Glaucoma is a leading cause of irreversible blindness that affects more than 4 million Americans. The eventual outcome is often blindness, starting with loss of peripheral vision followed by loss of central vision.

MRI Study of the Posterior Visual Pathways in Primary Open Angle Glaucoma

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Purpose of the Study: The purpose of the study was to evaluate neurodegeneration along brain visual pathways in primary open angle glaucoma (POAG) using improved analysis methods of volumetric and diffusion tensor magnetic resonance imaging (MRI) data.

Methods: Eleven POAG patients (60.0 ± 9.2 y) with primarily mild to moderate POAG and 11 age-matched controls (55.9 ± 7.5 y) were studied using structural and diffusion tensor MRI. Surface-based segmentation was applied to structural MRI to obtain visual cortical area and volume. Fiber tracking was applied to diffusion tensor data to obtain diffusion parameters along the optic tract and optic radiation. MRI parameters in glaucoma patients were compared with the corresponding left and right visual fields and retinal nerve fiber layer thicknesses, instead of with the left and right eye.

Results: Area and volume of the primary visual cortex were significantly reduced in POAG patients compared with controls (P < 0.05) but did not correlate with visual field loss. Fractional anisotropy was reduced at multiple locations along the optic tracts and optic radiations in POAG patients compared with controls. Axial and radial diffusivity along the fiber tracts showed trends but were not significantly different between POAG patients and controls when averaged over the whole structures. Only fractional anisotropy (P < 0.05) of the optic radiations was significantly correlated with visual field loss. No MRI parameters were correlated with retinal nerve fiber layer thickness.

Conclusions: Improved analysis techniques of MRI data improve delineation of degeneration in the brain visual pathways and further supports the notion that neurodegeneration is involved with glaucoma pathogenesis.

Key Words: fractional anisotropy, retinal nerve fiber layer, diffusion tensor imaging, visual field, magnetic resonance imaging (J Glaucoma 2016;00:000-000)

Glaucoma is characterized by cupping of the optic nerve head and thinning of the retinal nerve fiber layer (RNFL) due to loss of retinal ganglion cells, which becomes evident only after a substantial number of retinal ganglion cells have already died. Visual field measurements and RNFL thickness are often used to gauge the progression of vision loss and glaucoma severity. Elevated intraocular pressure (IOP) is a known risk factor, and lowering IOP is the only available treatment for glaucoma. However, many glaucoma patients continue to lose vision despite successful medical or surgical treatment to lower IOP. As such, there are likely other factors that contribute to the disease progression.

Neurodegeneration and transsynaptic degeneration in the optic nerve, optic tract, lateral geniculate nucleus, optic radiation, and visual cortex have been reported in glaucoma. Axonal damage of the retinal ganglion cells has been suggested to precede the loss of cell bodies. Shrinkage of the lateral geniculate nucleus has been documented in ocular hypertension in the absence of optic nerve fiber loss. Oxidative damage and glutamate toxicity have been implicated in transsynaptic central nervous system injury in glaucoma. As damage to the lateral geniculate nucleus and visual cortex can induce loss of retinal ganglion cells, degeneration in the posterior visual pathway could contribute to disease progression in glaucoma.

Recent magnetic resonance imaging (MRI) studies have provided further evidence of neurologic damage in glaucoma. Morphometric MRI studies found atrophy in the lateral geniculate nuclei (LGN) and visual cortex, optic nerve, optic chiasm, optic tract, and optic radiation in glaucoma patients. Diffusion tensor imaging (DTI) MRI studies found altered diffusivity and fractional anisotropy (FA) of the optic radiation and optic nerve in glaucoma. Abnormal DTI parameters have been shown to correlate with glaucoma severity. The majority of the previous studies employed voxel-based group analysis, which may not adequately pinpoint atrophy to specific regions in the brain. Moreover, previous studies of glaucoma patients compare MRI parameters with visual field loss of the left and right eyes (not left and right visual fields), whereas the visual pathways are segregated by visual field after the optic chiasm and thus the unilateral posterior visual pathway receives input from the ipsilateral retina and the contralateral visual field from both eyes. However, such correct comparison has not been made. In addition, comparison of MRI parameters with left and right visual fields (instead of left and right eyes) could also improve delineation of neurodegeneration in glaucoma.

The goal of this study was to employ improved analysis methods of volumetric and diffusion tensor MRI to evaluate changes in the optic tract, optic radiation, and primary visual cortex (V1) in primary open angle glaucoma.
(POAG) patients. Primarily mild and moderate POAG patients were studied and compared with age-matched controls. Glaucomatous damage in the left and right cerebral hemispheres was analyzed with respect to the corresponding visual field loss of the contralateral visual hemifields.\textsuperscript{23} Moreover, in contrast to most previous studies, which used voxel-based group analysis, a novel algorithm\textsuperscript{24} was employed to map the spatial profiles of the white matter tracts of the visual pathway of individual subjects. This study explored the hypothesis that with sophisticated analysis techniques, volumetric and diffusion tensor MRI will allow improved substructural delineation of neurodegenerative pathogenesis in the brain visual pathways.

**METHODS**

### Subjects

This study was approved by the local Institutional Review Board. Informed consent was obtained for all participants. Eleven patients with diagnosed POAG (age range, 36 to 72 y, average: 60.0 ± 9.2 y, 4 males) and 11 healthy age-matched adults (age range, 37 to 65 y, average: 55.9 ± 7.5 y, 7 males) were enrolled in the study. The clinical diagnosis of POAG was performed or confirmed by 2 qualified ophthalmologists (S.C. and K.S.N.). The glaucoma diagnosis was made based on the diagnostic criteria of the American Academy of Ophthalmology's Glaucoma Primary Open-Angle Glaucoma Preferred Practice Pattern Guidelines\textsuperscript{25} through assessment of the open anterior chamber angle, identification of visual field defects typical of glaucoma, optic disc cupping, or identification of an IOP of 21 mm Hg or greater. Exclusion criteria were any history of glaucoma, optic disc cupping, or identification of an IOP chamber angle, identification of visual field defects typical of glaucoma, optic disc cupping, or identification of an IOP of 21 mm Hg or greater. Exclusion criteria were any history of diabetes, eye surgery, other eye diseases (except near sightedness), and clinically abnormal structural brain MRI. Severity of glaucoma was categorized as mild, moderate, and severe based on established criteria.\textsuperscript{26,27} Normal controls were age-matched participants free of all eye diseases with the same exclusion criteria.

### Clinical Data

Glaucoma patients underwent standard clinical eye exams, which included visual field scores by automated perimetry (HFA II 750, Carl Zeiss, Dublin, CA), IOP by tonometry (Goldmann applanation, Haag-Streit Diagnostics, Bern, Switzerland), and RNFL thickness by optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) for glaucoma diagnosis. The pattern standard deviation (PSD) values of both right and left eyes were the standard outputs of the visual field tests. The visual pathways of the 2 eyes are combined by visual field after the optic chiasm and thus the unilateral posterior visual pathway receives input from the ipsilateral retina and the contralateral visual field from both eyes. Thus, it is necessary to combine visual data when compared with brain data. For such comparison with individual brain hemispheres, for each patient, the PSD values of right and left eyes were combined point by point by taking either the “mean” and the “best” location algorithm yielded similar results and conclusions when correlated with MRI data, and thus only the “mean” algorithm results were presented.

### MRI Acquisition

MRI data were acquired using a 3-T scanner (Magnetom Trio, Siemens, Erlangen, Germany) with a standard 8-channel head coil. Brain anatomic MRI was obtained using a T1-weighted MP-RAGE sequence for the whole brain with repetition time TR = 2200 ms, echo time TE = 2.8 ms, field of view = 176 × 256 × 208 mm, matrix size = 176 × 256 × 208, bandwidth = 190 Hz/pixel, flip angle = 13 degrees, and scan duration = 3 minutes. DTI was acquired using a single spin echo, twice refocused, echo planar imaging diffusion sequence covering the entire visual pathway of each subject. The parameters were: TR = 6000 ms, TE = 90 ms, field of view = 192 × 192 × 92 mm, matrix size = 64 × 64 × 46, with 64 directions at b = 1000 s/mm\(^2\) and one b = 0 s/mm\(^2\),\textsuperscript{29} bandwidth = 1420 Hz/pixel, and scan duration = 6.5 minutes.

### MRI Image Processing

T1-weighted anatomic images were first aligned to the anterior commissure–posterior commissure plane and were processed in Freesurfer (https://surfer.nmr.mgh.harvard.edu) to derive cortical and noncortical parcellations including the optic chiasm and V1. Gray matter surface reconstruction of cortical regions was then performed to obtain the cortical volume and surface area of V1.

Diffusion MRI images were processed in MATLAB (Math works, Natick, MA) using the mriDiffusion package (https://github.com/vistalab/vistasoft/mrDiffusion) with eddy-current correction and motion correction. The corrected nondiffusion image was aligned to the T1-weighted images in the anterior commissure–posterior commissure space. The Eigenvalues from the diffusion tensor, FA, radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD) were calculated.\textsuperscript{3}

Fiber tract profiles of the optic tract and optic radiation for both hemispheres were segmented using probabilistic fiber tracking (https://github.com/jreatman/AFQ).\textsuperscript{24} To identify the optic tract and optic radiation, regions of interest (ROIs) of the optic chiasm and V1 were obtained from automatic segmentation of the T1-weighted anatomic image in Freesurfer. For the LGN ROIs, 5-mm spheres for both hemispheres were manually defined lateral to the hypothalamus on the high-resolution anatomic images.\textsuperscript{30} The LGN ROIs were adjusted and confirmed by ensuring that they covered the end points of fibers from the optic chiasm. Fibers were “cleaned” by removing outliers and gray matter components.\textsuperscript{24} Taking tract length into consideration, 30 or 100 nodes\textsuperscript{31} were taken along the cleaned individual optic tract or optic radiation segments, respectively. Five nodes at the ends of each track were removed to avoid partial volume artifacts. Each diffusion measure (FA, RD, AD, and MD) was averaged at each node along the 2 tracts of the 2 hemispheres and rendered onto the tract profile. The spatial profiles of diffusion measures were plotted as functions of distance.

### Statistical Analysis

For gray matter area and volume of the V1, group comparisons were assessed by Analysis of Covariance with intracranial volume as a covariate factor (to regress the effects of head size). The POAG patients’ V1 area and
volume data per brain hemisphere were correlated to corresponding visual field scores or RNFL thicknesses, as well as head size, using multiple linear regressions. Mixed effects analysis of variance (group as fixed effect, subject and hemisphere as random effect) was applied to compare diffusion parameters for all nodes, as well as the group mean values of the entire optic tract and optic radiation between normal and POAG groups. Diffusion measures per brain hemisphere were correlated with corresponding left and right visual field scores and RNFL thicknesses using Spearman correlation. A threshold of \( P < 0.05 \) was considered statistically significant unless otherwise specified.

RESULTS

Demographic data of POAG patients, their visual field PSD, IOP, and average RNFL thickness are given in Table 1. There was no significant age difference between controls and glaucoma patients \( (P > 0.05) \). IOPs of POAG patients were within normal physiological ranges \((<21 \text{ mm Hg})\) as they were under standard clinical care, except 1 newly diagnosed POAG patient who had elevated IOP \( (\geq 35) \). Visual field scores of the majority of POAG patients were abnormal compared with the age-corrected normal population database. RNFL thicknesses of the majority of POAG patients were abnormal compared with the normative database. Severity of glaucoma ranged from mild to moderate, except 1 patient, who was diagnosed as having severe glaucoma.

Figure 1 shows a representative visual field test from the left and right eyes of a POAG patient, which were combined to give a binocular visual field using the “mean” and “best” of the 2 eyes. Darker shade and more negative values indicate worse visual defect. The binocular visual field clinical data were converted to the left and right visual field scores, which were used for correlation with MRI data per corresponding brain hemisphere.

The surface area and volume of the V1 of POAG patients were significantly reduced compared withagematched controls \( (P < 0.01, \text{Analysis of Covariance, Fig. 2}) \). V1 area and V1 volume of the POAG patients however showed no significant correlation with disease severity as indicated by visual field scores \((V1 \text{ area: multiple } R^2 = 0.212, P > 0.05 \text{; } V1 \text{ volume: multiple } R^2 = 0.060, P > 0.05) \).

Figure 3 shows the seed ROIs used for DTI analysis and the resulting fiber tracts. Seeds for fiber tracking were placed in the optic chiasm, lateral geniculate, and V1 from which fiber tracts and diffusion indices of the optic tract and optic radiation were derived. FA spatial profiles along the optic tract and optic radiation are plotted for POAG and control subjects \( (Fig. 4) \). FA in the optic tract close to the optic chiasm and LGN \( (\text{node 1 to 3, 12 to 14}) \), showed significant differences between POAG and control group. The FA in the optic radiation near the middle of the tract and close to V1 \( (\text{node 30 to 37, 47 to 48, 75 to 80, 87 to 88}) \), was significantly reduced \( (POAG, P < 0.05 \text{; node 39 to 46, 81 to 86}) \), whereas FA of the optic radiation did \( (R = 0.537, P < 0.05) \).

RD, AD, and MD profiles of the optic tract and optic radiation and their group means are displayed in Figure 5. RD showed a trend of being increased in POAG patients compared with controls in the optic radiation with node 43 and 75 to 76 showing significant difference \( (P < 0.05) \). Axial diffusivity showed a trend of decreasing in POAG patients compared with controls in the optic tract with node 17 to 19 showing significant difference \( (P < 0.05) \). Mean diffusivities were not significantly different between POAG patients and controls in neither the optic tract or optic radiation. None of the diffusivity values of the optic tract or optic radiation were significantly correlated with visual field data \( (P > 0.05) \).

None of the MRI parameters were significantly correlated with RNFL thickness \( (P > 0.05) \). Visual field scores were also not significantly correlated with RNFL thickness \( (P > 0.05) \). None of the MRI parameters were significantly correlated with RNFL thickness.

### TABLE 1. Demographic and Clinical Data of Individual POAG Patients

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<th>OS PSD</th>
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*Visual field [pattern SD (PSD)], intraocular pressure (IOP), and retinal nerve fiber layer (RNFL) thickness are shown for right (OD) and left (OS) eyes. *P < 0.05.

**P < 0.01 indicates RNFL thickness of inner cycle significantly different from normative data set.

F indicates female; M, male.
correlated with IOP (P > 0.05) as expected because IOPs of all but one POAG patient were maintained within normal physiological ranges by standard clinical treatments in our study.

**DISCUSSION**

This study evaluated glaucomatous damage along visual pathways of the brain using novel analysis approaches of volumetric and diffusion tensor MRI data. In contrast to the majority of previous studies that employed voxel-based group analysis, we used surface-based segmentation of gray matter and a novel algorithm to map the spatial profiles of the white matter tracts of the visual pathway on individual patient data. We also compared glaucomatous visual field loss from the left and right hemifield (instead of typical left and right eye) with gray matter and white matter from the corresponding contralateral hemispheres. The major findings in the present study are: (i) the visual cortex area and volume are significantly reduced in POAG patients compared with age-matched controls but they do not correlate with disease severity in mild to moderate POAG patients, (ii) FA of the optic tract and optic radiation is reduced at multiple locations along the fiber tracts in POAG patients compared with controls. RD, AD, and MD show trends between POAG patients and controls but did not reach overall statistical significance. Only the FA of optic radiations significantly correlate with the severity of visual field loss. These results lend credence to MRI as a potential biomarker for glaucoma staging, and support the notion that there is neurodegeneration in the brain visual pathways of POAG patients.

**V1 Area and Volume**

V1 gray matter area and volume were significantly different between POAG patients and normal controls using surface-based segmentation methods. Our results corroborated previous voxel-based morphometry reports on volumetric reduction of human visual cortex.\(^{15,16}\) Another study however only found trends of reduced area and volume of V1 area and volume in glaucoma, but head size was not taken into account as a covariate.\(^{33}\) Accounting for head size is likely important to detect differences as has been shown to be the case in the analysis of Alzheimer disease.\(^{34}\) A possible explanation for the gray matter degeneration is that the loss of visual function in glaucoma leads to fewer neural signals to the visual cortex from the retina and other brain regions, resulting in the disuse-driven atrophy or shrinkage of neurons. The exact mechanism of the distal gray matter (V1) atrophy in glaucoma remains to be investigated.

Although there were significant differences between glaucoma and control groups, we found gray matter area and volume did not correlate with disease severity as measured by visual fields in glaucoma patients. Similar studies of late blindness have also found no correlation between V1 volumetric atrophy and blindness duration.\(^{35,36}\) It is possible that visual cortex atrophy may occur at a relatively early stage of vision loss but does not progress. Another possible explanation for the lack of correlation is the narrow dynamic range of disease severity in our study, which included only mild and moderate glaucoma (except 1 severe glaucoma patient).

**White Matter Changes**

FA of the optic tract and optic radiation was reduced in glaucoma patients, in general agreement with previous reports.\(^{18,20,22,37}\) Conventional voxel-based morphometry,\(^{15,20}\) and tract-based spatial statistics\(^{38}\) analysis showed the spatial pattern of diffusion changes, although both
techniques relied on precise cross-subject registration to yield statistical maps that highlighted differences between groups.\textsuperscript{24,39} Imperfect image registration and intersubject variation in tract shapes and locations could lower the precision and sensitivity. Other DTI studies of glaucoma reported only the overall mean FA values of the entire white matter tracts by ROI analysis.\textsuperscript{18,22}

We used a different method of analysis in which FA abnormality along the length of the optic tract and optic radiation profiles were analyzed on an individual basis. Differences between groups were detected in the optic tract in both proximal and distal regions and in the optic radiation in the middle and near V1 regions. Brain diseases can affect different regions of brain substructures in a time-specific and disease-specific manner, and thus it is important to study these brain substructures. This method could be applied to individual glaucoma patients for assessment of optic tract and optic radiation profiles and compared with a normal population database.

The factors that contributed to FA changes may differ between the optic tract and optic radiation. FA difference along the optic tract was associated with reduced AD in glaucoma, whereas FA difference along the optic radiation was associated with increased RD. In the white matter structures, the myelin sheath wrapping around the axons does not constrain diffusivity along the fibers (AD),\textsuperscript{3} whereas it does restrict diffusion perpendicular to the fibers (RD).\textsuperscript{40} Thus, for glaucoma, decreased FA associated with reduced AD in optic tracts could reflect more general axonal degeneration, where the decreased FA associated

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**FIGURE 2.** Group comparison of (A) area and (B) volume of the primary visual cortex (V1) from normal controls and primary open angle glaucoma (POAG) subjects. Mean ± SEM. **P < 0.01.

**FIGURE 3.** (A) Typical region of interest seeds used for fiber tracking overlaid on an anatomic image from a representative normal subject: optic chiasm,\textsuperscript{3} lateral geniculate nucleus (red), and V1 (blue). (B) Fiber tracts of the optic tract (pink) and optic radiation (yellow). (C) The corresponding fractional anisotropy along the fiber tracts.
with increased RD in optic radiations could reflect demyelination. 41 Further studies are needed to explore this hypothesis. FA changes of both optic tract and optic radiation in our study are consistent with previously reported DTI results in Leber hereditary optic neuropathy. 31 It is possible that transsynaptic degeneration triggered by retinal ganglion cell death in both glaucoma and optic neuropathy may lead to white matter diffusion abnormality measured by FA.

Correlation of Unilateral Diffusion MRI With Visual Field

Another novelty of our analysis approach is that we separated the left and right visual fields for comparison. Most prior studies compared MRI data with the left and right eyes but not with left and right visual fields. 13,20,22 The visual pathways are segregated by visual fields after the optic chiasm, and thus comparison with visual fields is more appropriate and may improve delineation of neurodegeneration in glaucoma. Standard clinical visual field tests evaluate 1 eye at a time. There are several methods to derive binocular fields from monocular data typically used in clinical settings. 27,28,42 We evaluated 2 algorithms: “mean” and “best” location of the visual field maps using glaucoma PSD scores. The correlation results from the 2 methods were not statistically different from each other and thus only the results from the “mean” method were presented. Although there is no ideal way to generate binocular fields from monocular data typically used in clinical settings, 27,28,42 We evaluated 2 algorithms: “mean” and “best” location of the visual field maps using glaucoma PSD scores. The correlation results from the 2 methods were not statistically different from each other and thus only the results from the “mean” method were presented. Although there is no ideal way to generate binocular fields from monocular data, previous studies have shown this method to combine thicknesses is not more appropriate than the other to generate binocular visual field scores and RNFL for comparison with brain degeneration, but this needs further investigation.

Nonetheless, using this method, we found no significant correlation between MRI parameters (ie, volume and FA, etc) with RNFL thickness, whereas FA did correlate with visual fields. For the optic radiation, FA had a significant positive correlation with contralateral visual field scores. Previous studies have demonstrated that FA of the optic radiation was significantly correlated with glaucoma stages. 20 optic nerve head damage, and mean visual field score of both eyes. 22 Our results are in agreement with these findings and further underscore the notation that the FA values of the optic radiation could be used to evaluate the severity of visual field loss in glaucoma by separating left and right visual fields. For the optic tract, there was no significant correlation between contralateral field deficits and diffusion parameters. A possible reason for the lack of correlation could be that the optic tract is comparatively small (relative to the optic radiation) and contains fewer neuron bundles leading to lower sensitivity. 30

We found no significant correlation between RNFL thickness with any MRI parameters or with visual fields. There are a few possible explanations. First, visual field defects typically occur only after a substantial number of retinal ganglion cells have already died and often at later stages of glaucoma, 2–5 whereas thinning of the RNFL may occur at early stage with normal visual field function. 32 Thus, it is possible that the absence of correlation between structural and functional changes could be due to in part that our population included mostly mild to moderate POAG participants. Structure-function correlation likely becomes more apparent at more severe POAG stages. Second, it is also possible that the large inherent intersubject variability (scattering) in RNFL thickness and MRI parameters could contribute to the lack of correlation. In addition, combination of RNFL thickness between 2 eyes has not been reported to our knowledge, in contrast to visual fields, so it could be that combining thicknesses is not straightforward. Finally, the small sample sizes in our study could contribute to the lack of correlation.

In sum, multimodal MRI could complement standard clinical eye examination by providing added value and
unique information about neurodegeneration in the brain that contributes to glaucoma pathogenesis and progression.

Limitations and Future Directions

There are several limitations of this study. The number of subjects was relatively small although it is typical for many similar MRI-based studies. We expect that with larger sample sizes, some of the trends in diffusion parameters, and their correlations with visual field scores will likely become statistically significant. We do not have data on the duration and stability of glaucoma for all our participants. The small sample sizes also precluded such analysis. Future studies should include correlation with duration and stability of glaucoma with larger sample sizes.

The dynamic range of disease severity was narrow as the patients had mild or moderate glaucoma. Although these results indicate that neurodegenerative changes occur in the brain even in mild to moderate glaucoma, inclusion of severe glaucoma patients would help to confirm the link between visual field loss and brain atrophy. Future longitudinal studies of POAG by MRI could help to evaluate the progression of brain atrophy and its relation with retina damage progression in patients. Although our spatial resolution is high compared with most previous DTI studies of glaucoma, further improving spatial resolution as well as
using image acquisition with less spatial distortion (ie, nonecho planar imaging acquisition) would help to improve sensitivity. Advanced diffusion methods, such as high angular resolution diffusion method, could be used to resolve crossing fibers at the optic chiasm and provide more information of glaucoma damage to the optic nerve and optic tract. The MRI data could not be separated into regions corresponding to the left or right eye; therefore it is possible that asymmetry between the 2 eyes could confound the correlation results. Many POAG patients show asymmetric damage around the horizontal midline and thus subdividing white matter tracts with upper and lower visual field could provide additional information.

CONCLUSIONS

This study evaluated glaucomatous damage along visual pathways of the brain using novel analysis approaches of volumetric and diffusion tensor MRI. We found various regional abnormalities along the entire visual pathway in the brain. Some of the MRI indices are more sensitive than others in detecting these abnormalities. By comparing glaucomatous visual field loss from the left and right hemifields (instead of left and right eyes), white matter changes are correlated with the corresponding visual field loss. These findings support the hypothesis that improved analysis of MRI enables improved substructural delineation of neurodegenerative pathogenesis in the brain visual pathways in glaucoma. If neurodegeneration contributes to glaucomatous progression, then treatment strategies for glaucoma needs to consider neuroprotection of the brain to preserve visual function.

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