhibited strabismus (with the remaining two exhibiting a combination of the two). With small, imbalanced sample sizes such as these, it is prudent to keep in mind that the larger groups will pose greater statistical power. Accordingly, we advise some degree of caution when interpreting the statistical findings of these subgroup comparisons.

For the comparisons of pathway-specific white matter microstructural properties between different types of amblyopia, the left and right hemispheres’ fibers were averaged for each subject, and the resulting means are averaged into group means according to etiology. We excluded participants classified as exhibiting both etiologies due to the small (n = 2) number in our sample. A 1-way ANOVA was used to compare the average MD and FA between the anisometropic, strabismic, and control groups. A Tamhane’s T2 post hoc test, which is specialized for comparisons across samples of unequal size and variance, was used to test for pairwise differences. See Table 3 for the ANOVA test statistics and Figure 4 for plots comparing average diffusion measures across the five pathways of interest in anisometropic, strabismic, and control participants.

Participants with anisometropia exhibited significantly lower FA in the optic nerve (M = 0.24, SD = 0.05) and optic tract (M = 0.31, SD = 0.04) (Figs. 4A, 4B, respectively), as well as significantly greater MD in the optic radiation (M = 0.73, SD = 0.05) (Fig. 4H), compared to controls (M = 0.31, SD = 0.06; M = 0.33, SD = 0.07; M = 0.68, SD = 0.05, respectively). No other pathways or measurements significantly differed between anisometropic and control participants. No significant differences were observed between anisometropic and strabismic amblyopic participants nor between strabismic and control participants.

Akin to the previous group-averaged comparison with controls, 1-way ANOVAs comparing the FA and MD of participants with anisometropic amblyopia and strabismic amblyopia and control participants indicated significant differences in FA in the optic nerves and optic tracts as well as differences in MD in the optic radiation. Post hoc tests suggest these differences are driven by participants with anisometropic amblyopia. Again, because of low statistical power in the other groups, these findings should be interpreted only as preliminary evidence that differences may be present between anisometropic and strabismic ambylopes.

Measures/Attributes Predictive of White Matter Abnormalities

Linear regression models including age, sex, and initial visual acuity as predictor variables were unable to explain a significant amount of the abnormalities observed in FA and MD in the optic nerve, tract, or radiation (all, P(3,4) < 3.5, P > 0.1) in participants with amblyopia.

Discussion

Decreased Retinothalamic White Matter FA in Amblyopia

The amblyopic participants in our study showed significant reductions in optic nerve and optic tract microstructural integrity compared to controls. While similar reductions in optic nerve integrity have been previously demonstrated in animal models, this is the first study, to our knowledge, demonstrating in vivo microstructural abnormalities in the optic nerves and optic tracts of humans with amblyopia by using dMRI. This finding was unexpected, since decreases in FA of the optic nerves are more consistent with degenerative diseases like glaucoma.27–31 Unfortunately, we did not have access to RNFL thickness or other measures of retinal integrity for our participants, so it is not immediately clear what could be behind the decrease in optic nerve and optic tract FA in our sample.

It is additionally unclear what a common mechanism of action for degradation of prethalamic visual pathways would be in amblyopia, considering the varied nature of etiologies that can give rise to it. Indeed, when considering the types of amblyopia separately, we found clear effects in our anisometropic participants. It is less clear if strabismic ambylopes are
similarly affected. Some related studies report greater structural abnormalities in anisometropic compared to strabismic participants at the level of the retina\textsuperscript{32} and striate cortex\textsuperscript{33,34} that cannot be attributed to other factors such as age or severity of vision loss. It is possible this difference reflects inherent differences between the structural consequences of anisometropia-induced versus strabismus-induced amblyopia.

Specifically, because anisometropia results in a chronically blurred retinal image, it is possible that anisometropia leads to poor development of high spatial frequency receptive fields (RF) in the retina, which could lead to decreased integrity of the retinal projections akin to deprivation amblyopia.\textsuperscript{16} Strabismic misalignment of resting gaze position does not inherently induce blurring of the image on the retina, so the development of high spatial frequency RFs, and thus the structure of the optic nerve, may be relatively normal.\textsuperscript{16} However, reduced high spatial frequency processing has been observed in anisometropic amblyopes and reduced low spatial frequency processing in strabismic amblyopes, suggesting the loss of frequency channels might be roughly equal but shifted in frequency band.\textsuperscript{35}

Such a model, however, would not account for a lack of difference in FA reduction between the affected and fellow eyes in anisometropic amblyopia or a lack of a relationship between the degree of initial vision loss and the degree of abnormality in optic nerve/tract FA or optic radiation MD.

Fellow and Affected Eye Optic Nerves in Amblyopia
As discussed in the introduction, studies demonstrating ocular/retinal abnormalities in amblyopia often report structural differences between fellow and affected eyes in addition to overall differences between amblyopic and control participants.\textsuperscript{15,32,36} Although we did observe general reductions in microstructural integrity of the optic nerves in amblyopic participants compared to controls, we did not find structural differences between the fellow and affected eye optic nerves; rather, the magnitude of the reduction in FA was consistent in both fellow and affected eye optic nerves.

Future studies of visual system white matter properties should consider including correlations to measures of RNFL where possible. A recent tractography-based study showed similar, significant reductions in optic tract FA as well as correlations between RNFL thickness and optic tract FA in participants with childhood or age-related macular degeneration.\textsuperscript{37} These additional ophthalmologic measurements allow for a secondary level of verification of any microstructural abnormalities and provides a more precise mapping of the relationship between the various scales and measures of prethalamic microstructure integrity.

Thalamocortical and Corticocortical White Matter in Amblyopia
The current study reproduces several recent findings, including our own, with respect to abnormalities in thalamocortical white matter in amblyopia.\textsuperscript{4,7,8} The magnitude of the increase in mean diffusivity of the optic radiation was roughly consistent with our previous study (about 10% greater compared to controls). We previously suggested this finding provides cursory evidence of a feedback, rather than feedforward, model of cortical abnormality in amblyopia. That is, because the optic radiation is composed mostly of connections relaying information from the cortex to the thalamus, we interpreted increased diffusivity in this pathway as likely reflecting poor communication to, rather than from, the thalamus. The findings of the current study throw parts of

![Figure 3](Image 126x569 to 486x729)

**Figure 3.** Comparison of MD (A) and FA (B) between affected (teal, solid line) and fellow (teal, broken line) eye optic nerves (amblyopic) and dominant (black, solid line)/nondominant (black, broken line) (control) eye optic nerves along the normalized length of the pathway. There are no significant differences between control dominant and nondominant eye optic nerves or between affected and fellow eye optic nerves in amblyopic participants. The affected and fellow eyes both show significant reductions in FA compared to the control optic nerves, on average.

<table>
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<th>OR</th>
<th>V1-V1</th>
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<td>( F(2,22) = 3.53 )</td>
<td>( F(2,22) = 0.89 )</td>
<td>( F(2,22) = 0.09 )</td>
<td>( F(2,22) = 0.25 )</td>
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<td>( P = 0.04 )</td>
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<td>( P = 0.92 )</td>
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<td>MD</td>
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<td>( F(2,22) = 1.74 )</td>
<td>( F(2,22) = 4.37 )</td>
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<td>( P = 0.20 )</td>
<td>( P = 0.03 )</td>
<td>( P = 0.52 )</td>
<td>( P = 0.85 )</td>
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**Table 3.** Results of the 1-Way ANOVA, Comparing the Mean FA/MD of the Five Pathways of Interest Between Anisometropic, Strabismic, and Control Participants

Bolded text denotes statistically significant differences at \( P < 0.05 \).
FIGURE 4. Comparisons of (A–E) mean FA and (F–J) MD between participants with anisometropic amblyopia (blue), strabismic amblyopia (green), and control (black) participants in the five white matter pathways of interest. Values are averaged across hemisphere. All pairwise comparisons were conducted with a Tamhane’s T2 post hoc test.
this interpretation into question, since we find evidence of abnormal inputs to LGN not just from cortical feedback but from feedforward retinal signals as well.

It is also possible these optic nerve differences are demonstrating etiology-specific abnormalities rather than general trends in amblyopia. Strabismic and anisotropic amblyopia may disrupt visual system development differently, such that both develop structural abnormalities as a consequence of abnormal thalamocortical feedback, but anisotropia includes an additional peripheral, feedforward component. People with anisotropic amblyopia usually exhibit lower contrast sensitivity than do those with strabismic amblyopia, but they often show some spared depth perception. Therefore, the more severe binocular deficits seen in strabismus might manifest in abnormalities in networks involved in monocular segregation and integration (such as the optic radiation) while the more severe contrast and acuity sensitivity deficits seen in anisometropia manifests in abnormalities in the retina (and subsequently, the optic nerve/tract).

Consistent with our previous findings, microstructural integrity of the interhemispheric V1 and hMT+ pathways did not significantly differ between control and amblyopic participants. This is not to suggest visual corticocortical white matter is unaffected per se in amblyopia; once similar recent studies have shown abnormalities in late-stream occipital projections such as the vertical occipital fasciculus, occipito-frontal projections such as the inferior longitudinal fasciculus, and interhemispheric connections in the anterior frontal corpus callosum. Additionally, behavioral deficits such as difficulty inferring form from motion suggest amblyopia is associated with functional abnormalities more complex than can be explained by imbalanced binocular integration in thalamus and primary visual cortex. Without a more comprehensive cross-subject tractographic mapping of visual system white matter architecture, it is unclear the extent to which corticocortical pathway abnormalities reflect genuine differences versus overlap with voxels containing abnormal thalamocortical axons.

Microstructural Measures and Demographics

Demographic factors such as age and sex did not significantly correlate with our measures of microstructural integrity, nor could they explain observed differences between amblyopic and control participants or the differences between anisotropic and strabismic participants. Even though our sample included adults across a wide range of ages, we found no significant relationship between age and retinothalamic white matter integrity. This is somewhat consistent with human ophthalmologic studies, which often report no or only slight reductions in optic nerve fiber counts across the lifespan. In fact, at least one postmortem human study reported significant increases in optic nerve diameter with age and that the mean number of fibers with large (>4 µm) diameters was decreased compared to the younger sample. Collectively, these analyses indicate the observed differences in microstructural integrity of the optic nerves, tracts, and radiations of people with amblyopia are likely not due to demographic or other factors but instead reflect significant structural degradation along the entire visual pathway in amblyopia.

CONCLUSIONS

The behavioral and functional abnormalities that have long been characterized in amblyopic populations are often attributed to errors at the level of cortical integration of the information from otherwise neurotypical optic nerves. The results of this study indicate structural abnormalities in visual white matter may exist as early as in the optic nerves. These findings run counter to the commonly held model of amblyopia as a purely cortical disorder and suggest some degree of optic nerve dysfunction may also be present in people with untreated or unsuccessfully treated amblyopia. Future studies are needed to determine whether these abnormalities are specific to anisometric amblyopia or if they exist in other types, such as strabismic and deprivation amblyopia, as well.

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